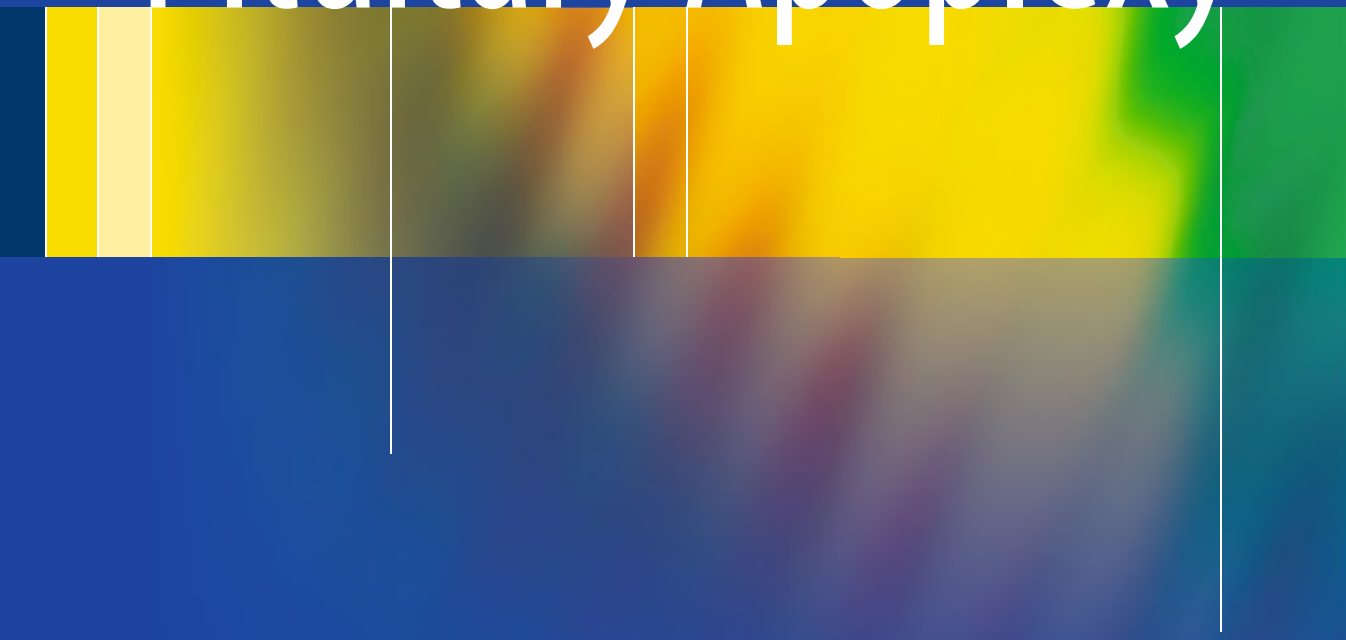
Mehmet Turgut
Ashok Kumar Mahapatra
Michael Powell
Natarajan Muthukumar
Editors

Pituitary Apoplexy



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Preface

Pituitary apoplexy is controversial in a number of ways. This book seeks to present a wide range of views from experts in the field in order to give the current position on management. Following these contributions, the editors sought the comments from two leading authorities, John Wass, Emeritus Professor of Endocrinology at Oxford, UK and Edward Laws, Professor of Neurosurgery, now at The Brigham Hospital in Boston, USA. Their supportive comments are 'A scientific prospective study is required and this is being attempted currently in the UK' (Wass) and 'I like what you have written. The differential diagnosis and initial steroid management are so critical. Like craniopharyngiomas, it is not useful to generalize about urgent surgical vs. conservative management. I have never regretted operating on a case of apoplexy. There is a lot of nonsense in the literature base on disparate definitions of apoplexy and different criteria for selecting patients. Most surgeons tend to see patients who really need surgery.' (Laws).

These views encapsulate the differing stance of two world leaders.

Our particular thanks go to Dr. Inga von Behrens from Springer DE (Heidelberg, Germany) for her invaluable advice and support in the planning of the present book.

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Introduction

Thirteen years after the new millennium, clinicians involved in pituitary disease have a clear idea of the aims of treatment and resultant outcomes for the various diseases caused by adenomas. There are generally agreed management strategies and consensus views on what constitutes cure of those various conditions.

Pituitary endocrinologists now work closely with their specialist surgeons. Management decisions are made in multi-disciplinary settings, to ensure agreement on individual patient management strategy, rather than individual clinicianacting alone. Their specialist neuro-oncologists have a range of improved techniques for delivering radiation when surgery fails, rather than crude delivery systems, which were the strategies of the past. Further, improvements in hormone assays, along with better drugs and technical advances in surgical equipment and training have led to steadily improving outcomes for our patients, in terms of endocrine function preservation, endocrine cure, visual improvement and reduction in recurrencerate.

Although there are still some minor differences in regional management, such as in the timing of use of long acting somatostatin analogues in acromegaly and the ongoing debate on the relative merits of endoscopic and microscopic surgery, essentially the differences are somewhat technical and of little longer term significance.

It is in the management of apoplexy that the least clarity exists. Perhaps, because of the complexities of it's presentation, which usually circumvent well-established adenoma referral routes, patients may arrive in neurosurgical units without endocrine assessment, under teams who are less used to managing complex endocrine conditions. It is also quite possible that the presentation be misdiagnosed and apoplexy patients may spend time on other non- specialist intensive care units, even coronary in care units. The diagnosis is often made rather later than might be ideal and as a consequence there is no fixed consensus regarding what constitutes 'early' management, particularly when surgical intervention is contemplated. It seems to counter intuitive that surgery within 7 days can still generally constitute 'early' intervention, but this is indeed the case.

Although there is a generally agreed view that apoplexy patients require endocrine stabilization first and foremost as a priority, what happens next depends on a number of factors. Many patients have complex visual problems but it is not necessarily easy to obtain unbiased objective assessment in a specialized ophthalmology setting, in an obtunded patient, at night or at the

weekend, as an emergency. Thus, the patients who may have objective evidence of long term loss of visual fields with optic atrophy, may be mistaken for the patients with an acute new change.

Despite the recent publication of UK guidelines, no international consensus view on management exists. This multi-author work seeks to present an over view, mainly from Europe and Asia. It is immediately apparent that these views are based on relatively few big clinical series, and equally, there is a distinct difference to the European stance, where the clinicians are prepared to wait and manage the patient conservatively, if visual involvement is mild, from that in the Indian Sub-continent where surgical intervention is clearly the norm. This may be because the tumours seen in Asia are notoriously much larger and their experience is biased by perceived poorer outcomes of apoplexy in conservatively managed patients.

The reader will make up his or her mind on the need and timing of surgical intervention, based on their own experiences along with the evidence that the book provides.

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Part I

Introduction

1 Definition, History, Frequency, Histopathology and Pathophysiology of Pituitary Apoplexy

Mehmet Turgut, M. Hakan Seyithanoğlu, and Saffet Tüzgen

Contents

1.1 Introduction

Pituitary apoplexy, a potentially life-threatening disorder, is one of the rare problems that is diagnostically and therapeutically challenging. It usually occurs as a consequence of the expansion of a pituitary tumour by haemorrhage, infarction or haemorrhagic infarction. Today, it is widely accepted that initial management in acute pituitary apoplexy consists of replacement of the deficient pituitary hormones, including corticosteroids as replacement therapy for adrenal insufficiency and the oedema on suprasellar structures (Janssen et al. 2012). In particular, conservative medical treatment should be the first choice of treatment in patients with a major pituitary apoplexy and visual field defects in pregnancy (Janssen et al. 2012). Due to limited individual experience as a result of its relative rarity and the variable clinical course of the condition, however, it is frequently misdiagnosed before surgery, and its optimal management following hormonal stabilization is controversial (Post et al. 1980; Cardosa and Peterson 1984; Cohen et al. 1985; McFadzean et al. 1991; Maccagnan et al. 1995; Sibal et al. 2004; Semple et al. 2005; Turgut et al. 2010; Rajasekaran et al. 2011). Unfortunately, as the existence of a pituitary adenoma is not frequently considered at the time of the apoplectic ictus, the cornerstone of diagnosis remains a high level of clinical suspicion. Furthermore, it is also difficult to decide if the clinical situation of the patient with pituitary apoplexy is appropriate for surgical intervention (Rajasekaran et al. 2011).

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At present, it is generally accepted that a patient with apoplexy should have surgical decompression in the presence of and significant neuro-ophthalmic signs or reduced level of consciousness. However, there is a clear divergence of views in the management of patients with pituitary apoplexy in the world; some believe that immediate neurosurgical intervention is necessary for such patients, whilst others insist that a more conservative approach with/without neurosurgical intervention carries similar results (Onesti et al. 1990; Bills et al. 1993; Randeva et al. 1999; Turgut et al. 2010; Rajasekaran et al. 2011; Ranabir and Baruah 2011). Thus, not only the role of neurosurgical decompression but also the timing of surgery remains controversial, and there is no consensus for the management of pituitary apoplexy throughout the world. Further, there are no randomized controlled evidence-based criteria to justify the clinical decision for either a conservative approach or neurosurgical intervention in the management of pituitary apoplexy (Rajasekaran et al. 2011).

In 2010, a 'pituitary apoplexy guidelines development group' developed 'UK Guidelines for the Management of Pituitary Apoplexy', to provide the guidance for neurosurgeons, endocrinologists, ophthalmologists and physicians (Rajasekaran et al. 2011). This document concluded that:

> 'Patients with severe neuro-ophthalmic signs … or deteriorating level of consciousness should be considered for surgical management' and
> 'Surgery should be performed preferably within the first 7 days of onset of symptoms'. (Rajasekaran et al. 2011)

To the best of our knowledge, there is no other national guideline on the management of patients with pituitary apoplexy published in the world to date.

In this chapter, the definition, history, frequency, histopathological findings and pathophysiology of clinical manifestations of this fascinating condition were given in detail. It is hoped that this book will provide a concise updated summary of these aspects of pituitary apoplexy needed by the neurosurgeons, endocrinologists, neuro-ophthalmologists, neuroradiologists and neuropathologists.

1.2 Definition and History of Pituitary Apoplexy

The term 'pituitary apoplexy' originating from Greek is used to describe acute haemorrhage and/or infarction of the pituitary tumour or, less commonly, of the surrounding normal gland tissue. Although a fatal case of haemorrhagic pituitary tumour was reported by Bailey in 1898 (Bailey 1898), acute necrosis of a pituitary adenoma was first documented as a pathologic entity by German physician Bleibtreu in 1905 in a young patient with acromegaly (Bleibtreu 1905). Then this pathology was firstly described in detail by Brougham et al. (1950) in five postmortem cases of pituitary adenoma associated with massive infarction, necrosis and haemorrhage of a pituitary tumour.

In general, there is haemorrhage, infarction or haemorrhagic infarction of a pre-existing pituitary adenoma in patients with pituitary apoplexy. As the primary event most often involves the adenoma, some authors suggested that the syndrome should be referred to as pituitary tumour apoplexy and not as pituitary apoplexy (Nawar et al. 2008; Ranabir and Baruah 2011). However, pituitary apoplexy may also occur in nonadenomatous or even the normal pituitary gland especially during pregnancy (Findling et al. 1981; Onesti et al. 1990). The term 'subclinical pituitary apoplexy' is generally used to define asymptomatic pituitary ischaemia (Findling et al. 1981) or haemorrhage (Onesti et al. 1990).

Pituitary apoplexy is a clinical diagnosis, not a pathological one, related with signs of compression of perisellar anatomical structures due to ischaemic and/or haemorrhagic infarction of a pituitary adenoma (Nawar et al. 2008). Clinically, 'classical' pituitary apoplexy syndrome is characterized by a sudden onset of headache, vomiting, decreased consciousness, mild or severe hormonal dysfunction, partial or complete ophthalmoplegia and visual impairment from involvement of the optic nerve and/or chiasm. Also, it has been suggested that pituitary apoplexy evolves within hours or days (Weisberg 1977).

It is interesting to note that the vast majority of the patients with pituitary apoplexy are asymptomatic. Although the clinical presentation is variable in symptomatic patients, the most frequent presentation is retro-orbital, sudden and

severe headache (Randeva et al. 1999). It has been speculated that the potential mechanisms underlying headache in pituitary apoplexy are compression and irritation of the meninges surrounding the sellar walls or involvement of the trigeminal nerve (Bills et al. 1993; Satyarthee and Mahapatra 2005). In patients with pituitary apoplexy, altered visual field or visual acuity can be due to involvement of the optic nerves, chiasma or optic tracts. Furthermore, the third, fourth, fifth and sixth cranial nerves are vulnerable at the cavernous sinus (Nawar et al. 2008). Altered mental status, ranging from mild lethargy to stupor and coma, is frequent in patients with pituitary apoplexy, possibly due to subarachnoid haemorrhage, increased intracranial pressure, obstructive hydrocephalus and hypothalamic compression (Rovit and Fein 1972; Chang et al. 2009). Moreover, neck stiffness due to subarachnoid haemorrhage may be observed in patients with pituitary apoplexy (Elsässer Imboden et al. 2005). Also, focal signs such as loss of muscle strength or aphasia due to internal carotid artery compression or vasospasm are less common (Das et al. 2008; Chokyu et al. 2011).

In contrast, 'asymptomatic' or 'subclinical' pituitary apoplexy detected accidentally on routine imaging or histopathological examination is not accepted as a diagnosis of pituitary apoplexy (Findling et al. 1981; Mohr and Hardy 1982; Onesti et al. 1990; Bonicki et al. 1993; Ranabir and Baruah 2011). It has been reported that spontaneous haemorrhage may occur without any clinical symptom in 25 % of patients with pituitary adenoma (Wakai et al. 1981; Mohr and Hardy 1982; Cardosa and Peterson 1984).

Moreover, haemorrhage into an existing Rathke's cyst or ischaemic insults following prolonged period of hypotension such as Sheehan's syndrome should be considered in the differential diagnosis of patients with pituitary apoplexy (Nawar et al. 2008).

1.3 Frequency of Pituitary Apoplexy

Pituitary apoplexy is a rare entity with an incidence ranging from 0.6 to 10.5 % in patients with pituitary tumour. The reported incidence of pituitary tumour apoplexy in published series varied between 0.6 and 10 %, with a mean of 2 % (Mohr and Hardy 1982; Kaplan et al. 1983; Cardosa and Peterson 1984; Onesti et al. 1990; McFadzean et al. 1991; Bills et al. 1993; Arafah et al. 1997; Randeva et al. 1999; Ayuk et al. 2004; Verrees et al. 2004; Semple et al. 2005; Nakahara et al. 2006; Turgut et al. 2010). In the majority of the cases, pituitary apoplexy is the first presentation of the pre-existing pituitary tumour, and the estimation of its true incidence is not easy due to diagnostic difficulties (Wakai et al. 1981; Biousse et al. 2001; Sibal et al. 2004; Semple et al. 2007). Mohr and Hardy (1982) noted typical symptomatic pituitary apoplexy to occur in only 0.6 % of patients with significant haemorrhagic and necrotic changes in 9.5 % of surgical specimens. There is no doubt that frequency of pituitary apoplexy increases if using only magnetic resonance imaging criteria without clinical symptom.

In a review of a series of 560 cases of pituitary tumours, Wakai et al. (1981) estimated the incidence or prevalence of pituitary apoplexy as 17 %, symptomatic in 9 % of the cases and asymptomatic in 8 % of the cases. Recently, Charalampaki et al. (2009) reported that there was only one case of pituitary apoplexy in a series of 150 patients underwent endoscopic pituitary surgery.

Pituitary apoplexy is limited to isolated case reports and small case series (Cardosa and Peterson 1984). In a review of the literature, a total of 135 cases of pituitary apoplexy was found in 1970, with an estimated incidence of 6 % (Lopez 1970). Most patients are between 40 and 60 years of age with a slight male preponderance ranging from 1.1 to 2.3:1.0 (McFadzean et al. 1991; Randeva et al. 1999; Sibal et al. 2004; Dubuisson et al. 2007). Recently, however, a slight female preponderance was found in combined clinical and subclinical cases (Liu et al. 2010).

1.4 Histopathological Findings in Pituitary Apoplexy

Anatomically, the pituitary gland is composed of two major parts: (a) 'adenohypophysis' situated at the anterior site corresponding to ¾ of the gland and (b) 'neurohypophysis' situated at the posterior site corresponding to remaining ¼ of the gland

(Chang et al. 2009). In autopsy series, areas of scarring or fibrosis in the nonadenomatous pituitary gland are relatively frequent (Nawar et al. 2008). Histologically, many of the patients with apoplexy have haemorrhagic and/or ischaemic necrosis within the anterior pituitary gland. In a review of a series of 324 pituitary adenomas, Chacko et al. (2002) found that 12 % of patients had surgical or histopathological evidence of haemorrhage with or without necrosis. In particular, cystic lesions as a pathological finding are very frequent in pituitary tumours. In a review of Cushing's series of 338 pituitary tumours, the frequency of cysts was found to be 17 % in chromophobe adenomas and 6 % in eosinophilic adenomas (Henderson 1939). Muller-Jensen and Ludecke (1981) reported an incidence of cystic lesions in cases with pituitary adenomas as 12 %.

At present, there is conflicting data about histopathological types of pituitary adenoma resulting with apoplexy. Rovit and Duane (1969) reported an increased risk for pituitary apoplexy in patients with hormonally active adenomas such as prolactinoma. In a review of 37 patients with symptomatic pituitary apoplexy, however, Bills et al. (1993) found that null-cell adenomas were the most frequent tumour type if immunostaining criteria were used. Muller-Jensen and Ludecke (1981) also found that the incidence of pituitary apoplexy was the highest in nonfunctioning or endocrinologically inactive macroadenomas. Recently, it has been reported that cavernous sinus invasion of the tumour may be a sign of increased risk of bleeding (Cinar et al. 2012). As a result, the diagnosis of pituitary apoplexy is frequently difficult and delayed, resulting in high morbidity or mortality.

At electron microscopic level the adenoma has immature vessels with low fenestration, fragmented basal membranes and perivascular spaces filled with red cells and proteins (Hirano et al. 1972).

1.5 Pathophysiology of Clinical Manifestations

Anatomically, the pituitary gland is located in the sella turcica circumscribed by the sphenoid bone covered by the diaphragma sellae (Ranabir and Baruah 2011). The surrounding structures are the optic chiasm and hypothalamus superiorly, and the internal carotid artery and the third, fourth, fifth and sixth cranial nerves within the cavernous sinus laterally. In the adult, it measures about 12×9×6 mm in diameter and 0.6 g in weight (Chang et al. 2009). The complex vascularization of the pituitary gland is through the hypothalamus to the pituitary gland, and it is the most irrigated region of the body as 0.8 ml/g/min (Chang et al. 2009).

The blood supply of the normal pituitary gland comes from (a) a capillary network, called 'hypophyseal portal system', originating from the superior and the inferior hypophyseal vessels in the infundibulum and (b) direct arterial blood supply from the 'superior hypophyseal arteries' for the anterior pituitary gland or the 'inferior hypophyseal arteries' for the posterior pituitary, originating from branches of the internal carotid artery (Xuereb et al. 1954; Gorczyca and Hardy 1988; Chanson et al. 2004; Semple et al. 2006). Importantly, the irrigation of the adenohypophysis predominantly comes from major portal vessels (Chang et al. 2009). Furthermore, it is important to know the existence of anastomotic vessels between the superior and the inferior hypophyseal circulation (Flerko 1980). The pituitary gland has a venous drainage to adjacent venous sinuses and then to the jugular veins (Fig. 1.1).

Pathophysiologically, the mechanism of pituitary apoplexy still remains both a poorly understood and potentially fatal condition (Onesti et al. 1990; McFadzean et al. 1991; Sibal et al. 2004; Semple et al. 2005). In contrast to the normal pituitary gland, the direct arterial source from hypophyseal arteries, rather than portal system, is dominant in pituitary adenomas (Baker 1972; Gorczyca and Hardy 1988). Importantly, it has been reported that the bleeding tendency of pituitary adenoma is five times compared to that of any other brain tumour owing to the unique rich vascular structure of the gland (Wakai et al. 1981). Moreover, the size of the adenoma is a critical factor for the development of pituitary apoplexy, with macroadenomas being at a much higher risk than microadenomas, but the exact cause for this predisposition is unknown (Mohanty et al. 1977; Jeffcoate and

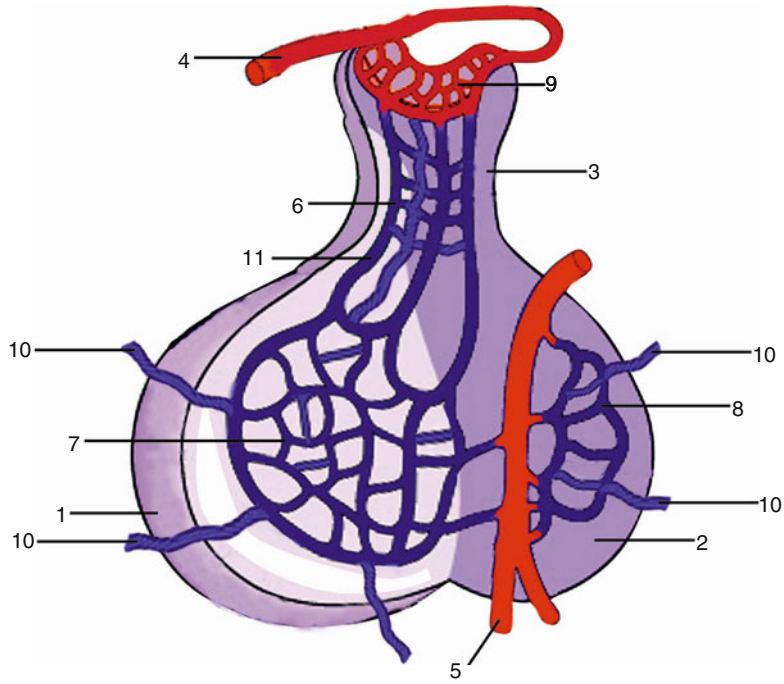

Fig. 1.1 Blood supply to the pituitary gland. Note that most of the blood supply to the anterior pituitary is provided by the portal vessels, but the blood supply to the adenomas by the inferior hypophyseal artery. *1* Anterior lobe of the pituitary gland (adenohypophysis), *2* posterior lobe of the pituitary gland (neurohypophysis), *3* infundibular stalk, *4* superior hypophyseal artery, *5* inferior hypophyseal artery, *6* primary plexus of hypophyseal portal system, *7* secondary plexus of hypophyseal portal system, *8* capillary plexus of infundibular process, *9* external plexus, *10* efferent hypophyseal vein to cavernous sinus, *11* hypophyseal portal vein

Birch 1986; Bills et al. 1993; Arafah et al. 1997; Verrees et al. 2004).

There are various theories upon the pathophysiology of pituitary apoplexy in the current literature. Rovit and Fein (1972) hypothesized that a tumour growing inside the narrow space situated between the pituitary stalk and diaphragm sellae results in compression and distortion of the hypophyseal stalk and the thin vascular network at the diaphragmatic notch, leading to ischaemia and subsequent necrosis of the anterior lobe of the pituitary gland (pars distalis) and the adenoma. Based on the results of angiographic studies, however, some authors oppose with this hypothesis because the blood supply of pituitary adenomas comes from the inferior hypophyseal artery, not the superior hypophyseal artery and its branches, which does not get compressed against the diaphragm sellae (Baker 1972; Cardosa and Peterson 1984; Gorczyca and Hardy 1988). Another theory is the presence of a relationship between the aggressive tumoural behaviour as an 'intrinsic' factor leading to haemorrhage (Fraioli et al. 1990).

The pathophysiological mechanisms of the clinical manifestations in patients with pituitary apoplexy are as follows:

1. An increase in the intrasellar contents during the pituitary apoplexy causes an increase in intrasellar pressure, resulting in compression of the following: (a) the normal pituitary tissue and its vascular blood supply and various clinical findings including hypopituitarism; (b) adjacent neurovascular structures including internal carotid artery and the third, fourth, fifth and sixth cranial nerves laterally; (c) the optic apparatus superiorly, leading to decreased visual acuity, visual field deficit and/or blindness; and (d) the hypothalamus and brain stem, causing to diminished level of consciousness (Arafah et al. 2000; Verrees et al. 2004; Nawar et al. 2008).
2. An increase in intrasellar pressure inferiorly may result in leakage of cerebrospinal fluid called rhinorrhoea (Nawar et al. 2008).
3. Leakage of blood from the intrasellar compartment to the subarachnoid space may cause the signs and symptoms of vasospasm and meningeal irritation (e.g. headache, nuchal rigidity, fever and alterations of consciousness) (Nawar et al. 2008).

Some risk factors such as increased intracranial pressure, arterial hypertension, diabetes mellitus,

cardiac surgery, radiation therapy, pregnancy, oestrogen or bromocriptine therapy, dynamic testing of the pituitary, coagulopathies or head trauma should be considered in the pathogenesis of pituitary apoplexy, although it can occur without any precipitating factor in most cases (Mohr and Hardy 1982; Onesti et al. 1990; Semple et al. 2005; Mou et al. 2009; Rajasekaran et al. 2011). In a recent study, Moller-Goede et al. (2011) compared the frequencies of potential risk factors between the patients with pituitary apoplexy and the control group of matched patients with pituitary adenomas. They found that sex, age, tumour size and tumour type revealed no significant difference between patients with pituitary apoplexy and the control group (Moller-Goede et al. 2011). According to results of their study, risk for pituitary apoplexy was significantly elevated in patients with antithrombotic drugs (vitamin K antagonist or platelet inhibitors), but not in patients with cardiovascular risk factors such as diabetes mellitus and arterial hypertension (Moller-Goede et al. 2011).

Conclusion

Pituitary apoplexy is an uncommon but potentially life-threatening complication due to acute infarction or haemorrhage in the pituitary gland. Pathophysiology of pituitary apoplexy, extrinsic compression of arterial supply or intrinsic tumoural factors, is controversial. Patients who may present with headache, visual defect and altered sensorium may be confused with subarachnoid haemorrhage or meningitis. Imaging studies such as CT or MRI play an important role in the diagnosis of pituitary apoplexy. Prompt institution of intravenous fluid and hydrocortisone must be started in patients with haemodynamic instability. Recent studies favour conservative management except for those with increasing neurological deficit and visual defect. Although the treatment of pituitary apoplexy is still a matter of debate with regard to surgery, the results of early transsphenoidal procedure within 1 week after pituitary apoplexy are satisfactory than patients operated later. Outcome is similar with either conservative management or surgery in more recent studies. Ideally, patients with pituitary apoplexy should be treated through a multidisciplinary team including neurosurgeons, endocrinologists, neuro-ophthalmologists, neuroradiologists, neurologists and radiation oncologists.

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Part II

Overview

2 Conservative Versus Surgical Decompression for Pituitary Apoplexy

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2.1 Introduction

Pituitary apoplexy is a rare condition resulting from haemorrhage or infarction of the pituitary gland and presenting with the classical clinical syndrome of headache, vomiting, neuro-ophthalmic dysfunction (abnormal acuity, field defect or ophthalmoplegia) and alterations in conscious level (Randeva et al. 1999). It is often seen complicating a known pituitary adenoma though, in 80 % of cases, it is the first presentation of a previously undiagnosed tumour. The incidence of apoplexy in patients with a pituitary adenoma is reported as between 2 and 7 % depending on diagnostic criteria (Rajasekaran et al. 2010). Haemorrhage of the pituitary without symptoms, or subclinical apoplexy, is more common and may be as high as 25 % (Ayuk et al. 2004).

Much of the clinical syndrome is the result of gland expansion, with subsequent compression of structures near to the pituitary gland. Headache is the presenting symptom in nearly 100 % of patients (Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004), but compression of the optic chiasm and involvement of the cavernous sinus result in visual defects and ophthalmoplegia, respectively. The incidence of these symptoms varies between case series, but up to 80–90 % can have visual symptoms (acuity and field defects combined) (Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006) and 40–70 % have ophthalmoplegia (typically including cranial nerve III) (Sibal et al. 2004; Rajasekaran et al. 2010).

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Due to the compressive nature of these symptoms, it seems logical (if simplistic) to presume that surgical decompression of the pituitary would alleviate symptoms. As with most things in medicine, things are not so straight forward. The role and timing of surgery is a greatly contentious subject and the focus of many studies, reviews and (more recently) guidelines. Most conclude that the evidence is of low quality, being primarily case series of a small number of patients, with substantial variation in outcome seen between different centres. There remains no good, high-level evidence (such as a randomised controlled trial) to answer the debate, and it is unlikely to be forthcoming given the rarity of the condition as well as the associated diagnostic challenges.

The large majority of reported cases focus on neuro-ophthalmic symptoms, using severity at presentation, progression over time and long-term visual outcomes as evidence for and against intervention. These symptoms include reduced visual acuity, visual field defects and cranial nerve palsies. Studies have also looked at endocrine outcome in conservative versus surgical groups, though less controversy exists around the importance of early medical stabilisation and replacement of corticosteroids, even before consideration of the surgical intent.

In this chapter I will lay the groundwork for this debate, touching on the evidence for and against surgical intervention in acute pituitary apoplexy and concluding with the most recent guidelines.

2.2 A Brief History of Apoplexy and Pituitary Surgery

The term pituitary apoplexy was first coined by Brougham et al. in 1950 to describe the clinical syndrome we use today, though cases of pituitary haemorrhage had been described as far back as 1898. The diagnostic term is typically reserved for the symptomatic cases, with asymptomatic pituitary haemorrhage being referred to as subclinical apoplexy (Randeva et al. 1999).

Surgery for the pituitary gland itself has been described as early as 1889 by Sir Victor Horsley with a variety of transcranial approaches being used initially. This was associated with a high rate of morbidity prior to the advent of antibiotics and steroids in the 1950s.

The first transsphenoidal resection is reported in 1907 by Hermann Schloffer, but the technique rapidly fell out of favour, though the reasons for this remain unclear. In the 1950s Gerard Guiot utilised fluoroscopy during surgery to improve on the previous transsphenoidal techniques. Along with the introduction of the operating microscope in the 1960s, this method led to a renewed interest in a transsphenoidal approach to the pituitary gland. This technique became the standard best practice for pituitary adenomas by the 1970s (Jane et al. 2002).

Surgery for pituitary apoplexy followed a similar historical path, with transsphenoidal approach, alongside routine use of steroids, showing greatly improved levels of postoperative mortality. By the 1970s operative mortality was down to 6.7 % compared to 22 of 36 patients dying in a case review from the 1960s (Cardoso and Peterson 1984). A review of five cases published in the *BMJ* in 1971 concluded that "neurological sequelae arising from pituitary apoplexy […] should be regarded as a neurosurgical emergency". This review also showed an early recognition of the importance of timescale for decompression and its relativity to the symptom severity, stating "rapid and severe loss of sight surgery has only to be postponed until the patient has been adequately resuscitated and covered by adrenocorticosteroids" (Epstein et al. 1971).

2.3 Surgical Versus Conservative Intervention

Reports discussing the management of acute pituitary apoplexy were limited greatly by cohort size and varied in their opinions, but in 1999 Randeva et al. reported the largest individual case series to that date, comprising of 35 patients presenting with clinical apoplexy over an 11-year period to Oxford, UK (Randeva et al. 1999).

The cohort demonstrated a typical distribution of symptoms, with 71 % having a visual field defect, 69 % ocular paresis and 66 % reduced visual acuity. Initial endocrine assessment

showed gonadotrophin deficiency in 79 %, 50 % had thyroid axis involvement and 76 % had hypocortisolism (defined as cortisol <170 nmol/L at 9 am). Hyperprolactinaemia was seen in only 6 %.

Thirty-one of 35 (89 %) patients underwent transsphenoidal decompression, and in these patients visual acuity improved in 86 %, field defects in 76 % and ocular paresis in 91 %. Postoperatively transient diabetes insipidus (DI) was seen in 16 %, with 6 % requiring long-term desmopressin treatment. Long-term steroid replacement was needed in 58 % of surgically treated patients, with 45 % requiring thyroxine and 43 % of men requiring testosterone replacement.

At the time Randeva et al. (1999) offered the largest single centre experience and stands as a seminal point in the discussion of surgery in pituitary apoplexy. They concluded that surgery was both a safe and effective treatment and should be performed within 7 days of symptom onset (Randeva et al. 1999).

However, not all reports agreed with the findings of Randeva et al. (1999). In 1995 Maccagnan et al (1995). reported a prospective review of 12 cases of pituitary apoplexy (Maccagnan et al. 1995). All patients had either visual symptoms (reduced acuity or field defect, $n=6$) and/or ophthalmoplegia ($n=9$, both in three patients). Surgery was performed in five patients and indicated when symptoms progressed despite steroid treatment within the first week or recurred when dexamethasone was ceased. All patients presenting or developing a field defect received surgery, although the two patients with reduced acuity (plus ophthalmoplegia) were treated conservatively.

Maccagnan et al. (1995) observed that ophthalmoplegia started to improve as early as 1 week into steroid therapy, with complete resolution within 6 weeks in six of seven cases. Two patients with blurred vision were noted to be hyperglycaemic on admission, with the blurring resolving within 24–48 h of steroids plus intensive glucose management (suggesting symptoms may have been, at least in part, due to osmotic lens changes secondary to hyperglycaemia). Endocrine evaluation in the conservative group compared to the surgical group at follow-up showed hypogonadism in 4/5 versus 1/4, hypothyroidism in 3/6 versus 1/5 and hypocortisolism in 2/6 versus 1/5, respectively (Maccagnan et al. 1995).

More recently, Ayuk et al. (2004) reported a series of 33 patients where 56 % of the cohort was treated conservatively. These patients had either stable or improving visual deficits, with full resolution of neuro-ophthalmic symptoms seen in all of those managed conservatively. There was no statistical difference in endocrine outcome between the groups either (Ayuk et al. 2004).

Sibal et al. (2004) also describe a series of 45 patients with apoplexy, of whom 27 underwent surgical decompression based on case by case multidisciplinary discussion. Nearly all patients in both groups achieved complete or near-complete resolution of impaired acuity (surgical – 8 complete, 5 partial, 1 unimproved; conservative – 3 complete, 1 partial), field defects (surgical – 7 complete, 8 partial, 1 unimproved; conservative – 3 complete, 1 partial) and ocular palsy (surgical – 9 complete, 4 partial, 1 unimproved; conservative – 6 complete, 2 partial) (Sibal et al. 2004).

Afterwards, similar findings were seen in a series of cases reported by Gruber et al. (2006), who describe 30 cases of apoplexy, with 20 being treated conservatively. They concluded that there was no evidence that surgery improved visual outcome more than conservative treatment, excepting those with blindness where they felt the outcome was likely poor already (Gruber et al. 2006). Only six patients had blindness (mono- or binocular). Four of these patients were managed conservatively, with two of the conservative group and one of the surgical group having partial improvement at follow-up (Gruber et al. 2006).

2.4 Sooner or Later?

Although deciding whether to operate, and on whom, is still debated, the timing of surgery is even more contentious. In their 1999 series Randeva et al. looked at outcome related to timing of surgery (Randeva et al. 1999). The time from symptom onset to surgical decompression ranged from 1 to 34 days, with a mean duration to surgery of 6 days. Visual acuity defects completely

resolved in all patients ($n=10$) having surgery within 8 days, compared to complete recovery in 46 % ($n=6$), partial recovery in 31 % ($n=4$) and no recovery in 23 % ($n=3$) where surgery was delayed beyond 8 days. Similar results were seen with visual field defects, where 75 % ($n=9$) had full recovery when operated early, compared to 23 % ($n=3$). These differences in recovery of acuity and field defects achieved a high level of significance ($P=0.007$ and $P=0.0036$ respectively). Despite the findings relating to acuity and field defects, there was no statistical difference ($P=0.101$) relating to recovery of ocular paresis between the groups.

In contrast, Peter and De Tribolet (1995) reported a series of 53 patients undergoing transsphenoidal surgery for pituitary tumours and their visual outcome. Thirteen of these cases presented as acute apoplexy, and all patients benefited from surgery, irrespective of timescale (average time to surgery was 1 month). Ayuk et al. (2004), as discussed earlier, also showed no significant difference between patients operated earlier than later.

Simon et al. (2011) describe a series of 23 patients with apoplexy, 18 of whom underwent surgery (15 transsphenoidal, 2 transcranial, 1 transsphenoidal/ethmoidal approach; 4 conservative treatment, 1 fatality). Twelve patients were operated within 1 week, and this included all patients with visual acuity defects and 7/8 patients with field defects. Recovery of visual acuity was partial in 75 % and complete in the remaining 25 %. Timing of surgery (less vs. more than 7 days) was not shown to be significantly associated with recovery of acuity, field defect or nerve palsy.

In support for Randeva (1999), Seuk et al. (2011) give a retrospective review of 29 patients (21 men, 8 women; age 25–68) presenting with acute pituitary apoplexy who underwent transsphenoidal resection. 26 (89.6 %) patients had reduced acuity, and 23 (79.3 %) had visual field defect at outset. There were no patients with blindness, and ophthalmoplegia was not covered in this paper. Twenty-one had surgery at a mean of 24.4 h (range 5–41 h) after presentation, and they were compared to eight patients with a mean time of 79 h (range 64–96 h).

Complete resolution of visual acuity was seen in 61.1 % ($n=11$) and of visual field defects in 64.8 % ($n=11$) when surgery was within 48 h, compared to 37.5 % ($n=3$) and 33.3 % ($n=2$), respectively, for those operated later. When also including those with partial resolution, the analysis reports statistical significance for acuity (83.3 % vs. 62.5 %, <48 h vs. >48 h, $p=0.014$) and field defects (88.2 % vs. 50.0 %, <48 h vs. >48 h, $p=0.037$). This not only supports the findings of Randeva (1999) but suggests that there may be benefit to be gained from intervening even earlier, within 48 h.

The question of very early intervention was further addressed in a large retrospective review of 186 cases published from the last century (Turgut et al. 2010). In this series all patients had either mono- or binocular blindness. Of 186 cases found, 41 had sufficient information relating to timing of surgery for analysis. Turgut et al. (2010) found that even though there was a greater rate of improvement for patients who had had blindness for <1 day at time of presentation (75 % vs. 58 %), there was no difference in recovery rates between patients operated within 3 days or between 4 and 7 days.

2.5 Evidence-Based Guidance

In 2009 the Society for Endocrinology formed a task force to address the issues and variance in managing pituitary apoplexy. In 2010 they released the UK guidelines for the management of pituitary apoplexy (Rajasekaran et al. 2010). As part of this guideline, there was consideration for the role and timing of surgery. The discussions echo the controversies and conclusions discussed above, with the final recommendations being:

1. Patients with pituitary apoplexy who are without any neuro-ophthalmic signs or mild and stable signs can be considered for conservative management with careful monitoring.
2. Patients with severe neuro-ophthalmic signs such as severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness should be considered for surgical management.

3. Ocular paresis because of involvement of III, IV or VI cranial nerves in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not in itself an indication for immediate surgery. Resolution will typically occur within days or weeks with conservative management.
4. Surgery should be performed preferably within the first 7 days of onset of symptoms.

The American Endocrine Society guidelines on pituitary incidentaloma are more succinct with their recommendation, advising simply that patients should be referred for surgery if they have "pituitary apoplexy with visual disturbance" Freda et al. (2011).

Conclusion

Over the last 120 years great steps have been made in the management of acute pituitary apoplexy, with modern surgical techniques and medical care allowing favourable postoperative outcomes. However, over the last 20 years the focus has moved more towards who we can safely *not* operate on. If intervention is required, the question is then how soon does surgery need to happen to offer the best visual outcomes. The concluding expert opinion is that "early" intervention (within 7 days), as opposed to "urgent" treatment, by an experienced pituitary surgeon is current guideline best practice.

As time goes on evidence is increasing for both camps of conservative versus surgical treatment. In a field which was once dominated by small case series, we are now seeing reports with significant numbers of patients and more intentional design. With each report, however, comes the recognition that there is no simple answer. It also becomes apparent that it is unlikely we will be seeing an end to this debate in the near future.

Cases of apoplexy are rare, each with their own complicating factors and diagnosis can often be difficult or overlooked. The clear conclusion is that, using what limited evidence we have, we must take each case carefully and on individual merits. These complex decisions require the involvement of an experienced multidisciplinary team including endocrine, neurosurgical and ophthalmological expertise if we aim to deliver the best care to our patients.

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Part III

Tumours Types Which Show Apoplexy

Predisposing Factors for Pituitary Apoplexy

3

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Abbreviations

ACTH	Adrenocorticotropic hormone
CT	Computed tomography
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
TSH	Thyroid-stimulating hormone

3.1 Introduction

Pituitary apoplexy is still misdiagnosed in clinical settings worldwide. However, there are useful clues for the diagnosis the treating physician should be aware of when a patient seeks care with the following signs and symptoms:

1. Acute severe headache
2. Visual loss
3. Ophthalmoplegia
4. Impaired consciousness level (Dekkers et al. 2007; Chang et al. 2009)

Additionally, an accurate interview will also highlight the so-called predisposing factors for pituitary apoplexy (Cardoso and Peterson 1984), which are not always present, but if promptly recognized, may turn out straightforward the diagnosis and management of these patients.

Herein, our aim is to pinpoint the main predisposing factors for pituitary apoplexy, discussing their relevance on the context of tailored individual management.

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3.2 Predisposing Factors

The list for predisposing factors in pituitary apoplexy is large accounting to up to 30 % of patients (Nawar et al. 2008; Murad-Kejbou and Eggenberger 2009), but may be gathered using the rationale as addressed on Table 3.1 (see below). Interestingly, even in asymptomatic pituitary adenomas known as "pituitary incidentalomas" during the course of 5 years, the likelihood of pituitary apoplexy is ~10 % (Arita et al. 2006).

Regarding different subtypes of pituitary tumours, the prevalence of apoplexy is homogeneous with a small trend for nonfunctioning adenomas and prolactinomas to develop apoplexy. Additionally, GH-, ACTH-, TSH- and gonadotropin-secreting tumours share similar pituitary apoplexy prevalence. With regard to asymptomatic versus symptomatic adenomas, pituitary apoplexy is slightly greater in the former (Arafah et al. 1997).

Table 3.1 Predisposing factors for pituitary apoplexy

Predisposing factors
Medications
Antithrombotic therapy
Dopamine agonists
Associated medical conditions
Diabetes mellitus
Arterial hypertension
Surgery
Cardiac surgery
Others
Head trauma
Endocrinological testing

3.2.1 Medications

Overall, the main medications associated with pituitary apoplexy are either antithrombotic therapy or dopamine agonists such as bromocriptine and cabergoline.

To illustrate this, patients undergoing antithrombotic therapy for myocardial infarction or arrhythmias are at risk to develop pituitary apoplexy (Biousse et al. 2001). In a large series evaluating 1,540 pituitary lesions, 24 patients presented with pituitary apoplexy. Among them the authors personally observed an apoplectic episode in three patients receiving anticoagulating or antiaggregant therapy, in one patient with von Willebrand disease and in three patients with a prolactin-secreting adenoma following cabergoline treatment (Dubuisson et al. 2007).

A study in 2009 investigated predisposing factors in 83 patients with pituitary apoplexy. Bromocriptine therapy was reported in 16 % of these patients (Mou et al. 2009).

Other medications have also been associated with pituitary apoplexy. Recently, our group published a case of a 51-year-old acromegalic woman who developed pituitary apoplexy within the context of high blood pressure and a single dose of long-acting octreotide, suggesting the combination of hypertension and octreotide therapy may enhance the risk of pituitary apoplexy (Chang et al. 2010). Another interesting case of pituitary apoplexy due to GnRH agonist therapy (leuprolide) was also described in a 61-year-old male patient with locally advanced prostate cancer (Davis et al. 2006).

3.2.2 Associated Medical Conditions

Diabetes or chronic systemic hypertension has also been considered to predispose to pituitary apoplexy because of degenerative changes in the gland's microvasculature (Biousse et al. 2001). However, this association remains elusive. One recent study (Möller-Goede et al. 2011) evaluated 42 patients who had pituitary apoplexy against 84 in the control group without pituitary apoplexy and found actually that the risk for pituitary apoplexy was significantly elevated in patients with antithrombotic drugs (vitamin K antagonist or platelet inhibitors) (odds ratio = 2.96, CI = 1.16–7.58, $P = 0.026$), but not

in patients with cardiovascular risk factors such as diabetes mellitus (odds ratio = 1.00, CI = 0.28–3.53, $P = 1.00$) and arterial hypertension (odds ratio = 0.93, CI = 0.38–2.29, $P = 1.00$).

3.2.3 Surgery

As a perioperative complication of cardiac surgery, pituitary apoplexy is rare, but according to one study the pituitaries of 15.2 % of patients who died within 10 days of cardiac surgery demonstrated ischaemic necrosis compared to unselected autopsy cases, in which only 1.4 % showed similar pituitary abnormalities (Kovacs and Yao 1975).

Although this is not the rule, exceptionally no surgical management of pituitary apoplexy is required, as in the case of this 71-year-old man with a past medical history significant for type II diabetes mellitus, hypercholesterolaemia and unstable angina who underwent five-vessel coronary artery bypass grafting with no intraoperative complications (Mukhida and Kolyvas 2007). This may occur when the apoplectic event leads to a spontaneous resolution of a previously undiagnosed nonfunctioning pituitary macroadenoma following cardiac surgery.

There are other surgeries associated with pituitary apoplexy and described as case reports throughout the literature: bilateral adrenalectomy, prostatectomy, lumbar laminectomy and radiotherapy.

3.2.4 Head Trauma

Head trauma (notably major injury) has been recognized as a predisposing factor for pituitary apoplexy. Nevertheless, this seems to be rare and statistical analyses of these cases are difficult (Möller-Goede et al. 2011). The mechanism of posttraumatic pituitary apoplexy is also unknown, but may be related to blood flow changes in pituitary adenomas due to fluctuations of intracranial pressure and blood pressure following severe head injury, leading to the apoplectic event in a pituitary adenoma (Biousse et al. 2001; Bao et al. 2007).

3.2.5 Endocrinological Testing

Other potential sources that may lead to pituitary apoplexy may be related to exogenous oestrogen administration and pregnancy, dynamic testing of the pituitary using gonadotropin-releasing hormone and thyrotropin-releasing hormone (Biousse et al. 2001).

To illustrate this, Szabolcs and co-workers reported the case of a 54-year-old male suffering from pituitary macroadenoma with suprasellar extension. This patient underwent 200 μg TRH test and shortly after 1 h complained about severe headache and starts vomiting. On the next day he already developed ophthalmoplegia. CT confirmed haemorrhage into the tumour. A chromophobic adenoma with macroscopic and histological signs of haemorrhage was removed via the transsphenoidal route. In the postoperative period the ophthalmoplegia gradually disappeared, but central hypoadrenia and hypothyroidism occurred (Szabolcs et al. 1997).

Conclusion

One caveat of addressing predisposing factors for pituitary apoplexy is that the majority of data reported are in the form of case reports; hence, effective estimation of the proportion of patients with pituitary apoplexy who may have a precipitating factor is intricate (Möller-Goede et al. 2011). Also, there is a lack of consistent agreement regarding what constitutes a precipitating factor, and finally there is a great likelihood that some patients may indeed have unrecognized precipitating factors therefore underestimating the real prevalence (Semple et al. 2007). Even though the clinical presentation of pituitary apoplexy in patients with and without predisposing factors may not be different, when there is an associated factor, altered mental status may be more frequent in patients with associated diseases.

In these patients, the visual prognosis is generally worse and the diagnosis more difficult to establish (Biousse et al. 2001). Therefore, it is important to recognize these aforementioned factors and provide a better management for patients, tailoring each clinical setting.

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Nonfunctioning Pituitary Tumour Apoplexy

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Aikaterini Theodoraki and Mark P.J. Vanderpump

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Abbreviations

ACTH	Adrenocorticotropic hormone
CT	Computerized tomography
FSH	Follicle-stimulating hormone
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
NFPAs	Nonfunctioning pituitary adenomas
PRL	Prolactin
TSH	Thyroid-stimulating hormone

4.1 Nonfunctioning Pituitary Adenomas

4.1.1 Definition, Incidence and Prevalence

Nonfunctioning pituitary adenomas (NFPAs) are slow-growing, benign, monoclonal adenomas characterized by the absence of clinical and biochemical evidence of pituitary hormonal overproduction. Immunohistochemistry shows that the majority of clinically nonfunctioning adenomas consist of cells staining positive for pituitary hormones (40–65 % for gonadotropins or their subunits, 10 % for ACTH and less for other hormones), whereas in 20–40 % the adenoma cells are immunohistochemically negative (Asa et al. 1986; Croue et al. 1992; Zhao et al. 2000; Dekkers et al. 2006). They account for one-third of all pituitary neoplasms, with an incidence of 7–9 new cases/10^6 every year. In the general population,

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the estimated prevalence of pituitary adenomas is 9.3 % with a range of 1.5–26.7 % (Hall et al. 1994; Molitch 2008; Orija et al. 2012). The prevalence of pituitary macroadenomas (diameter >1 cm) is lower and estimated to be only approximately 0.11–0.3 % (Orija et al. 2012). Pituitary microadenomas (diameter <1 cm) are more often functioning, compared with macroadenomas that tend to be nonfunctioning in 80 % of the patients (McComb et al. 1983; Sanno et al. 2003; Fernández-Balsells et al. 2011).

4.1.2 Clinical Signs and Symptoms

The clinical signs and symptoms of clinically nonfunctioning macroadenomas are determined by mass effects of the tumour. Presenting complaints include headache, visual field defects with or without decreased visual acuity and effects of hypopituitarism. Other presenting symptoms are apoplexy, cranial nerve deficits and optic nerve atrophy (Molitch 2008; Orija et al. 2012). Headache is present in 40–60 % of all patients and is caused by increased intracranial pressure and stretch of the dura mater (Ironside 2003; Wichers-Rother et al. 2004; Dekkers et al. 2006). Visual field defects result from compression of the optic chiasm (Nielsen et al. 2006). Typically macroadenomas cause a bitemporal visual field defect. Asymmetry of the visual field defects may be present between both eyes, depending on the growth pattern of the tumour. In the majority of patients presenting with nonfunctioning macroadenomas, pituitary insufficiency is present to some degree (Dekkers et al. 2006). As the diagnosis of clinically nonfunctioning pituitary adenomas is made by exclusion of hormone overproduction, the evaluation of the medical history and the physical examination should include a search for signs and symptoms of hormonally active pituitary adenomas such as acromegaly, Cushing's disease, hypogonadism and hyperprolactinaemia.

4.1.3 Laboratory Findings

Hypopituitarism in patients with macroadenomas results from compression of the pituitary stalk, compression of functioning pituitary tissue or hypothalamic involvement of the pituitary tumour. In terms of pituitary hormone deficiencies, GH deficiency is most commonly present (85 %), followed by LH and FSH deficiency (75 %), with ACTH and TSH deficiencies occurring less commonly (around 35 %) (Nomikos et al. 2004; Wichers-Rother et al. 2004; Dekkers et al. 2006). In addition to pituitary hormone deficiencies, nonfunctioning macroadenomas can be accompanied by hyperprolactinaemia. The secretion and release of prolactin are inhibited by hypothalamic release of dopamine. When the pituitary stalk is compressed by the presence of a tumour, dopamine delivery to the pituitary is disrupted resulting in hyperprolactinaemia. In general, prolactin levels less than 100 ug/l (or 2,000 mIU/l) are compatible with pituitary stalk compression. Levels above 100 ug/l are almost never encountered in clinically nonfunctioning macroadenomas (Karavitaki et al. 2006; Orija et al. 2012). Macroprolactinomas are typically associated with prolactin levels greater than 250 ug/l (1 ug/l is equivalent to 21.2 mIU/l) (Melmed et al. 2011). The high intrasellar pressure that results from the presence of an adenoma in the rigid sella turcica has been linked to the development of hyperprolactinaemia in pituitary adenomas and the residual pituitary function (Arafah et al. 2000). In contrast, during pituitary apoplexy the sudden development of extremely high intrasellar pressure results in ischaemic necrosis of the gland. This is associated with a low serum prolactin during the apoplectic event and development of pituitary hormone deficiencies postsurgical decompression (Zayour et al. 2004). In the assessment of hyperprolactinaemia, the 'hook effect' that may result in only mild to moderate elevation of serum prolactin in the context of a macroprolactinoma must be considered. This artefact can be resolved by diluting the serum sample (1:100) and re-assaying for prolactin measurement (Melmed et al. 2011).

4.1.4 Imaging

On magnetic resonance imaging (MRI) T1-weighted images, adenomas usually appear hypointense (darker) or isointense relative to normal pituitary

tissue. After contrast administration, the adenoma usually remains hypointense, while normal pituitary tissue enhances intensely as pituitary adenomas are less vascular compared with the normal gland (Elster 1993; Chaudhary and Bano 2011; Orija et al. 2012). On delayed scanning a reversal of the image contrast may be observed. A variety of advanced MR techniques have been evolved to help evaluate specific cases. Dynamic contrast MRI is the most reliable tool for the evaluation of pituitary adenomas (Chaudhary and Bano 2011). Computerized tomography (CT) is better than MRI at evaluating bony changes, such as changes of the sella turcica, and calcifications. On both unenhanced and enhanced CT imaging, pituitary adenomas usually appear less attenuated compared to the normal pituitary (Orija et al. 2012).

4.1.5 Progression

Progression from a NFP microadenoma to macroadenoma is a rare event. The proportion of patients with growth of the macroadenoma ranges between 7 and 51 %, and this probably increases during longer duration of follow-up. Eleven and twenty-nine percent patients may show spontaneous regression of tumour volume occurred during long-term follow-up (Dekkers et al. 2006). Clinically silent tumour ischaemia has been suggested as the mechanism linked to tumour regression. This is also likely be the mechanism leading to symptomatic pituitary apoplexy in NFPAs. During a 5-year follow-up study of incidentally found macroadenomas, apoplexy developed in about 9.5 % of cases (Arita et al. 2006).

NFPA recurrence rates are reported to be 6–46 % after transsphenoidal surgery, whereas after post-operative radiotherapy recurrence rates of 0–36 % are reported (Dekkers et al. 2008). At follow-up the incidence of new pituitary insufficiency in patients with NFPAs is not higher than in patients with prolactinoma or acromegaly. Patients with NFPAs had a lower remission percentage compared with those patients with functioning adenomas (Roelfsema et al. 2012).

4.1.6 Treatment

The main aims for treatment of patients with clinically nonfunctioning macroadenomas are the preservation or restoration of visual function and adequate long-term tumour control. Transsphenoidal surgery is the treatment of choice in patients with visual field defects because this is the only treatment modality leading to immediate decompression of the optic nerve. Surgery improves visual function in approximately 80 % of all patients (Dekkers et al. 2006). Visual recovery can be demonstrated within the first days after surgery (Jakobsson et al. 2002), although improvement of visual function can continue even until 1 year after surgical treatment (Dekkers et al. 2007). Recovery from headaches is likely to occur after surgery for macroadenomas (Wichers-Rother et al. 2004).

If treated conservatively, regular assessments of pituitary endocrine functions and repeat MRI are recommended because remaining pituitary function can be compromised by growth of the macroadenoma. Thereafter, radiological assessment by MRI is recommended with yearly intervals, which may be extended to two yearly intervals in the absence of progression of the macroadenoma. The interval for visual field assessment depends upon the distance between the pituitary adenoma and the optic chiasm (Dekkers et al. 2008).

Post-operatively, visual function if compromised usually improves. However, often pituitary function does not improve after removal of the adenoma and occasionally it may deteriorate (Comtois et al. 1991; Webb et al. 1999; Nomikos et al. 2004; Wichers-Rother et al. 2004). Radiotherapy is usually not given routinely post-operatively in patients without a tumour remnant because the chance of recurrence in these patients is small (Dekkers et al. 2006; Reddy et al. 2011). When radiotherapy is not routinely offered post-operatively, there does not seem to be a plateau in the incidence of adenoma regrowth, and these patients need to be followed long term with pituitary imaging in order to ensure that no recurrence is missed (Reddy et al. 2011). Conventional external beam radiotherapy is associated with the development of hypopituitarism, secondary brain tumours and optic nerve atrophy (Brada et al.

1993; Tsang et al. 1994; Castinetti et al. 2010; Castro et al. 2010). Gamma knife stereotactic radiosurgery has been used in the post-operative treatment of NFPA resulting in low tumour recurrence rates and high tumour control rates (Castinetti et al. 2010), with improved outcome compared to conventional radiotherapy (Wilson et al. 2012).

Patients with NFPAs need to be referred to an endocrinology team, experienced in managing patients with pituitary tumours. Pituitary hormone replacement needs to be initiated and monitored as appropriate. A multidisciplinary approach between endocrinologists and neurosurgeons (and radiotherapy physicians when indicated) is necessary for patients to decide on the appropriateness of surgical intervention.

4.2 Pituitary Apoplexy in Pituitary Adenomas

4.2.1 Incidence of Pituitary Apoplexy in Nonfunctioning Pituitary Adenomas

Pituitary apoplexy is defined as a clinical syndrome characterized by sudden onset headache, vomiting, ophthalmoplegia, visual disturbance and altered consciousness due to acute haemorrhage usually into a pre-existing pituitary adenoma (Rajasekaran et al. 2011). The reported prevalence in published series varies between 0.6 and 10 %, with a mean of 2 % of all surgically resected adenomas (Nawar et al. 2008). Recent epidemiological data from Oxford showed that 7.9 % of pituitary adenomas presented with pituitary apoplexy (Fernandez et al. 2010). Classical pituitary apoplexy has to be differentiated from subclinical apoplexy that goes clinically undetected and is discovered on pituitary imaging or surgical specimens.

Forty-five percent of all pituitary tumours that develop apoplexy are nonfunctioning (Nawar et al. 2008). There is a higher incidence of apoplexy in nonfunctioning tumours compared with other pituitary tumours (Randeva et al. 1999; Sibal et al. 2004; Möller-Goede et al. 2011). In a UK population epidemiological study, 6.2 cases of apoplexy/100,000 population were found and all occurred in nonfunctioning adenomas (Fernandez et al. 2010).

Due to the rarity of apoplectic events, the only available evidence in pituitary apoplexy is from retrospective cohort comparison studies and single centre audits. This limits the systematic assessment of interventions in the management of patients with pituitary apoplexy (Rajasekaran et al. 2011).

4.2.2 Mechanisms for Development of Apoplexy in Pituitary Adenomas

The blood supply to the anterior pituitary lobe is provided by portal vessels through the infundibulum, where the perfusion pressure is known to be low. Pituitary adenomas seem to be susceptible to increments of intrasellar pressure caused by a tumour therefore creating a relative ischaemic state in the adenoma tissue (Bjerre et al. 1982). It has also been suggested that intrinsic vascular changes in pituitary adenomas may contribute to their susceptibility to infarction and haemorrhage (Cardoso and Peterson 1984).

4.2.3 Risk Factors for Development of Apoplexy in Nonfunctioning Pituitary Adenomas

Risk factors for the development of pituitary apoplexy are present in 4–50 % (mean 26 %) of patients presenting with apoplexy (Nawar et al. 2008). The risk factors studied more systematically include male gender, shown to predispose in some, but not all studies (Möller-Goede et al. 2011), use of anticoagulants (Möller-Goede et al. 2011) and the presence of a macroadenoma as opposed to a pituitary microadenoma (Murad-Kejbou and Eggenberger 2009). A variety of other precipitating factors have been linked to the occurrence of pituitary apoplexy (Table 4.1) (Nawar et al. 2008; Murad-Kejbou and Eggenberger 2009).

Table 4.1 List of precipitating factors in pituitary apoplexy

Precipitating factors in pituitary apoplexy
Head trauma
Major surgery – especially coronary artery bypass surgery, but also aortic abdominal aneurysm surgery, cholecystectomy, shoulder arthroplasty and others
Hypotension
Hypertension
Pregnancy
Oestrogen therapy (oral contraceptive pill or hormone replacement treatment)
Anticoagulants (warfarin)
Antiplatelets (aspirin)
Coagulopathies (factor V Leiden mutation, idiopathic thrombocytopenic purpura, secondary polycythaemia)
Dopamine agonists (cabergoline)
Somatostatin analogues (octreotide)
Pituitary dynamic testing – with TRH, GnRH, CRH, insulin-induced hypoglycaemia, metyrapone test
Irradiation

4.2.4 Clinical, Laboratory and Imaging Assessment in Nonfunctioning Pituitary Adenoma Apoplexy

Pituitary apoplexy constitutes a medical emergency, and all patients presenting with symptoms suggestive of pituitary apoplexy need to be assessed urgently, regarding their pituitary hormone reserve (random cortisol, thyroid function tests, LH, FSH, prolactin, testosterone in men/oestradiol in women, IGF-1, GH), serum electrolytes, renal and liver function, clotting and full blood count (Rajasekaran et al. 2011). Haemodynamic and visual function assessment (visual acuity, visual fields, oculomotor nerves) are mandatory.

MRI is the radiological investigation of choice and has been found to confirm the diagnosis of pituitary apoplexy in over 90 % of the patients. The appearance on different MRI sequences can be used to date the haemorrhage. In the first 1–2 days post apoplexy, intra-parenchymal haemorrhage is hyperintense on T1-weighted images and hypointense on T2-weighted images (Tosaka et al. 2007; Semple et al. 2008). On days 3–15, haemorrhage appears bright on both T1- and T2-weighted images. After day 15, a fluid level within the haemorrhage may be visualized (Semple et al. 2008). CT scan which is the modality commonly available in the acute setting is diagnostic in a lower proportion of patients, although it can identify macroadenomas (Davis et al. 1985; Semple et al. 2008). In Fig. 4.1, CT and MR imaging from our centre's archive for a patient who presented with classical apoplexy and was found to have a NFPA is shown.

4.2.5 Management of Pituitary Apoplexy

In patients who are haemodynamically unstable, hydrocortisone should be administered after blood sampling for pituitary hormones. Hydrocortisone 100–200 mg as an intravenous bolus is appropriate followed either by 2–4 mg/h by continuous intravenous infusion or by 50–100 mg six hourly by intramuscular injection. Ideally patients should be managed in a Neurosurgical High Dependency Unit, with access to an experienced neurosurgical team and input from endocrinology and ophthalmology. The decision for conservative or surgical management should be taken jointly by neurosurgeons, endocrinologists, ophthalmologists and neuroradiologists in a multidisciplinary manner (Rajasekaran et al. 2011).

In one study, surgery within the first 8 days of presentation was associated with improved visual acuity and visual field defects, compared with surgical management at later stages (Randeva et al. 1999). Surgery by an experienced neurosurgeon in pituitary disease is recommended as opposed to a non-specialist on-call neurosurgical team. Deterioration of the patients visual or neurological function warrants further assessment for surgical intervention (Rajasekaran et al. 2011).

4.2.6 Recurrence of Apoplectic and Non-apoplectic Nonfunctioning Pituitary Adenoma

Recurrence of NFPA following apoplexy is reported as 10.8 % (4/37 – a mean follow-up of 5.5 years) (Chen et al. 2010), 11.1 % (all patients

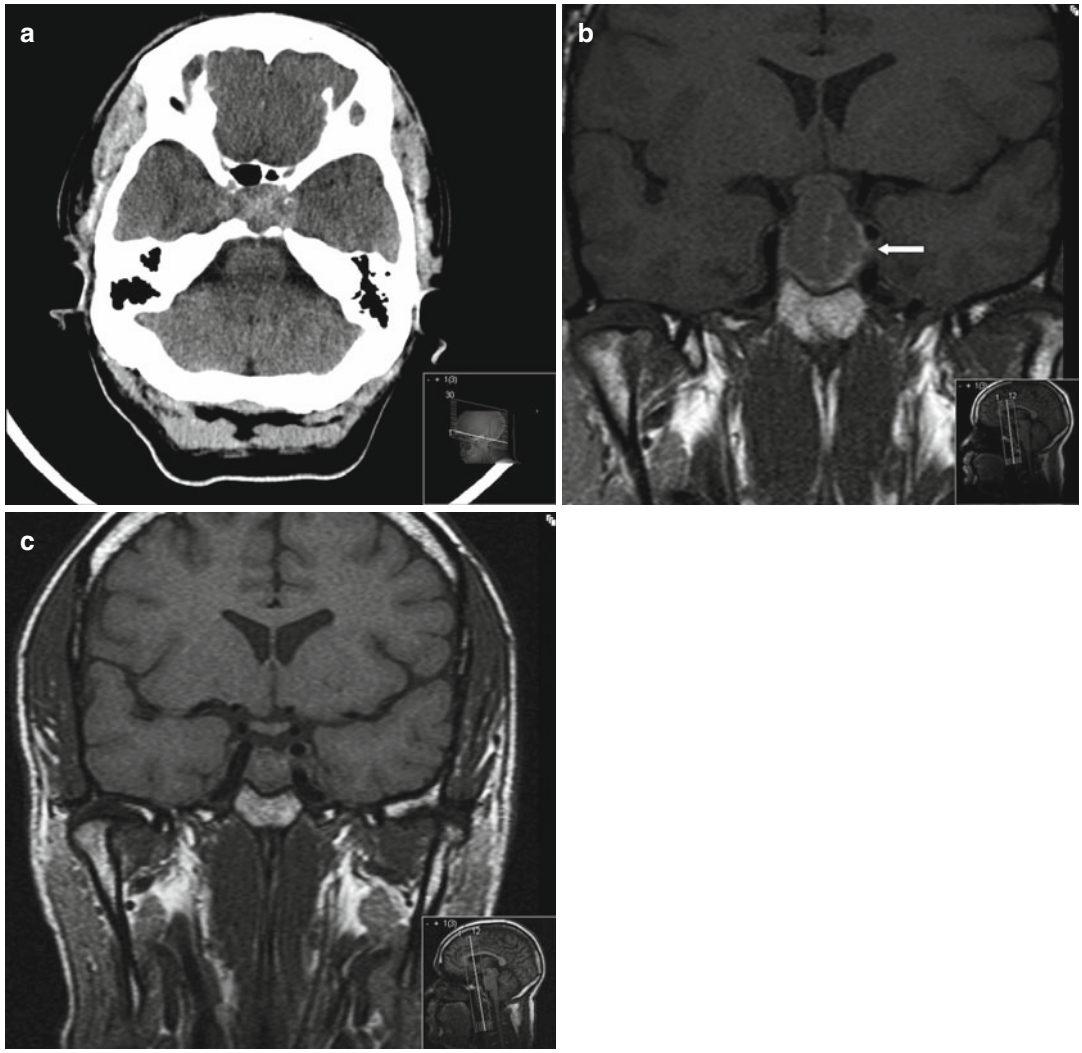

Fig. 4.1 A 53-year-old man presented to our department with a 2-day history of headache, nausea, vomiting and blurred vision. (**a**) A haemorrhagic pituitary mass was shown on urgent CT scanning. (**b**) A pituitary macroadenoma with signs of recent haemorrhage was confirmed on pituitary MRI (T1 sequence with no contrast, *white block arrow* points to the haemorrhagic area with an intense signal compared to the pituitary adenoma). (**c**) Two months after the acute event, there was a substantial reduction in the size of the macroadenoma (T1 sequence with no contrast)

had incomplete tumour removal following surgery and mean follow-up 6.6 years) (Pal et al. 2011) and 12.4 % in 185 patients with subclinical pituitary adenoma apoplexy (37.3 % of these patients had a nonfunctioning adenoma – mean follow-up 7.4 years) (Zhang et al. 2009).

Non-apoplectic NFPAs not treated with radiotherapy seem to relapse more often compared with apoplectic nonfunctioning adenomas. Recurrence rates that have been reported include 32 % at a mean of 5.4 years (Turner et al. 1999), 34.8 % at a mean time of 6.1 years in a series of 155 patients with relapse in 20.4 % of cases 20 years or longer after the initial operation (Reddy et al. 2011) and 33.5 % at median follow-up of 4.1 years with overall recurrence rates of 24.4 and 51.5 % at 5 and 10 years, respectively (O'Sullivan et al. 2009). The relapse rate at 5 years was 53 % in those with a residual postoperative extrasellar tumour compared with 20 %

with an intrasellar tumour (Reddy et al. 2011). The time to regrowth was shorter for those with an extrasellar remnant post-operatively, 3.3 ± 2.17 years for those with a cavernous sinus remnant and 5.3 ± 3.1 years for those without cavernous involvement. There were only two recurrences observed in those who had no residual tumour on the post-operative scans, one at 5.3 years and the other at 25.8 years (Reddy et al. 2011). Whether a conservative versus a surgical approach in nonfunctioning adenomas pituitary apoplexy alters the rate of recurrence is not known.

Nonfunctioning pituitary adenomas with silent ACTH staining do not seem to relapse more often compared with null-cell adenomas (Bradley et al. 2003; Cho et al. 2010; Reddy et al. 2011), although not all cohort studies have shown that (Cooper et al. 2010). However, when they do relapse their course tends to be more aggressive (Bradley et al. 2003; Cho et al. 2010).

4.3 Ten Practical Tips for Nonfunctioning Pituitary Adenomas and Pituitary Apoplexy

1. Patients with pituitary tumours need to be referred to an endocrinology team experienced in managing patients with pituitary pathology.
2. Pituitary hormone levels need to be assessed and replacement needs to be initiated and monitored as appropriate.
3. Hyperprolactinaemia occurs in NFPAs and prolactinomas; however, prolactin values above 100 ug/l (or 2,000 mIU/l) almost never occur in clinically nonfunctioning macroadenomas.
4. The decision for conservative or surgical management should be taken jointly by neurosurgeons, endocrinologists, ophthalmologists and neuroradiologists in a multidisciplinary manner.
5. Post-operatively, patients with NFPAs need to be assessed and managed as inpatients for pituitary hormone deficiencies. We routinely commence oral hydrocortisone replacement post pituitary surgery pending 9 am serum cortisol assessment.
6. Patients who have been diagnosed with pituitary tumour should be given clear information regarding the signs and symptoms of pituitary apoplexy and the precipitating factors (Rajasekaran et al. 2011).
7. In patients with suspected pituitary apoplexy who are haemodynamically unstable, intravenous hydrocortisone should be administered after drawing blood samples for baseline endocrine function tests.
8. Patients with pituitary apoplexy should be managed in a Neurosurgical High Dependency Unit with access to an experienced neurosurgical team and input from endocrinology and ophthalmology specialists.
9. Patients with pituitary apoplexy and severe neuro-ophthalmic signs such as severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness should be considered for surgical management (Rajasekaran et al. 2011).
10. Non-apoplectic NFPAs not treated with radiotherapy seem to relapse more often compared with apoplectic nonfunctioning adenomas. Patients need to have long-term follow-up with clinical assessment and imaging.

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Apoplexy in Previously Known Tumours

5

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Contents

Abbreviations

ACTH	Adrenocorticotropic hormone
CRH	Corticotropin hormone
Gd-DTPA	Gadolinium-diethylenetriaminepentaacetic acid
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
MRI	Magnetic resonance imaging
PRL	Prolactin
TRH	Thyrotropin-releasing hormone

5.1 Introduction

Pituitary apoplexy (haemorrhage or infarction) usually occurs in patients who were not previously diagnosed to have pituitary adenomas. In many instances pituitary apoplexy is the initial presentation of pituitary adenoma. But there are several reports of pituitary apoplexy in patients who have been previously diagnosed to have pituitary adenomas (Pelkonen et al. 1978; Onesti et al. 1990; Bills et al. 1993; Bonicki et al. 1993; Randeva et al. 1999; Sibal et al. 2004; Imboden et al. 2005; Dubuisson et al. 2007; Semple et al. 2007; Leyer et al. 2011). The onset of apoplexy may vary according to tumour type. And apoplexy may occur after 0.5–18 years after the initial diagnosis of pituitary tumour (Randeva et al. 1999). Recurrence of pituitary apoplexy has also been reported after several years following the initial treatment (Wakai et al. 1981; Bills et al. 1993; Acikgoz et al. 2004; Dubuisson et al. 2007).

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5.2 Prevalence

Several retrospective studies on pituitary apoplexy have reported the prevalence of pituitary apoplexy among those with known tumours range from 9 % to 33 % (Mohr and Hardy 1982; Onesti et al. 1990; Bills et al. 1993; Bonicki et al. 1993; Randeva et al. 1999; Sibal et al. 2004; Imboden et al. 2005; Nielsen et al. 2006; Dubuisson et al. 2007; Semple et al. 2007; Leyer et al. 2011). However, in a recent study only one case had a known pituitary tumour among 42 cases of pituitary apoplexy (Moller-Goede et al. 2011). Prospective studies reported pituitary apoplexy in 9–23 % patients with clinically non-functioning pituitary adenomas (Arita et al. 2006; Chen et al. 2011).

5.3 Risk Factors for Pituitary Apoplexy

5.3.1 Tumour Type

Pituitary apoplexy has been described in several types of pituitary tumours. Pelkonen et al. (1978) reported three cases of pituitary apoplexy in patients, who were already diagnosed to have pituitary tumours. One patient was diagnosed to have acromegaly, and another two cases were suffering from Cushing's syndrome. In a retrospective study of 35 pituitary apoplexy cases, 7 patients were previously diagnosed to have functional tumours (3 growth hormone-secreting tumours, 2 prolactin-secreting tumours and 2 ACTH-secreting tumours). There was no patient with previously diagnosed non-functioning tumour, among those who developed apoplexy. The onset of apoplexy may vary according to tumour type. Growth hormone-secreting tumour developed apoplexy after 7–18 years of diagnosis, prolactin-secreting tumour developed apoplexy after 0.5–2 years and ACTH-secreting tumour after 1–2.5 years (Randeva et al. 1999). In another study of 36 cases of pituitary apoplexy, 6 had previously diagnosed adenomas (3 prolactinomas and 3 non-secreting pituitary adenomas) (Biousse et al. 2001).

In a larger study of 43 patients with pituitary apoplexy, 8 were already diagnosed to have pituitary adenoma. Among those, 3 were of Cushing's disease, 2 non-functioning adenomas, 2 prolactinomas and 1 acromegaly (Sibal et al. 2004). And in a smaller series with 8 cases, 2 were already diagnosed to have pituitary tumours, out of which one was non-secreting macroadenoma and the other one was macroprolactinoma (Imboden et al. 2005). In another study of 24 cases of pituitary apoplexy, 6 had known adenoma including 1 Nelson syndrome and 3 prolactinomas. In 2 patients, apoplexy developed in recurrent adenomas even after 5 and 15 years of surgery for pituitary adenomas (Dubuisson et al. 2007).

The retrospective studies which had reported the occurrence of pituitary apoplexy in previously known tumours are shown in Table 5.1.

5.3.2 Precipitating Factors

5.3.2.1 Medications

Several medications used in the management of pituitary tumours had been implicated as precipitating factor for pituitary apoplexy. Bromocriptine, a dopamine receptor agonist, used in the treatment of prolactin-producing tumours is commonly implicated. Pituitary apoplexy might occur a few weeks after discontinuation of bromocriptine which might be due to acute enlargement of the pituitary adenoma (Biousse et al. 2001). There were other studies reporting pituitary apoplexy in prolactin-secreting pituitary macroadenomas while on bromocriptine therapy (Pinto et al. 1998; Imboden et al. 2005).

Patients with acromegaly had also developed pituitary apoplexy during bromocriptine therapy. Necrosis of adenoma due to bromocriptine might be responsible for apoplexy (Wakai et al. 1981).

Cabergoline, the newer dopamine receptor agonist which is now widely used because of lesser side effects, had also been shown to be a precipitating factor for pituitary apoplexy in several studies (Knoepfelmacher et al. 2004; Dubuisson et al. 2007; Balarini Lima et al. 2008).

Clomiphene has also been associated with pituitary apoplexy. Pituitary apoplexy occurred in a patient with GH-secreting pituitary macroadenoma after clomiphene therapy. Clomiphene

Table 5.1 Retrospective studies which had reported the occurrence of pituitary apoplexy in previously known tumours

Author(s)/ year	No. of cases with pituitary apoplexy	No. of previously diagnosed tumours with pituitary apoplexy	Previously known tumour according to hormone secreted (number)
Pelkonen et al. (1978)	9	3	GH (2), ACTH (1)
Onesti et al. (1990)	21	4	–[a]
Bonicki et al. (1993)	113	16	–[a]
Randeva et al. (1999)	35	7	GH (3), ACTH(2), PRL (2)
Biousse et al. (2001)	36	6	Non-functional (3), PRL(3)
Sibal et al. (2004)	43	8	GH (1), ACTH(3), Non-functional (2), PRL (2)
Imboden et al. (2005)	8	2	Non-functional (1), PRL (1),
Lubina et al. (2005)	40	4	GH (1), non-functional (1), PRL (2)
Dubuisson et al. (2007)	24	6	PRL(3), Nelson's tumour (1), Recurrent adenomas (2)[a]

GH growth hormone, *ACTH* adrenocorticotropic hormone, *PRL* prolactin
[a]Tumour type not specified

might lead to infarction of tumour by increasing the blood GnRH concentration thereby indirectly leading to vasospasm or rapid tumour expansion with the resultant ischaemic necrosis (Walker et al. 1996).

Octreotide, a somatostatin analogue, is another drug shown to be associated with pituitary apoplexy. Patient with acromegaly might develop pituitary apoplexy after stopping subcutaneous octreotide (Sibal et al. 2004).

5.3.2.2 Surgery

Various surgical procedures have been implicated in pituitary apoplexy. Semple et al. (2007) reported four patients with known pituitary adenomas who developed pituitary apoplexy. Two macroadenomas on conservative management developed pituitary apoplexy after hip replacement surgery and orchidectomy.

Pituitary apoplexy has been reported in patients who underwent partial resection for large pituitary tumours. Goel et al. (1995) described two cases of pituitary apoplexy in residual tumours after partial resection of giant pituitary tumours. Surgery might compromise blood supply to remaining tumour resulting in apoplexy (Ahmad et al. 2005).

5.3.2.3 Pituitary Stimulation Tests

Pituitary stimulation tests have been implicated as a cause in many cases of pituitary apoplexy. Pituitary apoplexy had been reported in patient with pituitary macroadenoma with suprasellar extension following TRH testing (Szabolcs et al. 1997). Similar report was also available in case of acromegaly following TRH stimulation test (Wang et al. 2007).

Several mechanisms have been postulated for apoplexy after pituitary stimulation test. TRH-induced vasospasm may precipitate pituitary gland infarction (Bernstein et al. 1984). Pressure effect of catecholamines released after TRH injection may precipitate pituitary tumour infarction (Dokmetas et al. 1999). Direct effect of TRH on tumour cells along with increased blood flow and volume thereby may lead to abrupt tumour expansion and pituitary apoplexy (Okuda et al. 1994; Masago et al. 1995).

For the first time in 1984, pituitary apoplexy in a FSH-secreting adenoma, which developed infarction after GnRH, was described (Korsic et al. 1984). Following that there were several reports of pituitary apoplexy in patients with macroadenoma after GnRH (Arafah et al. 1989; Masson et al. 1993; Hiroi et al. 2001). Acute GnRH stimulation of gonadotropic cells might increase the metabolic activity of the tumour, resulting in excessive gonadotropin production to such an extent that a vascular accident could

occur (Korsic et al. 1984). GnRH might also have a direct action on tumour vasculature (Masson et al. 1993; White and Masson 1994).

Several cases of pituitary apoplexy after TRH and GnRH stimulation test had been reported (Masago et al. 1995; Dokmetas et al. 1999; Lee et al. 2000; Kilicli et al. 2010). Triple stimulation tests using GnRH, TRH and insulin might also lead to pituitary apoplexy (Okuda et al. 1994; Masago et al. 1995; Lee et al. 2000; Matsuura et al. 2001; Yoshino et al. 2007).

Pituitary apoplexy may also develop with other stimulation tests. Pituitary apoplexy had developed in Cushing's disease following CRH administration (Rotman-Pikielny et al. 2003) and also after metyrapone test (Sibal et al. 2004).

5.3.2.4 Radiological Study

There were reports of apoplexy in patients with pituitary adenoma following radiological procedures. Apoplexy had been reported after cerebral angiography in a case of GH-secreting pituitary macroadenoma (Louwerens et al. 1996). Pituitary apoplexy might occur following air encephalography (AEG) performed to delineate the extent of tumour (Sahdev et al. 1981). Pituitary apoplexy had also occurred following administration of Gd-DTPA in acromegaly (Wichers et al. 1997).

5.3.2.5 Others

Patients with acromegaly might develop pituitary apoplexy after external irradiation (Sachdev et al. 1981; Wakai et al. 1981). Also reported pituitary apoplexy had been reported within 12 h of Gamma Knife surgery (Semple et al. 2007). Patient with known pituitary tumour might develop pituitary apoplexy with no predisposing factor (Semple et al. 2007).

5.4 Resolution of Hormonal Hypersecretion Following Pituitary Apoplexy

There are several reports available in the literature on resolution of hormonal hypersecretion following pituitary apoplexy on follow-up. In 1978, Pelkonen et al. reported that a patient with acromegaly became inactive, and one out of two Cushing's syndrome patients resolved after the occurrence of apoplexy (Pelkonen et al. 1978). There were other reports of resolution of Cushing's syndrome after apoplexy (Randeva et al. 1999; Rotman-Pikielny et al. 2003).

Pituitary adenoma on treatment with levothyroxine had resolved after the occurrence of apoplexy in a patient with repeat MRI after 3 months showing no evidence of residual tumour (Schatz et al. 2000).

Patient with acromegaly due to macroadenoma who developed pituitary apoplexy following intravenous injection of Gd-DTPA had resolution of clinical and hormonal evidence of acromegaly with shrinkage of sellar content on MRI after 14 months (Wichers et al. 1997).

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Postoperative Pituitary Apoplexy

6

Sachin A. Borkar and Ashok Kumar Mahapatra

Contents

Abbreviations

ACTH	Adrenocorticotrophic hormone
CT	Computerized tomography
GH	Growth hormone
MRI	Magnetic resonance imaging

6.1 Introduction

Pituitary apoplexy is a rare, life-threatening clinical syndrome caused by rapid enlargement of a pituitary adenoma secondary to haemorrhage, infarction or both (Semple et al. 2005, 2006). It is characterized by sudden onset of headache, vomiting, ophthalmoplegia, visual disturbance and sometimes alteration in sensorium (Ebersold et al. 1983; Semple et al. 2005).

Bailey was the first to describe a clinical case of pituitary apoplexy, resulting from a catastrophic haemorrhage of a pituitary adenoma in 1898 (Ebersold et al. 1983; Randeva et al. 1999). In 1905, Bleibtreu reported an old haemorrhage in a pituitary adenoma at post-mortem, in a young man with acromegaly (Bleibtreu 1905). Dingley and Lond, in 1932, reported two patients, both of whom underwent post-mortem for sudden death, in whom large pituitary tumours with haemorrhage were found (Dingley and Lond 1932). The term "apoplexy" is derived from Greek and implies accumulation of blood or fluid within any organ of the body. The term "pituitary apoplexy" was first coined by Brougham et al. in 1950, in post-mortem examination of a series of 5 patients

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who died owing to haemorrhagic necrosis of a pituitary adenoma (Brougham et al. 1950).

Although pituitary adenomas are common brain tumours, pituitary apoplexy is much less common with incidence ranging from 0.6 to 10.5 % as per different published series (Cardoso and Peterson 1984; Bills et al. 1993; Randeva et al. 1999; Semple et al. 2005; Turgut et al. 2010). The phenomenon of "postoperative pituitary apoplexy" following a subtotal or a partial resection of giant pituitary adenomas was described by Goel et al. in 1995 (Goel et al. 1995). In this article, we review the literature regarding this life-threatening complication and its implications on pituitary tumour surgical philosophy.

6.2 Anatomical Considerations

The pituitary gland, also called as hypophysis cerebri, lies in the sella turcica of the sphenoid bone under the hypothalamus and optic chiasm and is enclosed with the diaphragma sellae. In the adult, it measures approximately 12×9×6 mm in dimensions and weighs 0.6 g. The pituitary gland can be divided into two major parts: one situated at the anterior site corresponding to 80 % of the gland (adenohypophysis) and the remaining 20 % on the posterior site of the gland (neurohypophysis) (Nawar et al. 2008).

There are up to ten portal pituitary vessels that originate dorsally at capillaries from the median eminence. These vessels move alongside the ventral surface of the anterior pituitary stalk and drain to the adeno-pituitary making anastomosis with the neuro-pituitary capillaries. The circulation is predominantly through the hypothalamus to the pituitary gland and allows the pituitary to be the most irrigated region of the body (0.8 ml/g/min) (Chacko et al. 2002).

It is believed that 70–90 % of adenohypophysis blood supply comes from major portal vessels and the remaining from lesser ones (Chacko et al. 2002). A further potential source of direct arterial supply for the adenohypophysis is the capsular arteries, originated from inferior hypophyseal arteries. On the other side, venous drainage takes place within adjacent venous sinus to the jugular veins (Lazaro et al. 1994).

In short, the pituitary gland is one of the greatest irrigated structures of human body with a complex vascular system (Mohr and Hardy 1982), and therefore pituitary adenomas have a 5.4 greater chance to bleed than any other brain tumour (Semple et al. 2007).

6.3 Etiopathogenesis

The pathogenesis of pituitary apoplexy is not completely understood, and as a result a number of hypotheses regarding its pathogenesis have been published (Mohr and Hardy 1982; Cardoso and Peterson 1984; Bills et al. 1993; Lazaro et al. 1994; Chacko et al. 2002; Semple et al. 2007). Some authors have proposed that a rapidly growing adenoma that outstrips its blood supply may lead to ischaemic necrosis of the gland (Onesti et al. 1990). Others propose direct compression of the pituitary infundibulum by an expanding mass, thus compromising the blood flow from the portal vessels, resulting in necrosis of the entire gland with haemorrhage as a secondary occurrence. Sudden release of tumour vessels from the internal carotid artery due to reduced tumour burden and compromise of the venous drainage of the tumour during surgery has also been proposed (Cunha-Neto et al. 2007). Tumour manipulation during surgery, swelling and subsequent compression of the hypophyseal arteries causing haemorrhagic necrosis is also a plausible hypothesis. However, Cardoso and Peterson (1984) did not agree with the above theory since angiographic studies show that pituitary adenomas derive their blood supply from inferior hypophyseal arteries and not from superior hypophyseal arteries, which get compressed with the impaction of the enlarging tumour against the diaphragmatic notch.

The hypothesis of tumoural "intrinsic" factors leading to haemorrhage is also suggested. There is a statistically significant relationship between the aggressive and invasive tumoural behaviour and haemorrhage (Fraioli et al. 1990; McFadzean et al. 1991).

Semple et al. (2006) in a recent retrospective series of 59 patients with pituitary apoplexy compared the clinical features and outcome in patients

who were found to have ischaemic necrosis alone on histological examination to those with haemorrhagic necrosis or haemorrhage alone. This patient series suggested that those patients with ischaemic necrosis alone may have a more benign course with a more protracted onset of symptoms, less severe clinical features and a better outcome when compared with those patients in whom haemorrhagic necrosis or haemorrhage alone was found at histological examination.

6.4 Clinical Features

Numerous conditions have been linked to pituitary apoplexy, but in the majority of cases, it happens without any predisposing factor. The main predisposing factors associated to pituitary apoplexy are medication (bromocriptine and cabergoline), radiotherapy, pituitary function tests, diabetes mellitus, trauma, thrombocytopenia or recent surgery. High blood pressure is also considered as a risk factor for pituitary apoplexy although this association is not always seen (Chang et al. 2009).

Headache is the major symptom of pituitary apoplexy in patients without altered mental status, and it can have sudden onset with severe pain. Occasionally it is generalized, but most often retro-orbital. The potential mechanisms underlying headache in pituitary apoplexy are meningeal irritation, dura mater compression, enlargement of sella turcica walls or involvement of the superior division of the trigeminal nerve inside the cavernous sinus (Bills et al. 1993).

Altered visual field or visual acuity means involvement of the optic nerves, chiasm or optic tracts. Cranial nerves III, IV and VI are vulnerable at the cavernous sinus, and therefore in the majority of patients that do not show altered mental status, headache is associated with diplopia (Chacko et al. 2002; Nawar et al. 2008). The medial aspect of the cavernous sinus corresponds to the lateral aspect of the pituitary fossa, and therefore, an acute haemorrhage or necrosis within this region can shift the oculomotor nerves. Ipsilateral mydriasis and ptosis are owing to cranial nerve III involvement. Facial numbness may also take place due to the cranial nerve V first division involvement (Nawar et al. 2008).

Altered mental status is the most severe neurological finding in patients with pituitary apoplexy (Chacko et al. 2002). Its mechanism remains elusive and might be related to subarachnoid haemorrhage, increased intracranial pressure, obstructive hydrocephalus, adrenal insufficiency leading to arterial hypotension and hypoglycaemia and hypothalamic compression.

Nausea and vomiting may occur due to adrenal insufficiency, meningeal irritation and hypothalamic dysfunction or raised intracranial pressure. Neck stiffness is observed in patients with pituitary apoplexy and should raise the attention for subarachnoid haemorrhage (Elsässer Imboden et al. 2005). Focal signs such as hemiparesis or aphasia are less common and are attributed to internal carotid artery compression or vasospasm (Biousse et al. 2001; Kasliwal et al. 2008).

The majority of patients present with, at least, partial hypopituitarism. Reviewing a series of patients that had pituitary apoplexy, Veldhuis and Hammond (1980) found multiple hormonal deficiencies such as GH deficit (88 %), ACTH hyposecretion (66 %), hypothyroidism (42 %) and hypogonadotrophic hypogonadism (85 %) (Veldhuis and Hammond 1980).

6.5 Imaging

Postoperative pituitary apoplexy appears as hyperdense sign on brain computerized tomography (CT) scan (Chang et al. 2009). CT scan also demonstrates subarachnoid haemorrhage and whether there is involvement of the brain and ventricles. In the subacute and chronic stages of pituitary apoplexy, brain magnetic resonance imaging (MRI) is considerably better than CT (Cardoso and Peterson 1984). One of the advantages of MRI is the possibility of estimating the onset of bleeding. In the acute stage of pituitary apoplexy (first 7 days), it is seen on MRI characteristic hypo- or isointense lesions on T1- and T2-weighted images; between 7 and 14 days in the subacute stage, there is marginal signal reinforcement although the haematoma core remains isointense; in the chronic stage there is an overall increase on T1 and T2 signal. Figure 6.1 demonstrates postoperative pituitary apoplexy in a giant pituitary adenoma.

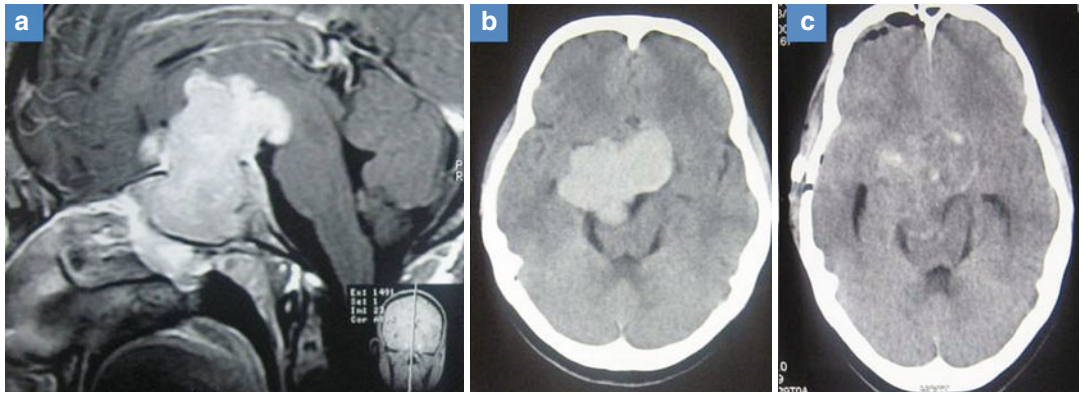

Fig. 6.1 Sagittal contrast-enhanced MRI (**a**) and CECT head (**b**) showing a giant pituitary adenoma with parasellar and subfrontal extensions. Figure (**c**) showing postoperative pituitary apoplexy in the residual tumour

Semple et al. (2008) correlated the MRI findings with the histopathological results to assess how accurately the histopathology was predicted by the MRI. When they compared the histopathological diagnosis with preoperative MRI findings, the histopathology correlated with the MRI in 68 % of patients with a histopathological diagnosis of haemorrhagic infarction/haemorrhage and in 82 % of patients with infarction alone (Semple et al. 2008). The histopathological diagnosis could therefore be equated with the MRI findings in the majority of cases, although the findings were less accurate in the haemorrhagic group (Semple et al. 2008).

6.6 Differential Diagnoses

Clinical conditions frequently misdiagnosed as pituitary apoplexy are subarachnoid haemorrhage due to ruptured intracranial aneurysm and meningitis. Other diseases that may have similar clinical characteristics are hypertensive encephalopathy, brain abscess or cyst, cavernous sinus thrombosis, intracerebral haematoma, basilar artery occlusion, encephalitis, retrobulbar neuritis, temporal arteritis and ophthalmoplegic migraine (Chang et al. 2009).

6.7 Discussion

Pituitary apoplexy is a dangerous condition, often characterized by acute onset of headache, nausea, visual field loss and ocular paresis (Bills et al. 1993; Randeva et al. 1999). Massive swelling and haemorrhage in a pituitary tumour or the phenomenon of "postoperative pituitary apoplexy" following a subtotal or a partial resection of giant pituitary adenomas was described by Goel et al. in 1995 (Goel et al. 1995). The senior author has also previously published a series of four cases of postoperative pituitary apoplexy (Ahmad et al. 2005). All the four patients in our series and in the series reported by Goel et al. (1995) had giant pituitary tumours. There was postoperative worsening in the neurological status in all the four reported cases. There was no evidence of alteration of coagulation parameters. Despite the decompression of the haemorrhagic tumour during the reoperations, all the patients had a stormy postoperative course and subsequently died.

In a recently published article, the senior author has presented our institute experience of managing postoperative pituitary apoplexy (Kurwale et al. 2012). Patients with postoperative pituitary apoplexy were critically reviewed for clinical presentation, endocrine status, preoperative imaging and postoperative course with outcome. Operative findings and histopathology were correlated. Thirteen patients over 11 years with a mean age of 36 years were reviewed. All patients had giant pituitary adenomas. Four patients had functional adenomas. All patients were optimized for endocrine status before surgery. Twelve patients underwent transsphenoidal excision of the tumour. Only partial excision could be achieved in all cases. Deterioration of consciousness (nine patients), visual deterioration

(three patients), delayed reversal and excessive bleeding (one patient) were the primary indicators toward apoplexy. Ten patients were reexplored within 24 h of first surgery. All except one were explored transcranially a second time. Twelve patients died with variable postoperative course. Hypothalamic dysfunction and dyselectrolytaemia (nine patients) were leading causes of death, followed by meningitis and raised intracranial pressure. The authors concluded that postoperative pituitary apoplexy is associated with high mortality, despite early and best management (Kurwale et al. 2012). Partial resection of the giant pituitary adenoma is directly responsible for postoperative apoplexy. Maximum possible resection of the tumour by suitable exposure should be the optimal goal of surgery. Surgical exposure, either transcranial or transsphenoidal, should be dictated by tumour configuration on preoperative imaging. Endocrine status, histology of the tumour and clinical presentation do not appear to contribute to postoperative pituitary apoplexy.

6.8 Treatment

As soon as diagnosis of pituitary apoplexy is made and after collecting blood sample for haematological, biochemistry and hormonal analysis, glucocorticoids should be administered in supraphysiological doses to serve not only as replacement for endogenous hormone deficiency but also to help control the effect of oedema. Dose recommended is between 8 and 16 mg dexamethasone or hydrocortisone 50 mg intravenously every 6 h during the first 48 h (Chacko et al. 2002; Dubuisson et al. 2007). Occasionally, patients are clinically or biochemically hypothyroid at presentation, a factor to be considered prior to surgical intervention. However, hypothyroidism is not a contraindication for surgery (Chang et al. 2009).

If there is altered mental status without recovery after neurological and endocrinological treatment, surgical intervention is required (Chang et al. 2009). The choice of surgical approach has to be decided on a case to case basis. Surgical exposure, either transcranial or transsphenoidal, should be dictated by tumour configuration on preoperative imaging (Kurwale et al. 2012)

It is important to note that endocrinological follow-up after surgery is necessary since many patients need hormonal replacement for a long-term basis (Chang et al. 2009).

Conclusion

Postoperative pituitary apoplexy is associated with high mortality, despite early and best management. Partial resection of the giant pituitary adenoma is directly responsible for postoperative apoplexy. Maximum possible resection of the tumour should be the optimal goal of surgery. Surgical exposure, either transcranial or transsphenoidal, should be dictated by tumour configuration on preoperative imaging.

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Part IV

Clinical Features

Clinical Features of Pituitary Apoplexy

7

Ilan Shimon

Contents

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
CT	Computerized tomography
GH	Growth hormone
IGF-1	Insulin-like growth factor-1
MRI	Magnetic resonance imaging

7.1 Introduction

Pituitary apoplexy is a rare clinical situation occurring in patients harbouring pituitary adenomas, usually large macroadenomas. It was first recognized more than 110 years ago when Pearce Bailey described the first case of haemorrhage in pituitary adenoma in 1898 (Baily 1898). It was only in 1950 that Brougham et al. used the term pituitary apoplexy when reported five patients with apoplexy (Brougham et al. 1950). It results from spontaneous acute or subacute haemorrhage or hypoxic infarction within a large pituitary tumour. The tumour outgrows its blood supply, leading to areas of necrosis and haemorrhage. Because these pituitary tumours, mostly clinically nonfunctioning adenomas, grow and progress very slowly, they may present themselves acutely as a dramatic event with potential catastrophic consequences when sudden tumour enlargement appears because of rapid and severe haemorrhage. Thus, most of the patients presenting with pituitary apoplexy have undiagnosed pituitary adenoma at the time of apoplexy presentation, and

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apoplexy is the first manifestation of the tumour (Elsässer Imboden et al. 2005; Lubina et al. 2005).

Pituitary apoplexy is reported in 2–14 % of patients operated on for known pituitary adenomas (Onesti et al. 1990; da Motta et al. 1999; Randeva et al. 1999; Bills et al. 1993; Bonicki et al. 1993), usually in less than 5 %, but the precise prevalence of pituitary apoplexy is unknown, as all data are based on numbers of surgically treated patients with adenomas. Importantly, 14–26 % of patients with pituitary adenomas have pituitary haemorrhage or necrosis according to pituitary imaging or surgical findings, but without presenting with the classical symptoms of pituitary apoplexy (Mohanty et al. 1977; Wakai et al. 1981; Bills et al. 2005). These patients have subclinical or asymptomatic apoplectic event, with no symptoms or only mild and nonspecific complaints. Thus, the majority of these pituitary pathologies are clinically silent, and only part of them present with classical symptoms suggesting apoplexy.

Subjects with typical apoplexy present with acute symptoms of headaches, nausea and vomiting, syncope, diplopia, visual deficits, ophthalmoplegia and mental deterioration, but the clinical presentation is widely variable. It depends on the predominant mechanism of tumour expansion, blood extravasation into subarachnoid space and suprasellar or lateral compression by the necrotic adenoma. This emergency condition may evolve over 1–2 days, and patients with visual or mental deterioration are referred for urgent transsphenoidal pituitary decompression. Spontaneous clinical recovery may occur in those treated conservatively, but most affected patients develop long-standing complete or partial anterior pituitary failure, requiring life-long pituitary hormone replacement (Bills et al. 1993; Randeva et al. 1999; Lubina et al. 2005; Nawar et al. 2008).

7.2 Clinical Characteristics

In the reported series in the literature, about two-thirds of the patients are males (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Lubina et al. 2005; Nawar et al. 2008). Patients of all ages have been reported, and in all large series the mean age at presentation is between 49 and 56 years (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Lubina et al. 2005; Nawar et al. 2008). Patients with pituitary apoplexy can commonly present with signs that mimic other intracranial pathologies including subarachnoid haemorrhage, meningitis, brain infarction and cavernous sinus thrombosis. The incidence of subclinical or asymptomatic pituitary apoplexy is higher than the typical clinical apoplexy.

Table 7.1 Presenting symptoms in patients with pituitary apoplexy

Symptoms or signs	Percentage of patients
Headache	Up to 100 %
Nausea and vomiting	40–70 %
Meningeal irritation	25 %
Photophobia	33 %
Mental deterioration	20 %
Ocular paresis (diplopia and ophthalmoplegia)	50–70 %
Decreased visual acuity	75 %
Visual field defects	60–70 %
Pituitary hormone deficiencies	80 %

7.3 Neurologic Symptoms

Headache is the earliest, most consistent and most frequent symptom (up to 100 %) of pituitary tumour apoplexy (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Elsässer Imboden et al. 2005; Lubina et al. 2005; Nawar et al. 2008; Rajasekaran et al. 2011) (Table 7.1). The rapid increase in the intrasellar contents (blood) and intrasellar pressure presents usually as sudden, severe, retroorbital headache, sometimes bifrontal, suboccipital or diffuse. Headache is commonly accompanied by nausea and vomiting. Meningeal irritation with neck stiffness, photophobia, lethargy, fever and mental deterioration may occur if blood or necrotic tissue leaks into the subarachnoid space (Ayuk et al. 2004; Sibal et al. 2004; Nawar et al. 2008). Mental deterioration and unconsciousness may be related also to increased intracranial pressure (Zayour et al. 2004), obstructive hydrocephalus or hypothalamic compression (Chang et al. 2009). Infrequently, acute pituitary apoplexy due to massive haemorrhage may lead to a fatal outcome (da Motta et al. 1999; Shields et al. 2012). Lateral compression of the apoplectic pituitary adenoma

can increase the pressure inside the cavernous sinus, affecting the third, fourth and sixth cranial nerves, leading to motor ocular paresis (diplopia and ophthalmoplegia) in 40–70 % of the patients (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Elsässer Imboden et al. 2005; Lubina et al. 2005; Nawar et al. 2008; Rajasekaran et al. 2011). The third cranial nerve (oculomotor) palsy, occurring either alone or together with damage to the other cranial nerves, is the most common nerve to be affected (Ayuk et al. 2004; Sibal et al. 2004; Nawar et al. 2008; Rajasekaran et al. 2011). Rarely, pituitary apoplexy may present as isolated sixth cranial nerve (abducens) palsy (Zoli et al. 2012). Facial numbness due to the fifth cranial nerve 1st branch involvement can also occur.

7.4 Visual Deterioration

Compression of the necrotic intrasellar mass superiorly towards the optic nerves and optic chiasma causes visual symptoms in most (75 %) patients (Table 7.1) (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Elsässer Imboden et al. 2005; Lubina et al. 2005; Nawar et al. 2008; Rajasekaran et al. 2011), including decreased visual acuity, visual field defects, especially bitemporal hemianopsia and also complete blindness and monoocular blindness. The visual signs tend to improve spontaneously in many patients, probably due to decrease in intrasellar pressure, when necrotic tissue absorption occurs after several days. However, early pituitary decompression will improve visual functions in most cases, including visual recovery in blind eyes (Bills et al. 1993; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Elsässer Imboden et al. 2005; Lubina et al. 2005; Nawar et al. 2008; Rajasekaran et al. 2011; Turgut et al. 2010).

7.5 Pituitary Imaging

Both computerized tomography (CT) scan and magnetic resonance imaging (MRI) are performed in patients suspected to have pituitary tumour apoplexy, to define pituitary anatomical changes (adenoma size, invasiveness, chiasmal compression)

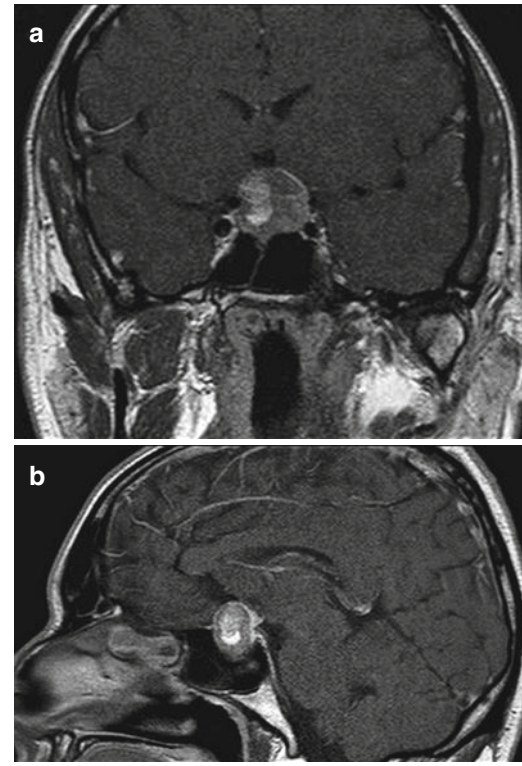

Fig. 7.1 A 39-year-old healthy male with a typical presentation of pituitary apoplexy. On admission he had headaches and bitemporal upper quadrianopsia (left>right). MRI depicted a large pituitary adenoma with suprasellar extension and chiasmal compression. Pituitary haemorrhage is seen on coronal (**a**) and sagittal (**b**) T1-weighted images in the right side of the adenoma. Hormonal evaluation before operation revealed low cortisol and low testosterone levels that returned to normal after pituitary decompression. Pathology report was compatible with apoplexy of a nonfunctioning pituitary adenoma

and to establish the diagnosis (pituitary haemorrhage). CT scans indicate the presence of a pituitary tumour in most affected patients but have usually low sensitivity in detecting pituitary apoplexy at the acute phase (less than 2 days) and are diagnostic then in only 21–28 % of studied cases (Onesti et al. 1990; Ayuk et al. 2004; Sibal et al. 2004; Rajasekaran et al. 2011). MRI is the preferred imaging technique and can detect haemorrhage in a pituitary mass, thus confirming the diagnosis of pituitary apoplexy in 80–90 % of affected patients (Onesti et al. 1990; Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004; Lubina et al. 2005; Rajasekaran et al. 2011). Typically, in the acute phase (less than 2 days) pituitary haemorrhage is seen as hyperintensity on T1-weighted images (Fig. 7.1) and as hypointensity

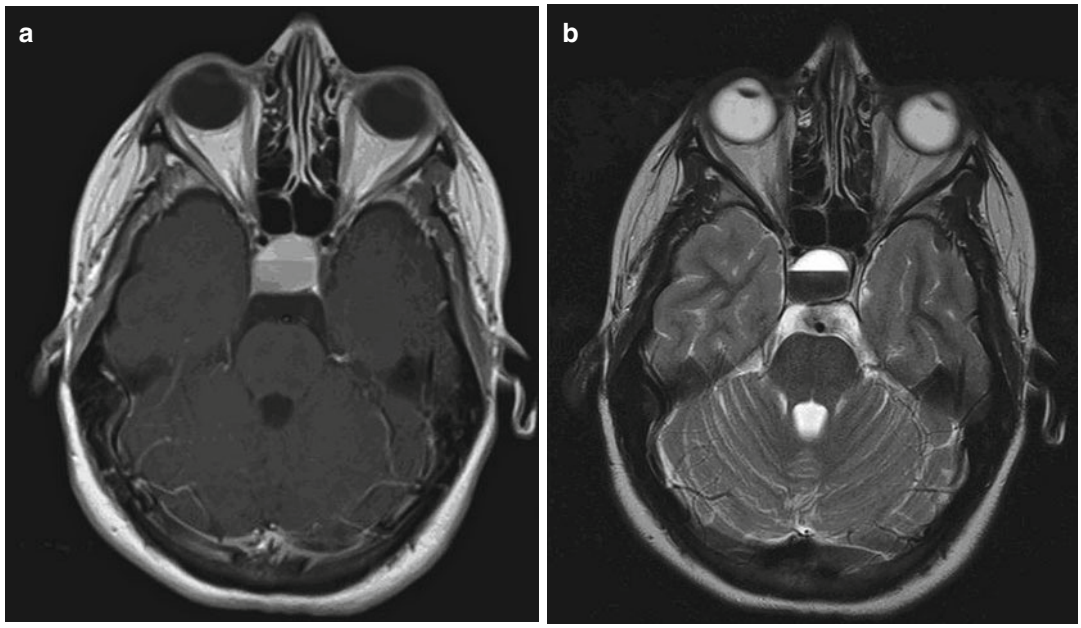

Fig. 7.2 A 22-year-old female with a microprolactinoma was treated with cabergoline. When becoming pregnant medical treatment was stopped. After delivery she began lactation. One month later she developed severe headache without vomiting. MRI performed after 2 weeks demonstrated a fluid level in a large pituitary mass on both (**a**) T1- and (**b**) T2-weighted images

on T2-weighted images. Later, after 3 days, hyperintense signals are depicted on both T1- and T2-weighted images. Several weeks later, during the chronic phase, the digestion of blood and necrotic tissue will appear classically as a fluid level in the pituitary mass (Fig. 7.2).

7.6 Endocrine Dysfunction

Hypopituitarism is very common at the time of apoplexy presentation. Clinical hypopituitarism will occur only when 70–75 % of the anterior pituitary is destroyed, and complete pituitary failure requires more than 90 % loss of pituitary tissue. The extent and severity of pituitary hormone deficiency are poorly investigated in published series of patients presented with apoplexy. Moreover, as most patients with pituitary tumour apoplexy harbour macroadenomas, many of them would have preexisting pituitary insufficiency even before the acute apoplexy episode. This is reflected by the high rate (~50 %) of patients with clinical endocrine symptoms before the apoplexy, including hypogonadism, altered menstruation, impotence, cold intolerance, chronic fatigue and anaemia (Randeva et al. 1999; Ayuk et al. 2004). At presentation, most patients with apoplexy (about 80 %) have deficiency of one or more pituitary hormones (Randeva et al. 1999; Ayuk et al. 2004; Sibal et al. 2004). Hypogonadotrophic hypogonadism was reported in 50–79 % of patients, central hypothyroidism in 35–57 % and cortisol deficiency due to adrenocorticotropic hormone (ACTH) deficiency in 50–76 % of subjects presented with pituitary apoplexy (Table 7.2) (Randeva et al. 1999; Ayuk

Table 7.2 Pituitary dysfunction when pituitary apoplexy is diagnosed

Hormone deficiency	Percentage of patients
Hypogonadotrophic hypogonadism	50–79 %
Central hypothyroidism	35–57 %
ACTH-cortisol deficiency	50–76 %
GH-IGF-1 deficiency	Unknown
Hypoprolactinemia	25–40 %
Hyperprolactinemia	30–40 %
Diabetes insipidus	Rare

et al. 2004; Sibal et al. 2004; Lubina et al. 2005; Rajasekaran et al. 2011). Growth hormone deficiency with low IGF-1 levels was also noticed in a subset of patients (Elsässer Imboden et al. 2005). Hyperprolactinemia is noted in 30–40 % of studied patients (Ayuk et al. 2004; Sibal et al. 2004) and hypoprolactinemia in 25–40 % (Ayuk et al. 2004; Sibal et al. 2004). Hyponatremia is reported in up to 44 % of the patients in some reports (Randeva et al. 1999; Elsässer Imboden et al. 2005; Rajasekaran et al. 2011), but in other series this electrolyte disturbance is less common (Sibal et al. 2004; Lubina et al. 2005). Hyponatremia in these patients results from either severe hypocortisolism or inappropriate antidiuretic hormone (ADH) secretion (Ebner et al. 2010). On the contrary, diabetes insipidus is very rare despite frequent and significant suprasellar extension in many cases.

Patients with functioning pituitary adenomas can present with signs of acromegaly or Cushing's disease, but apoplexy usually does not result in normalization of hormone hypersecretion in many of these cases (Elsässer Imboden et al. 2005). However, some functioning tumours can be destroyed by such haemorrhage, and cases of pituitary apoplexy in GH-secreting and ACTH-cell adenomas resulting in amelioration of acromegaly (Fraser et al. 2009; Login et al. 2010) and Cushing's disease (Quevedo Juanals et al. 2010), respectively, were reported.

7.7 Pathologies Mimicking Pituitary Apoplexy

The symptoms and signs of several intracranial pathologies can mimic pituitary apoplexy. These include subarachnoid haemorrhage, bacterial meningitis, brain infarction and cavernous sinus thrombosis. Also other rare entities like haemorrhagic chondroid chordoma involving the sella turcica (Lee et al. 1998), spontaneous haemorrhage into an empty sella turcica (Alatakis et al. 2000), a Rathke's cleft cyst associated with a ruptured aneurysm of the anterior cerebral artery (Binning et al. 2008), and a ruptured internal carotid artery cavernous aneurysm (Romano et al. 2006) may have clinical signs similar to apoplexy. All these haemorrhagic events in the sellar and/or suprasellar regions presented with headaches, vomiting and visual deterioration. The accurate diagnosis was made during cerebral angiography and subsequent surgery. Also, benign and malignant intrasellar tumours can mimic pituitary apoplexy when presented. Patients with intrasellar meningiomas (Kudo et al. 1997), metastatic carcinomas to the pituitary (Furuta et al. 1999), central nervous system lymphoma (Quintero Wolfe et al. 2009) and hypothalamic lymphoma (Akhaddar et al. 2009) all had the typical clinical presentation of pituitary apoplexy.

Conclusion

Patients harbouring a pituitary macroadenoma may present with apoplexy as the initial manifestation of the existing large adenoma. Most apoplectic events occur spontaneously. Patients have then a wide range of symptoms and signs, most commonly acute onset headache (often frontal or orbital), nausea and vomiting, ocular paresis and visual deficits. Anterior pituitary hormone deficiency is common. Some patients with pituitary apoplexy can present in a subacute or delayed way. These patients have more subtle symptoms. Silent cases of pituitary haemorrhage can also occur. Pituitary apoplexy can clinically mimic other intracranial pathologies not related to the pituitary. Apoplexy should be considered in any patient with acute headache and visual deterioration. In such patients, a careful assessment of symptoms and signs of pituitary dysfunction (e.g., hypogonadism, hypocortisolism), brain and pituitary imaging, formal visual field assessment and pituitary hormone measurements should be performed (Rajasekaran et al. 2011). As pituitary apoplexy is a rare entity, a high index of clinical suspicion is usually required to suspect this in the appropriate clinical context and to correctly diagnose and treat this situation.

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Subarachnoid Haemorrhage with Pituitary Adenoma

8

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Abbreviations

ACA	Anterior cerebral artery
ACTH	Adrenocorticotropic hormone
CSF	Cerebrospinal fluid
CT	Computerised tomography
FSH	Follicle-stimulating hormone
GH	Growth hormone
ICA	Internal carotid artery
IGF-1	Insulin growth factor 1
LH	Luteinizing hormone
MCA	Middle cerebral artery
MEN-1	Multiple endocrine neoplasia syndrome type 1
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PCoA	Posterior communicating artery
SAH	Subarachnoid haemorrhage
SIADH	Syndrome of inappropriate antidiuretic hormone
T4	Thyroxine
TSH	Thyroid-stimulating hormone

8.1 Introduction

Concurrent subarachnoid haemorrhage (SAH) and pituitary adenoma are a rare but important association. Between the years 1938 and 2010,

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32 such cases have been reported globally within the medical literature (Table 8.1). Four (13.3 %) were thought to have occurred intraoperatively (for instance, due to rupture of an undetected aneurysm or iatrogenic injury; Tsuchida et al. 1983; Matsuno et al. 1993; Kuroyanagi et al.

Table 8.1 Published case reports of pituitary adenomas diagnosed with SAH pre- or intraoperatively

Author (year)	Case index	Pre-/ intraoperatively	Visual symptoms	Comment
Voss (1938)	1	Pre	Unknown	
Jefferson (1940)	1 Male GH-secreting adenoma	Pre	Oculomotor palsy	Heavily blood-stained CSF on LP. Radiographs elicited gross enlargement of the sella turcica and features of acromegaly
Kirschbaum and Chapman (1948)	1 Male GH-secreting adenoma	Pre	No	Fatal SAH
Wakai et al. (1981)	3	Pre	Unknown	Authors reviewed a large series of 560 cases of pituitary adenoma over 30 years where extension into the subarachnoid space was rare, being found in 0.5 % and without detectable intratumoral haematoma in any of them
Majchrzak et al. (1983)	1	Pre	Unknown	Massive left-sided paralysis ischaemia of the right frontal lobe as a result of occlusion of the anterior cerebral artery. Removal of the tumour 3 weeks after SAH did not resolve vascular compromise
Tsuchida et al. (1983)	1 Male Nonfunctioning adenoma	Intra	Unknown	Previously undetected ACA aneurysm that ruptured during transsphenoidal surgery
Beard et al. (1985)	1 Female GH-secreting adenoma	Pre	No	SAH diagnosed at postmortem
Fong and Fabinyi (1985)	1 Prolactinoma	Pre	Visual loss and abducens nerve palsy	
Bjerre et al. (1986)	1	Pre	Unknown	Patient with panhypopituitarism
Jaunsolo et al. (1986)	1 Male GH-secretory adenoma	Pre	No	Right MCA aneurysm
Itoyama et al. (1990)	1 Male GH-secretory adenoma	Pre	Left acuity diminution only	Apoplexy following head trauma. Right hemiparesis. Arterial vasospasm in left ACA and MCA
Fujiwara et al. (1991)	1	Pre	No	Pituitary adenoma associated with carotid artery aneurysm
Adachi et al. (1993)	1 Female Prolactinoma	Pre	No	Fatal SAH. Patient developed Werner's syndrome and had a pituitary adenoma with ruptured cerebral (anterior communicating artery) aneurysm. Also developed hyperparathyroidism and amenorrhoea

Table 8.1 (continued)

Author (year)	Case index	Pre-/ intraoperatively	Visual symptoms	Comment
Matsuno et al. (1993)	1	Intra	Unknown	Patient suffered severe SAH due to an indirect injury of the intradural internal carotid artery during or immediately after transsphenoidal surgery. An autopsy suggested that a small branch of the intradural internal carotid artery was strongly adherent to the suprasellar portion of the tumour capsule and its avulsion from the internal carotid artery might have been caused as the capsule fell down during the intracapsular removal of the tumour
Kuroyanagi et al. (1994)	1 Female Nonfunctioning adenoma	Intra (suspected)	No	The SAH revealed immediately after surgery. Posterior communicating artery (PCoA) may have been stretched with possible adhesion to the tumour capsule. Posterior thalamoperforating arteries may have been pulled and injured by the descent of the capsule as the tumour was resected
Otsuka et al. (1998)	1 Female Eosinophilic adenoma	Pre	Bilateral hemianopsia	Apoplexy developed after combined anterior pituitary function tests. Surgery performed 4 days later which resolved visual symptoms
Sanno et al. (1999)	1 Male FSHoma	Pre	No	SAH after apoplexy after pituitary function tests. Vasospasm in MCA led to left hemiparesis and deterioration in consciousness
Bontha et al. (2000)	1 Male Nonfunctioning adenoma	Pre	Visual deficit and ophthalmoplegia	Initially interpreted as sterile meningitis
Wohaibi et al. (2000)	1 Female Nonfunctioning adenoma	Pre	No	Died 3 days post admission
Gazioğlu et al. (2002)	1 Female ACTH-secreting adenoma	Pre	Oculomotor and abducens nerve palsies	Patient with Nelson's syndrome. Visual symptoms worsened due to postoperative hydrocephalus but only left abducens nerve palsy remained post-shunting
Laidlaw et al. (2003)	1 Female Nonfunctioning adenoma	Pre	Premorbid poor vision in left eye particularly. Blurred vision, reduced acuity, left Marcus-Gunn pupillary reaction. Complete left temporal field loss and enlarged blind spot on the left and some peripheral restriction (particularly in the upper quadrants) on the right	Minor SAH picked up on MRI and missed on CT. MRA suggested right ICA aneurysm arising at the PCoA origin and suggested the possibility of a very small aneurysm on the A1 segment of the left ACA

(continued)

Table 8.1 (continued)

Author (year)	Case index	Pre-/ intraoperatively	Visual symptoms	Comment
Bhansali et al. (2005)	1 Male Nonfunctioning adenoma	Pre	Complete blindness	Pituitary apoplexy led to SAH, then anterior cerebral artery spasm and then frontal lobe syndrome
Satyarthee and Mahapatra (2005)	1 Male Nonfunctioning adenoma	Pre	Diminution of visual acuity and bitemporal field defect	Visual symptoms resolved postoperatively
Nakahara et al. (2006)	1 Female Nonfunctioning (chromogranin A) adenoma	Pre	No	Cerebral angiography revealed marked elevation of the bilateral A1 portions of ACAs. MRI showed SAH resolution after 10 days
Shahlaie et al. (2006)	1 Female Suspected prolactinoma	Pre	Blurred vision reported by patient	Patient had unusual cerebrovascular anatomy. The recurrent hypophyseal artery discovered intraoperatively supplied the pituitary gland and originated adjacent to the anterior communicating artery aneurysm. Therefore, apoplexy may have resulted from compromised blood flow through this aberrant artery due to a vascular event associated with an aneurysm 2 weeks prior to rupture. Subsequent reperfusion may have resulted in haemorrhagic expansion of the intrasellar mass, resulting in pituitary apoplexy
Bao et al. (2007)	1 Male Nonfunctioning adenoma	Pre	No	CT initially done after head trauma revealing a pituitary incidentaloma. The cranial CT repeated 6 h after the injury discovered that the SAH was almost absorbed, and a heterogeneous iso- or hyperdense mass was found
Charalampaki et al. (2007)	1	Intra	Unknown	SAH and subsequent raised ICP due to an injury of the posterior cerebral artery (PCA) caused by a sharp piece of the sphenoid septum broken into the sellar floor with perforation of the dura and the PCA through the thin bone of the posterior clinoid process
Sergides et al. (2009)	1 Male Nonfunctioning adenoma	Pre	Unable to perceive light	8-month interval between SAH and pituitary adenoma diagnosed by imaging
Mohindra et al. (2010)	1 Female Nonfunctioning adenoma	Pre	No right pupillary reflex	CT revealed SAH 12 h post-presentation and initial MRI. Patient expired prior to surgery from fatal bilateral ACA territory infarcts
Zheng et al. (2010)	1 Female Nonfunctioning adenoma	Pre	No	Suspected SAH on lumbar puncture but no radiological evidence besides suprasellar mass with intratumoural haemorrhage on MRI

1994; Charalampaki et al. 2007), and the others were identified as having occurred prior to surgical intervention. Refer to "subarachnoid haemorrhage after transsphenoidal surgery" (Chap. 20) for information and literature on SAH post-transsphenoidal surgery. Fatal SAH has also been reported in five cases (Kirschbaum and Chapman 1948; Beard et al. 1985; Adachi et al. 1993; Matsuno et al. 1993; Wohaibi et al. 2000), with one dying prior to surgery from fatal bilateral anterior cerebral artery (ACA) territory infarcts (Mohindra et al. 2010).

8.2 Epidemiology

There is a growing recognition of an association between pituitary adenoma and existence of intracranial aneurysms which increase the risk of SAH. Reports in the literature suggest the association lies somewhere between 1.4 % (2/144 over 4 years, Acqui et al. 1987) and 7.4 % (7/95 over 5 years, Wakai et al. 1979). In a series of 800 patients with pituitary adenoma, the incidence of intracranial aneurysm was 2.3 % (Oh et al. 2012). Intracranial aneurysms are probably due to microanatomical changes in the cerebral circulation from compression or traction with consequent hyperaemia (Pia et al. 1972; Goyal et al. 2012). Hori et al. (1982) suggested that an internal carotid artery (ICA) aneurysm arose and enlarged as a result of a traction mechanism that a GH-secreting macroadenoma exerted as it reduced in size. Oh et al. (2012) reported that that age ($p=0.04$) and cavernous sinus invasion ($p<0.001$) were independently associated factors, whereas hormone type, immunohistochemistry staining and patient sex failed to demonstrate any statistically significant correlation. Pant et al. (1997) also reported that the association between intracranial aneurysms and pituitary adenoma was a function of increasing age ($p<0.001$) but that no independent association existed with hormone secretion or the size and malignancy of tumour. Manara et al. (2011) also claimed no independent association between aneurysm formation and either adenoma size or invasiveness. Interestingly, intracranial aneurysms are also significantly more prevalent in patients with pituitary adenomas when compared to other brain tumours (1.1 %, $p<0.001$, Wakai et al. 1979).

A meta-analysis by Vlak et al. (2011), which included 68 studies on 83 populations and 1,450 intracranial aneurysms in 94,912 patients from 21 countries (years 1998–2011), reported the prevalence ratio of unruptured intracranial aneurysms for pituitary adenomas was 2.0 (95 % CI 0.9–4.6). However, compared with patients who did not have the relevant comorbidity or risk factor, sex-adjusted and age-adjusted prevalence ratios were not significantly higher for patients with pituitary adenoma (from a total of 26 studies including 31 populations and 6,000 unruptured intracranial aneurysms). Nevertheless, Oh et al. (2012) performed an age-matched comparison of the prevalence of intracranial aneurysms in 800 patients with pituitary adenoma, which demonstrated an increased prevalence when compared with controls ($p=0.014$) with the sixth decade showing the most significant difference ($p=0.039$). Patients with acromegaly presented with a significantly higher prevalence of intracranial aneurysms and, presumably, therefore an increased risk of SAH compared with controls (26/150 vs. 5/71). This difference persisted when acromegalic patients were compared with positive controls above the age of 40 years (25/126 vs. 5/52; Manara et al. 2011).

8.3 Pathophysiology

The association between pituitary adenomatous haemorrhagic apoplexy and SAH is rare (Mohanty et al. 1979; Laidlaw et al. 2003; Nakahara et al. 2006; Bao et al. 2007; Kim and Cho 2007) in spite of adenomas being very vascular (Jefferson 1940; Beard et al. 1985). Reports of pituitary haemorrhage in association with SAH simulating aneurysm rupture are also rare (Gazioğlu et al. 2002). The most extensive adenomas are malignant such as those which burst through the tumour

capsule and not only form an intracranial mass but also invade the cavernous sinuses and through the arachnoid membrane (Jefferson 1940; Gazioğlu et al. 2002). Extravasation into subarachnoid space may also occur in the absence of suprasellar extension of the tumour (Cardoso and Peterson 1984). Necrotic haemorrhage within pituitary adenoma is the modal cause of apoplexy which can lead to frank SAH. Although rare, it is an important cause of angiogram-negative SAH (Laidlaw et al. 2003).

SAH can follow discharge of necrotic tissue and blood extravasation from the sella turcica either through the diaphragmatic aperture or after its rupture (Wakai et al. 1981) into the adjacent subarachnoid space of basal cisterns. It occurs when the pressure gradient within the sella exceeds the peripheral resistance of adjacent structures as the intrasellar pressure constantly rises proportionally with the extent of intratumoral haemorrhage and localised inflammation in pituitary apoplexy (Itoyama et al. 1990; Gaini et al. 2004; Satyarthee and Mahapatra 2005; Bao et al. 2007). Itoyama et al. (1990) alternatively hypothesised that apoplexy-associated SAH follows the penetration of atypical lymphocytes via ameboid reaction through the tumour capsule.

Causes of extrasellar haemorrhagic extension depend on the intrinsic growth urge of the adenoma and its potential for malignancy, the integrity of the interclinoid ligaments of the sellar diaphragm, and fixation of the optic chiasm (Jefferson 1940). The latter is important as an abnormally fixed optic chiasm can delay onset of visual disturbance on compression by a macroadenoma. Early vasospasm which could lead to SAH may result from secretion of potent vasoactive agents from the pituitary adenoma (Pozzati et al. 1987; Itoyama et al. 1990). Although vasospasm may be attributable to SAH (Itoyama et al. 1990), SAH can subsequently cause cerebral infarction due to further vasospasm in surrounding vessels because of the irritant effect of blood (Bhansali et al. 2005). Refer to cerebral ischaemia in pituitary apoplexy (Chap. 9) for more information. Alternatively, rupture of an intracranial aneurysm may mimic or even result in pituitary apoplexy (Shahlaie et al. 2006). Refer to mimicking conditions (Part VI) for other differentials.

8.4 Trends in Aneurysm Detection

In a study by Pant et al. (1997) of 467 patients with pituitary adenomas, 5.4 % ($n=25$) were found to have intracranial aneurysms as diagnosed by magnetic resonance imaging (MRI) and cerebral angiography. 97 % of these were found to have intracranial aneurysms within the anterior circulation, 92 % were incidental findings, 12 % had multiple aneurysms, and only 8 % presented with aneurysmal rupture. The association was most commonly observed among patients with nonfunctioning adenomas (8.8 %) and least frequent among those with a prolactinoma (2.4 %) which also reflected the influence of the age factor (Pant et al. 1997). Although the population distribution of intracranial aneurysms was not significantly different according to Oh et al. (2012), Jakubowski and Kendall (1978) report two-thirds of patients with acromegaly involved the cavernous carotid artery, whereas one-third of the aneurysms in the patients with chromophobe adenoma were thus located. Two patients in their study were found with cavernous aneurysms after treatment with local yttrium implantation for acromegaly.

Manara et al. (2011) reported that 67.5 % (27/40) of newly diagnosed aneurysms among patients with acromegaly (26/151) were located in the intracranial tract of the internal carotid artery (vs. 23–42 % in general population). 22.5 % were in the intracavernous segment compared to 2–9 % in the general population, 17.5 % (7/40) were detected at the level of the middle cerebral artery (MCA; vs. 30–42 % in general population), whereas 15 % (6/40) were found in the ACA (vs. 24 % in general population), but none within the vertebrobasilar circulation (vs. 10 % in general population).

8.5 Causal Relationships Between Pituitary Adenoma and Intracranial Aneurysm Formation

Pituitary adenoma-related intracranial aneurysms are hypothesised to occur due to mechanical compression (or invasion) of the regional arteries by the tumour, vasculopathy, microcirculatory, and haemodynamic changes in the regional vessels near the adenoma, skull base deformities, endocrine dysfunction that potentially induces fibromuscular dysplasia of arterial walls (e.g. multiple endocrine neoplasia syndromes) and specific hormonal factors associated with GH-secreting adenomas (usually macroadenomas) having a predisposing influence on aneurysmal formation in up to 50 % secondary to vascular disease (Jakubowski and Kendall 1978; Cardoso and Peterson 1984; Acqui et al. 1987; Weir 1992; Adachi et al. 1993; Bulsara et al. 2007; Manara et al. 2011). Furthermore, the fact that larger aneurysms are often adjacent to pituitary tumours suggests a direct, local effect of growth hormone in addition to generalised arteriectasia (Weir 1992). Additionally, those with multiple endocrine neoplasia syndrome type 1 (MEN-1) are likely associated with Marfanoid pathomorphology or von Recklinghausen's disease which includes vascular abnormalities and medial necrosis of arterial walls which could contribute to cerebral aneurysm formation (Adachi et al. 1993). Wakai et al. (1979) reported the rate of coincidental intracranial aneurysms was 12 % in 25 cases of acromegaly, 8 % in 11 cases of prolactinomas and 3.4 % in their cases with nonfunctioning chromophobe adenomas. Furthermore, Jakubowski and Kendall (1978) calculated an incidence of 13.8 % for intracranial aneurysms associated with GH-secreting adenomas (4/29), 5.1 % with chromophobe adenomas (6/117) and no cases for basophilic adenomas (0/4). Bilateral aneurysms with pituitary adenomas have also been reported (Weir 1992).

Manara et al. (2011) showed that excess serum GH carried a significantly increased risk of developing intracranial aneurysms and that there is a positive correlation with poor disease control. 17.3 % (26/152) were found to have 40 newly diagnosed intracranial aneurysms with two patients having undergone aneurysm clipping due to previous SAH. 10.7 % (16/150) of the study population had a single aneurysm, 4.7 % (7/150) had two aneurysms, whereas 1.3 % (2/150) and 0.7 % (1/150) had three and four aneurysms, respectively. Otherwise, aneurysms in acromegaly do not correlate with comorbidities, previous pituitary surgery, radiotherapy, or imaging features of adenoma.

In one case of recurrent pituitary adenoma, development of an aneurysm was observed 17 years after the initial angiography. The change of haemodynamism is likely to have a key role in producing intracranial aneurysm (Fujiwara et al. 1991). Each of mycotic, iatrogenic, and traumatic aneurysms can also develop as complications of pituitary surgery (Weir 1992; Manara et al. 2011).

8.6 Clinical Presentation

The clinical features depend upon extent of tumour expansion, amount of blood extravasation into the subarachnoid space and degree of pituitary damage. The presentation of aneurysmal SAH and pituitary apoplexy can be similar, with both causing abrupt onset of headache, altered consciousness, sensorimotor visual symptoms (such as photophobia and ophthalmoplegia), aseptic meningism, seizures, paresis (secondary to localised vasospasm), state of hypoperfusion (due to carotid arterial compression against the clinoid process; Sadek et al. 2011) and pyrexia (Epstein et al. 1971; Cardoso and Peterson 1984; Laidlaw et al. 2003; Kim and Cho 2007; Rajasekaran et al. 2011; Tedd et al. 2012). The interval between the onset of headache and alteration of consciousness is longer in cases of pituitary apoplexy than aneurysmal SAH (Cardoso and Peterson 1984). Jefferson (1940) showed that invasion and intrinsic compression of structures within the cavernous sinuses will inevitably lead to oculomotor paresis (presenting

as diplopia and paralysis) and trigeminal sensory neuropathy (presenting as anaesthesia). Refer to clinical features of pituitary apoplexy (Chap. 7) for more information.

Patients should routinely undergo neuro-ophthalmic evaluation pre- and postoperatively by the same neuro-ophthalmological team. Visual acuity should be assessed using a Snellen's chart and Ishihara plates for colour vision. Global visual fields can be assessed at bedside with red-headed pin for peripheral vision and a white-headed pin for central scotomas. Otherwise more accurate evaluations can be obtained using automated perimetry. Extraocular muscular function should be assessed to exclude ophthalmoplegia and diplopia, and fundoscopy must be carried out in all cases to exclude other ophthalmological pathologies as well as papill-oedema secondary to raised intracranial pressure from a growing haematoma. Refer to visual acuity, eye movements, and visual fields (Chap. 10) and visual outcome following pituitary apoplexy (Chap. 11).

8.7 Laboratory Investigations

All patients with suspected pituitary apoplexy and SAH must be investigated with both general and specific biochemical tests.

Blood testing: Depending on the severity and the duration, even basic tests can offer useful information but may risk delaying appropriate intervention.

(a) Haematological: Microcytic anaemia (reduced haemoglobin and mean cell volume) as sign of decompensated intracranial haemorrhaging, as well as possible pleocystosis (Sadek et al. 2011).
(b) Electrolytes: Electrolyte disturbances reflecting hypopituitarism including hypernatremia (which may also be an effect of syndrome of inappropriate antidiuretic hormone [SIADH]) should be identified early and corrected.
(c) Endocrine profile: Endocrine testing is necessary to exclude pituitary dysfunction by measuring for deficiencies in ACTH, cortisol, oestrogen, testosterone, FSH, LH, TSH, T4, GH, prolactin and IGF-1 (Tedd et al. 2012). Functioning pituitary adenomas may increase hormone concentration, whereas apoplexy will often decrease their serum concentrations.

Refer to preoperative endocrine function and fluid electrolyte balance (Chap. 12) for more information.

Cerebrospinal fluid (CSF) sampling:

1. A lumbar puncture will often be indicated to determine opening and closing pressure and CSF constituents which can exclude intracranial haemorrhaging and hydrocephalus except for those at normal pressure.
2. Xanthochromia (pink-, orange- or straw-coloured CSF) may indicate haemolysis including the presence of bilirubin, which would be consistent with SAH. CSF should undergo microscopy (red blood cells that may also be seen in a traumatic tap as well as intracranial haemorrhaging), biochemistry (especially glucose, protein, bilirubin, and lactate dehydrogenase), cytology, and microbiology.

8.8 Imaging

1. Plain radiograph: Presence of an enlarged sella turcica on plain skull radiographs should raise the suspicion of pituitary apoplexy in patients presenting with symptoms or signs suggestive of SAH or meningitis (Fitz-Patrick et al. 1980; Cardoso and Peterson 1984). However, this modality of imaging is now rarely used for the above purpose.
2. Computerised tomography (CT): CT scanning is useful not alone in the pre- and postoperative assessment but as well as a prognostic indicator (Wohaibi et al. 2000). CT can delineate the spread and severity of haemorrhage in the subarachnoid space (Cardoso and Peterson 1984). This modality safely and rapidly demonstrates a suprasellar mass and, after infusion with contrast medium, may show a peripheral ring-like enhancement consistent with a necrotic pituitary adenoma (Fitz-Patrick et al. 1980). Conversely, diagnosing patients presenting with symptoms of apoplexy can be further complicated by CT

appearance of a suprasellar mass often being indistinguishable between suprasellar aneurysm and pituitary tumour (Laidlaw et al. 2003). Recently, 3-dimensional CT angiography has become more popular in the detection of intracranial aneurysms as well as in the detection of vasospasm after SAH associated with pituitary apoplexy (Sanno et al. 1999). It has been suggested that CT performed within 4 days after SAH can offer important information for predicting cerebral vasospasm (Mizukami et al. 1980). Furthermore, a dedicated pituitary CT scan is indicated if the MRI scan is either contraindicated or not possible (Rajasekaran et al. 2011).

3. Magnetic Resonance Imaging (MRI): MRI and magnetic resonance angiography (MRA) are the optimal imaging modalities for delineating pituitary tumours, apoplexy and associated haemorrhage. UK guidelines recommend this modality (Satyarthee and Mahapatra 2005; Rajasekaran et al. 2011; Tedd et al. 2012). MRI should be the initial diagnostic study in patients with symptoms of a parasellar mass and in differentiating parasellar aneurysms from pituitary tumours, with support from CT imaging and angiography (Hirsch et al. 1988). MRI and MRA were used to assess the coexistence of intracranial aneurysms in 800 patients with surgically confirmed pituitary adenoma (Oh et al. 2012). A neuroradiological assessment to exclude subclinical intracranial aneurysms, especially of the Circle of Willis, in patients with acromegaly is supported by a number of authorities (Manara et al. 2011).

   MRI is superior to CT in the diagnosis of pituitary tumours, distinguishing them from aneurysms (Laidlaw et al. 2003) as well as eliciting associated haemorrhage or infarction (Wohaibi et al. 2000). Furthermore, MRI may elicit consequential oedematous or haemorrhagic thickening of surrounding structures, including the optic tract. Contrast-enhanced MRI may also reveal the site of rupture within the tumour capsule (Wohaibi et al. 2000) as well as defining the arterial anatomy to exclude all but very small coexistent and subclinical aneurysms (Weir 1992).

4. Angiography: Angiography has been used to elicit intratumoral haemorrhage, SAH, and associated intracranial aneurysms (Hori et al. 1982; Majchrzak et al. 1983; Cardoso and Peterson 1984; Gazioğlu et al. 2002; Bao et al. 2007). It is the optimal imaging modality for diagnosing and excluding aneurysms (Laidlaw et al. 2003). However, carotid arteriography is the most certain and systematic way to evaluate suprasellar masses and differentiates pituitary tumours from aneurysms (Houdart et al. 1975; Bulsara et al. 2007). Since associated intracranial aneurysms may be subclinical, one important reason for routine angiography in patients with pituitary tumours is to reveal incidental aneurysms (Jakubowski and Kendall 1978).

   Importantly, cerebral angiography should be performed in cases where MRI elicits carotid artery or intracranial aneurysms associated with pituitary adenoma (Fujiwara et al. 1991; Pant et al. 1997) to help differentiating SAH of aneurysmal origin and that caused by pituitary apoplexy (Satyarthee and Mahapatra 2005). Small or clinically occult aneurysms can be identified on an MRA and confirmed with contrast arteriography or intraoperatively (Hermier et al. 1994), particularly in patients with angiogram-negative SAH and visual symptoms (Satyarthee and Mahapatra 2005). Digital subtraction angiography can also be utilised, particularly for intrasellar aneurysms to avoid potentially fatal iatrogenic surgical trauma (Sade et al. 2004).

   The sensitivity and specificity of angiography do not reach 100 % as false negatives have been reported. Approximately 15 % of patients with SAH have negative angiograms (Sergides et al. 2009). Bjerre et al. (1986) reported a case series of ten consecutive patients with SAH of unknown cause who were examined for sellar abnormalities and pituitary dysfunction. All were diagnosed with SAH after confirmation on clerking, the presence of blood in CSF on lumbar puncture and CT scanning. Additionally, four-vessel angiography was performed in all patients with five requiring repeat angiography. With respect to follow-up, endocrinological assessment was performed after the initial angiography, and any abnormal findings were reassessed 3 months later

together as well as high-resolution CT scan of the sellar area. Whereas suboptimal growth hormone secretion with or without low plasma concentrations of sex hormones was found in 7 patients, one patient with panhypopituitarism had a spontaneous development of a partly empty sella from an adenoma with suprasellar extension leading to pituitary apoplexy with resulting SAH. Further, the sella was enlarged in three patients, and four patients had at follow-up a partially empty sella. Hence, haemorrhagic necrosis in a pituitary adenoma is an important cause of SAH with normal angiography.

8.9 Initial Management

Initial management consists of intravenous fluids for electrolyte replacement and intravenous steroid replacement (Rajasekaran et al. 2011) to treat adrenal insufficiency in those with pituitary apoplexy. Guidelines state that the patient must be referred early to a tertiary centre for combined care from neurosurgical, endocrine and ophthalmology specialties with access to high-dependency units (Rajasekaran et al. 2011; Tedd et al. 2012). Transsphenoidal surgery has only been suggested especially if there is rapidly progressive deterioration in vision or level of consciousness; but there has been much resistance due to increased risk of iatrogenic aneurysmal rupture intraoperatively and massive haemorrhaging leading to medicolegal problems (Wohaibi et al. 2000; Laidlaw et al. 2003; Sade et al. 2004; Tedd et al. 2012). In such cases, a dedicated pituitary surgeon (rather than the on-call team) must weigh out the benefits and risks for each individual patient with the judicious use of evidence-based medicine. Refer to conservative versus surgical decompression for pituitary apoplexy (Chap. 2) for more information.

8.10 Surgery

Recognition of the relationship between pituitary adenoma, apoplexy, SAH, and intracranial aneurysm has important clinical implications which should modify the surgical approach (Hermier et al. 1994). In particular, patient selection and thorough preoperative radiological assessment for accurate delineation of pathology are vital. Revuelta et al. (2002) described a case in which an incidental left carotid aneurysm was elicited during the preoperative evaluation of a nonfunctioning pituitary adenoma. Both lesions were treated concomitantly through a left supraorbital minimally invasive approach after MRI and angiography delineated their anatomy. As there were no postoperative sequelae, careful patient selection may lead to successful treatment of concurrent conditions through a minimally invasive approach, resulting in low morbidity, shorter hospital stay, and overall better postoperative outcome.

On the other hand, Matsuno et al. (1993) described a patient with severe SAH due to iatrogenic injury of the intradural internal carotid artery during or immediately after transsphenoidal surgery for pituitary adenoma. An autopsy in this case discovered that a small branch was strongly adherent to the suprasellar portion of the tumour capsule which may have been avulsed during the intracapsular resection of the tumour. This highlights the importance of accounting for SAH secondary to arterial trauma as a complication of pituitary adenoma resection via a transsphenoidal approach, albeit rare.

Pituitary adenomas can only be safely excised via a transsphenoidal approach if the precise location of an intracranial aneurysm is known and it is unruptured; otherwise, this approach should be avoided as this can lead to the rupture of the aneurysm (Bulsara et al. 2007). Significant greater improvement in visual acuity and visual field defects (but not ocular paresis) has been reported in patients who had early surgery within 8 days (Randeva et al. 1999). UK guidelines state that surgery should be performed preferably within the first 7 days of onset of symptoms (Rajasekaran et al. 2011). Simultaneous treatment of both lesions is often recommended via a craniotomy, particularly if there is any suspicion of recent aneurysmal rupture (Laidlaw et al. 2003). Heiskanen and Poranen (1987) suggested that, if pituitary tumours and aneurysms are found concurrently, a subfrontal approach should be preferred to the transsphenoidal approach.

The simultaneous treatment of the pituitary adenoma with aneurysm is also recommended through frontotemporal approach by Fujiwara et al. (1991). Priority of surgical intervention for each lesion depends on the individual clinical scenario and severity of symptomatology. If the pituitary adenoma is not causing neurological compromise or drastically affecting the patient's quality of life, then complete endovascular obliteration of an associated aneurysm may be achieved using Guglielmi detachable coils, and the patency of the internal carotid artery maintained before resecting the pituitary adenoma via a transsphenoidal microsurgical approach months later (Sade et al. 2004). Refer to management (Part VII) and complications (Part VIII) for more information.

However, it is important to remember that patients with pituitary adenoma undergoing surgery and radiotherapy ($n = 334$) have an increased risk of cerebrovascular mortality compared to the general population (Brada et al. 2002). The relative risk of mortality from SAH in these patients was 5.51 (95 % CI 1.14–16.09).

Conclusion

Pituitary apoplexy is a rare medical and surgical urgency, as early surgery within the first week of apoplectic ictus is adequate according to recent literature, resulting from ischaemic or haemorrhagic necrosis of an existing pituitary adenoma that could result in SAH. Patients present with sudden-onset severe headache, reduced consciousness, visual loss, and meningeal irritation to name a few symptoms. 32 confirmed cases have been confirmed in medical literature. There is also an association with increased risk of intracranial aneurysm and hence SAH after rupture.

It is vital to confirm the diagnosis preoperatively between pituitary apoplexy and SAH to avoid unnecessary and risky surgical intervention which could cause iatrogenic aneurysmal rupture. Importantly, transsphenoidal excision of a pituitary adenoma risks rupture of an unidentified intracranial aneurysm. Therefore, a patient with pituitary apoplexy can only be safely operated using transsphenoidal or endoscopic technique after exclusion of ruptured or unruptured intracranial aneurysm via MRA or preferably conventional angiography. However, MRA may be used for differential diagnosis if there is progressive deterioration in vision or level of consciousness in spite of potential of misdiagnosis in the preoperative period.

This chapter reviews the epidemiology, pathophysiology, symptomatology, investigations, and management of pituitary adenomas, intracranial aneurysms, and SAH.

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Cerebral Ischaemia in Pituitary Apoplexy

9

Sandeep Mohindra

Contents

Abbreviations

ACA	Anterior cerebral artery
CT	Computed tomography
CTA	Computerized tomographic angiogram
ICA	Internal carotid artery
MCA	Middle cerebral artery
SAH	Subarachnoid haemorrhage

9.1 Introduction

Pituitary apoplexy (Fig. 9.1) can cause narrowing of intracranial vessels either by mechanical obstruction due to an enlarged suprasellar mass (Rosenbaum et al. 1977) or by cerebral vasospasm (Cardoso and Peterson 1983). Exact incidence of cerebral vasospasm in pituitary apoplexy remains far from established owing to rarity of such an event. Asymptomatic vasospasm in pituitary apoplexy or sellar surgery remains underestimated (Lomban et al. 2006). Only a few cases become symptomatic owing to development of delayed ischaemic neurological deficits, consequent to infarct formation.

9.2 Pathophysiology

Pathophysiology of vasospasm following pituitary apoplexy remains unknown. Transdiaphragmatic rupture of the sellar tumour into the subarachnoid space is the most probable cause behind vasospasm. Documented cases of

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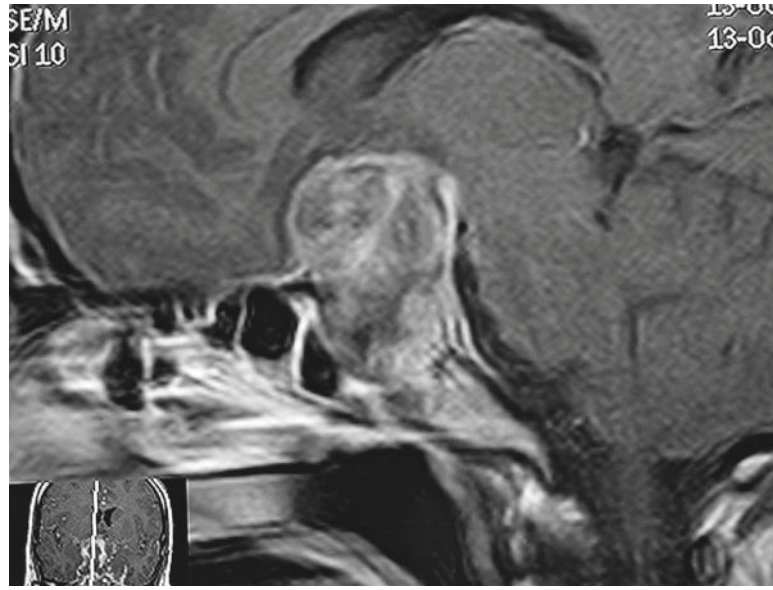

Fig. 9.1 Sagittal section of contrast-enhanced MRI scan showing apoplexy within pituitary tumour

cerebral infarction in consequence to pituitary apoplexy are a few (Mohindra et al. 2010).

As discussed earlier, mechanical obstruction has been cited by many authors as an important cause behind development of ischaemic neurological deficits. As intra-tumoural pressures in comparison to arterial pressures have not been documented, this theory is far from facts and remains a mere presumption.

Totally occluded great vessels as visualized on angiograms have been attributed to mechanical obstruction by the authors. Nevertheless, such an angiogram may be seen on account of severe vasospasm also, and hence, both theories go hand in hand in explaining ischaemic neurological deficits.

Closed loop of circle of Willis is bonded by internal carotid artery (ICA) and anterior cerebral artery (ACA) and should bear the brunt of mechanical occlusion in cases of pituitary apoplexy and raised intra-tumoral pressures. Middle cerebral artery (MCA), being not a part of closed loop, escapes mechanical brunt. However, partial occlusion of ICA may cause MCA territory ischaemia, especially when MCA being an end artery while ACA has dual supply.

Vasospasm as the pathophysiology behind cerebral ischaemia, in cases of pituitary apoplexy, assumes importance owing to significant number of patients demonstrating subarachnoid bleed on CT scans (Mohindra et al. 2010). Literature has described ten such cases and subarachnoid haemorrhage (SAH) on CT scans was evident in four cases (Mohindra et al. 2010).

9.3 Presentation

Pituitary apoplexy usually does not present with focal neurological deficits or side preponderance. Henceforth, new-onset focal neurological deficits or side preponderance in association with clinical features of pituitary apoplexy indicates cerebral ischaemia superimposed upon apoplexy. Focal neurological deficits like hemiparesis, dysphasia or frontal lobe syndrome have been described as the presenting features (Mohindra et al. 2010).

Whenever ischaemic insult is suspected, urgent CT scan of brain may be performed (Figs. 9.2 and 9.3). CT scan may demonstrate florid subarachnoid bleed in association with haemorrhagic mass in sellar-suprasellar region. As clear diagnostic criteria are not available, digital subtraction angiogram may be performed to delineate the exact site of occlusion. None of the reported cases have performed computerized tomographic angiogram (CTA), but CTA may be considered in the present era owing to its non-invasive nature. Varying sites of cerebral infarction have been described. These include ACA

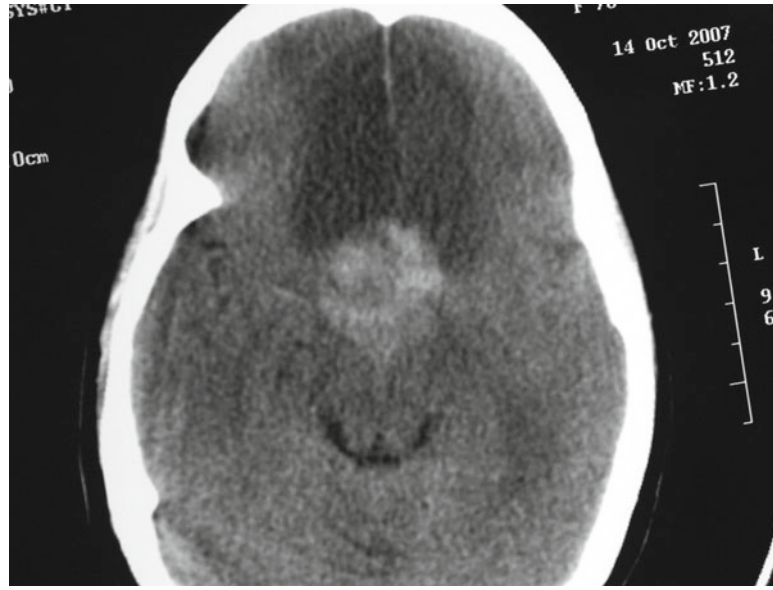

Fig. 9.2 Axial section of plain CT scan showing apoplectic pituitary tumour and spillage of blood in bilateral Sylvian fissures suggestive of subarachnoid bleed

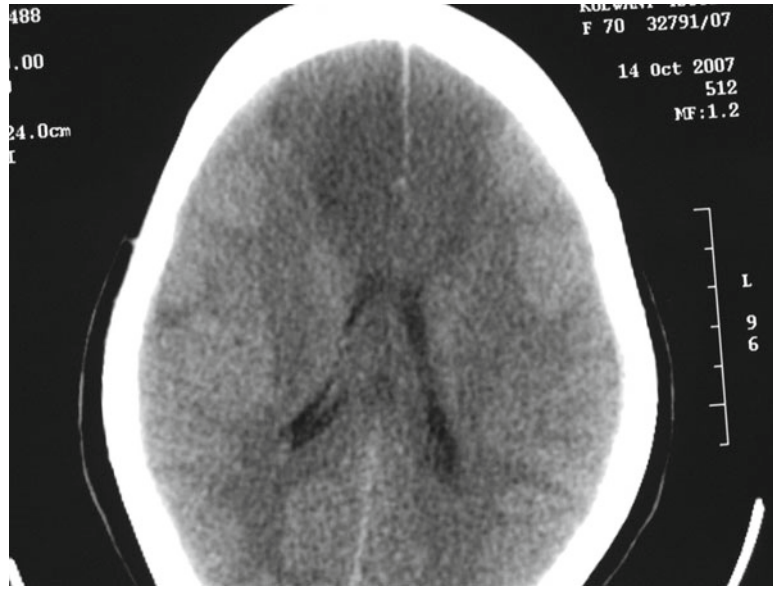

Fig. 9.3 Axial section of plain CT scan showing hypo-densities in bilateral ACA territories visualized after 72 h of pituitary apoplexy

territory, MCA territory, areas of deep nuclei and even multiple cortical regions.

9.4 Management

The management is aimed at apoplectic sellar tumour, rather than ischaemic cerebral territories. In none of the reported cases, any surgical intervention like decompressive craniectomy was performed for ischaemic supratentorial infarction so as to prevent transtentorial herniation.

Early trans-nasal or endoscopic approach to sellar apoplectic tumour is warranted and should be performed.

9.5 Outcome

Half of the reported cases expired and hence such a complication harbingers poor prognosis. Further, only one case has been described with favourable outcome, while the rest four had partial recovery.

Conclusion

Symptomatic cerebral ischaemia in cases of pituitary apoplexy remains a rare event, and asymptomatic cases are common but do not carry any clinical importance. Clinicians should remain alert in noting focal neurological deficits owing to cerebral ischaemia in such cases of pituitary apoplexy as these cases warrant early surgical intervention for pituitary tumour. Apoplectic pituitary tumour having subarachnoid bleeding should always alert clinicians for possible vasospasm and cerebral ischaemia. Once symptomatic ischaemia is noted, the outcome deteriorates dramatically and asks for a cautioned approach to the patient and his or her relatives.

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Part V

Visual and Endocrine Assessment

Visual Acuity, Eye Movements and Visual Fields

10

Thomas Michael Jenkins and Ahmed Tahir Toosy

Contents

Abbreviations

CF	Counting fingers
HM	Hand movements
LogMAR	Logarithm of the minimum angle of resolution
NPL	No perception of light
PL	Perception of light

10.1 Introduction

Pituitary apoplexy remains a diagnostic challenge. In the majority of cases, there is no known history of pituitary tumour to alert the clinician. Most patients present with a sudden-onset "thunderclap" headache, for which more familiar and common diagnoses, such as aneurysmal subarachnoid haemorrhage, infective meningitis or migraine are often initially considered more likely by the assessing doctor. Associated features such as vomiting and abnormalities of consciousness may not help discriminate pituitary apoplexy from some of the other diagnostic possibilities. Therefore, a reduction of visual acuity, the presence of a characteristic visual field defect (e.g. bitemporal hemianopia or bitemporal superior quadrantanopia) or ophthalmoparesis can be helpful in localising the pathology to the parasellar region. In this chapter, we consider reduction of visual acuity, visual field defects and ophthalmoparesis in the context of acute pituitary apoplexy, taking each symptom in turn. We consider how often each clinical feature is

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seen in patients with acute apoplexy and perform a new meta-analysis of the literature, with the aim of providing more accurate estimates of the frequency of clinical involvement of each structure. In this chapter, we discuss the influence of visual involvement on management and prognosis.

10.2 Typical Clinical Features

A "classical" presentation of pituitary apoplexy might be a male in his early 50s with no known history of pituitary tumour (but perhaps with symptoms and signs of pituitary dysfunction on careful systemic inquiry), complaining of a sudden-onset headache associated with vomiting, followed within a few hours by meningism, diplopia and visual loss. A marked reduction in acuity, bitemporal hemianopia and ophthalmoparesis could be present on examination.

In other cases, patients may present *in extremis*, for example, comatose and hypotensive. There are also a number of less common, but well recognised, features of pituitary apoplexy. These include facial pain, facial sensory loss and hemiparesis. Epistaxis can result from inferior extension of pituitary haemorrhage through the sella. Horner's syndrome, optic atrophy and occasionally optic nerve swelling may be found at the time of presentation.

Subacute presentations can occur, characterised by a longer history of milder symptoms and signs. "Subclinical" presentations are recognised too, characterised by radiologically or pathologically proven pituitary haemorrhage without associated acute clinical symptoms. These syndromes are generally considered distinct from the usual clinical definition of acute pituitary apoplexy by most authors. Therefore, we will not include subacute or "subclinical" cases in the following discussion, except where explicitly stated.

10.3 Applied Neuroanatomy of Pituitary Fossa

In order to understand the patterns of clinical deficit associated with pituitary apoplexy, it is necessary to have a working knowledge of the anatomy of the parasellar region (Fig. 10.1). The pituitary lies in the sella turcica in close proximity to the optic chiasm and optic nerves, which lie superiorly and anteriorly, and the cavernous sinuses, which lie laterally in the same axial plane. The cavernous sinuses contain the oculomotor (CN III), trochlear (CN IV) and abducens (CN VI) cranial nerves, as well as the ophthalmic and maxillary divisions of the trigeminal nerve. The abducens nerve lies free within the sinus. The oculomotor and trochlear nerves are situated within the lateral wall.

Loss of visual acuity is due to damage to the afferent visual pathway, usually to either the optic chiasm or optic nerves. Damage to fibres subserving the macular region usually has a significant impact on acuity, whereas loss of fibres innervating the peripheral retina results in peripheral field defects which are sometimes not noticed by the patient. Diplopia and ophthalmoparesis result from damage to the oculomotor, trochlear and abducens nerves either singly or in combination. Oculomotor nerve damage can result in ptosis and pupillary dilatation.

Facial pain or sensory loss may result from damage to the trigeminal nerve, most frequently the ophthalmic branch. Horner's syndrome may occur due to involvement of sympathetic fibres which accompany the ophthalmic division of the trigeminal nerve. Hemiparesis can be due to anterior circulation stroke either from compression of the carotid siphon against the anterior clinoid process or through compression of the intracavernous segment of the carotid artery. Coma may result from extension of blood into the subarachnoid space or compression of the hypothalamus or brainstem.

10.4 Neuro-ophthalmological Signs in Acute Pituitary Apoplexy

The literature describing the clinical features of pituitary apoplexy consists of a large number of small, mainly retrospective case series, reflecting the rarity of the condition. The frequency of neuro-ophthalmological signs reported in patients with apoplexy varies widely between studies. In this chapter, we have attempted to

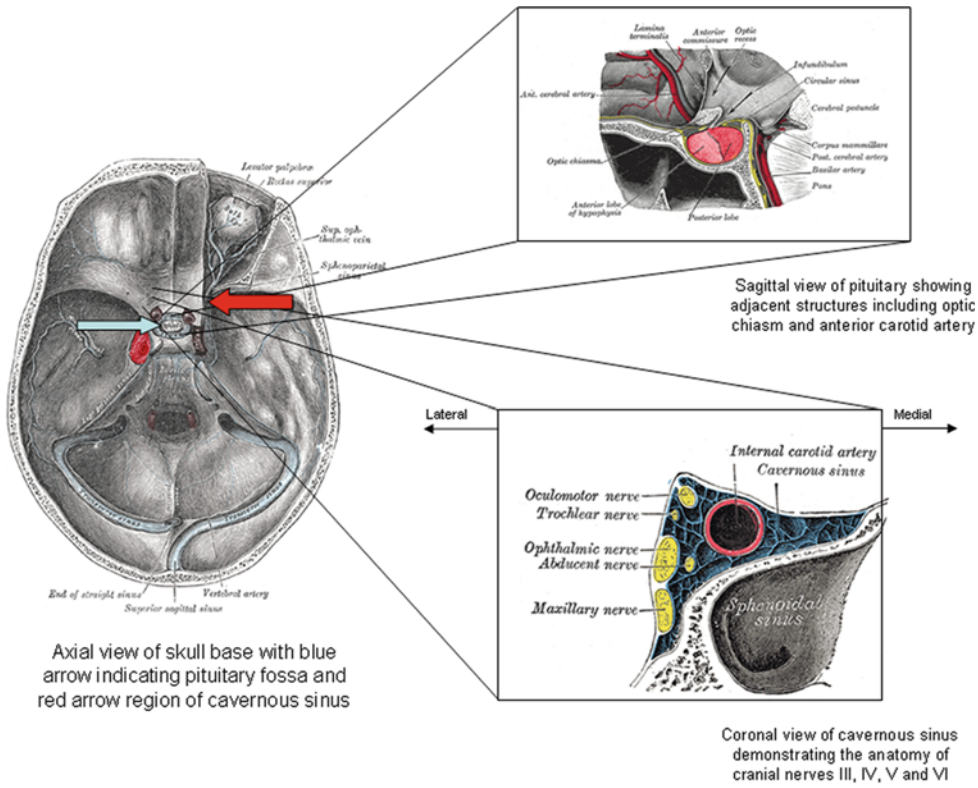

Fig. 10.1 Anatomy of the pituitary fossa and cavernous sinus (Adapted with kind permission from Gray (1918); Bartleby.com, 2000. www.bartleby.com/107)

estimate the prevalence of each neuro-ophthalmological feature by combining data from these series. This approach is limited by differing methodologies in the various studies. We have aimed to limit heterogeneity by including only patient groups presenting with an acute apoplectic syndrome and have excluded pathologically defined cases in which the time course of the symptomatology was unclear and could have included "subclinical" cases. The various studies are summarised in Table 10.1. We will discuss some of the larger case series in more detail in the following sections, after a brief description of a clinical approach to neuro-ophthalmological examination.

10.4.1 Loss of Visual Acuity

Examination: In routine clinical practice, visual acuity is most commonly measured using a Snellen chart comprising a series of letters for the patient to read which gradually decrease in size. Good vision is documented 6/6 in the UK, referring to the 6 m distance at which one of the lower lines of letters should be legible. In the USA, the same acuity is documented 20/20, referring to the equivalent distance measured in feet. If a patient's vision is so poor that they are only able to read the largest letter on the top line of the chart at 6 m, acuity is documented as 6/60 or 20/200. If even reading the top letter at 6 m proves impossible, the chart is moved closer. Reading the top letter at 1 m is documented 1/60 or 3/200. Acuities worse than this are consecutively described as counting fingers (CF), hand movements (HM), perception of light (PL) or no perception of light (NPL). Alternative scoring methods exist, such as logMAR (logarithm of the minimum angle of resolution), which are often used in research practice. Letter characteristics, for example, spacing, are more standardised in this system, but the principles are otherwise identical. LogMAR scores of 0, 1 and 1.7 correspond to 6/6, 6/60 and NPL, respectively.

Table 10.1 Summary of case series of patients with pituitary apoplexy which reported prevalence of neuro-ophthalmological features (percentages in brackets)

Study group	No. of patients in study	No. of patients with sign (%)		
		Reduced acuity	Field defects	Ophthalmoparesis
Brougham et al. (1950)	5	1/3 (33 %)	0/3 (0 %)	3/4 (75 %)
Epstein et al. (1971)	5	5/5 (100 %)	2/5 (40 %)	1/5 (20 %)
Rovit and Fein (1972)	9	3/9 (33 %)	2/9 (22 %)	8/9 (89 %)
Lloyd and Belchetz (1977)	3	2/3 (67 %)	2/3 (67 %)	2/3 (67 %)
Weisberg (1977)	14	NR	12/12 (100 %)	5/14 (36 %)
Wakai et al. (1981)	38	30/38 (79 %)		6/38 (16 %)
Muller-Jensen and Ludecke (1981)	58	32/58 (55 %)		24/58 (41 %)
Symon and Mohanty (1982)	7	5/7 (71 %)		6/7 (85 %)
Mohr and Hardy (1982)	4	2/4 (50 %)	3/4 (75 %)	3/4 (75 %)
Kaplan et al. (1983)	6	5/6 (83 %)	3/6 (50 %)	5/6 (83 %)
Tsitsopoulous et al. (1986)*	13	10/13 (77 %)	11/13 (85 %)	6/13 (46 %)
Ahmed et al. (1989)	13	13/13 (100 %)	8/13 (62 %)	NR
Seyer et al. (1989)	12	NR		11/12 (92 %)
Arafah et al. (1990)	8	7/8 (88 %)		4/8 (50 %)
Onesti et al. (1990)	16	9/16 (56 %)	11/16(69 %)	7/16 (44 %)
Fraioli et al. (1990)	13	7/13 (54 %)		6/13 (46 %)
Parent (1990)	11	9/11 (82 %)		7/11 (64 %)
McFadzean et al. (1991)	15	12/15 (80 %)	12/15 (80 %)	9/15 (60 %)
Vidal et al. (1992)	12	4/12 (33 %)	NR	7/12 (58 %)
Bills et al. (1993)	37	19/37 (52 %)	24/37 (64 %)	29/37 (78 %)
Bonicki et al. (1993)	39	17/39 (44 %)	8/39 (21 %)	Ptosis 15/39 (38 %) Diplopia 11/39 (28 %)
Maccagnan et al. (1995)	12	8/12 (67 %)	NR	9/12 (75 %)
Pliam et al. (1995)	2	0/2 (0 %)	0/2 (0 %)	2/2 (100 %)
Milazzo et al. (1996)	14	5/11 (55 %)	5/11 (55 %)	9/11 (82 %)
Da Motta et al. (1999)	16	10/16 (63 %)		9/16 (56 %)
Randeva et al. (1999)	35	23/35 (66 %)	25/35 (71 %)	24/35 (69 %)
Biousse et al. (2001)	30	11/30 (37 %)	14/30 (47 %)	17/30 (57 %)
Carral San Laureano et al. (2001)	9	7/9 (78 %)		3/9 (33 %)
Ayuk et al. (2004)	33	27/33 (82 %)		15/33 (46 %)
Sibal et al. (2004)	45	18/39 (46 %)	20/42 (48 %)	22/43 (51 %)
Semple et al. (2004)	62	35/57 (61 %)	21/49 (43 %)	26/60 (43 %)
Lubina et al. (2005)	40	19/31 (61 %)		16/40 (40 %)
Gruber et al. (2006)	30	18/30 (60 %)	10/30 (33 %)	15/30 (50 %)
Nielsen et al. (2006)	23	9/23 (39 %)	NR	16/23 (70 %)
Dubuisson et al. (2007)	24	12/24 (50 %)		13/24 (54 %)
Mou et al. (2009)*	83	69/83 (81 %)	41/83 (49 %)	9/83 (11 %)
Liu et al. (2010)	25	22/25 (88 %)		Ophthalmoparesis 3/25 (12 %) Diplopia 7/25 (28 %) Ptosis 5/25 (20 %)

(continued)

Study group	No. of patients in study	No. of patients with sign (%)		
		Reduced acuity	Field defects	Ophthalmoparesis
Simon et al. (2011)	23	11/20 (55 %)	10/21 (48 %)	14/23 (61 %)
		Afferent visual involvement 444/710 (63 %)		
Total	748	Reduced acuity 230/454 (51 %)	Field defects 192/382 (50 %)	375/727 (52 %)

Totals are calculated from studies in which pituitary apoplexy was defined as an acute clinical syndrome. Asterisked studies may include subacute or "subclinical" cases and have not been included in the meta-analysis of prevalence estimates
NR not reported

Regardless of the scoring system used, if visual impairment is identified, it is important to use a pinhole to correct any refractive errors and also to take a careful history for preexisting amblyopia.

Testing colour and low-contrast acuity using Ishihara plates or Sloan charts can increase sensitivity to detect mild optic nerve pathology, but visual loss in pituitary apoplexy is often marked and may be dramatic, so these techniques tend to be more useful in a less acute setting.

Relative afferent pupillary defects are not frequently reported in the apoplexy literature. This could be because the visual apparatus is commonly involved bilaterally at the chiasm. Oculomotor nerve damage may result in an efferent pupillary defect.

Reduction in visual acuity was noted in some of the earliest descriptions of pituitary apoplexy (Kux 1931) and was evident in two of the five cases from the original series describing the clinical syndrome (Brougham et al. 1950). In the accompanying postmortem pathological descriptions, compression of the right optic nerve against the overlying anterior cerebral artery was noted.

One of the early studies with a sizeable cohort came from a group in Tokyo and investigated the incidence of apoplexy in patients with pituitary tumours (Wakai et al. 1981). They reported a retrospective case series of 560 patients with pituitary tumours operated over a 30-year period. Ninety-three of these cases (16.6 %) had either clinical or surgical evidence of haemorrhage, but only 51 (9.1 %) presented with acute symptoms. They further subdivided this group into "major" and "minor" attacks. A major attack was defined as disturbance of consciousness, hemiparesis, visual loss or ocular palsy; there were 38 patients in this group (6.8 %). The other 2.3 % of patients with a minor attack had headache, nausea, vomiting or vertigo. Of the group with "major" symptoms typical of the clinical pituitary apoplexy syndrome, 79 % had visual loss, the nature of which was not specified.

Another study from the same year came from a German group (Muller-Jensen and Ludecke 1981). They investigated 586 surgical cases and found 72 with evidence of cystic necrosis with or without haemorrhage. Fifty-eight of these cases had clinical symptoms, and the authors report rates of 70 and 58 % visual disturbance depending on whether the tumour had ruptured or not. The nature of the visual disturbance was not defined further.

An important study from the USA focussed on clinical presentation and visual outcome (Bills et al. 1993). They studied 37 patients who presented with an acute syndrome characterised by abrupt onset headache and/or visual disturbance in the presence of a pituitary adenoma between 1975 and 1991. They reported reduced visual acuity in 52 %. All of the patients except one underwent transsphenoidal surgery. Visual acuity improved following surgery in 88 %, and surgery within a week of symptom onset was associated with better visual recovery. Two of three patients who presented with blindness (defined as CF or worse) improved to 20/20 following early surgery within a week; the third had delayed surgery and recovered to 20/80. The authors advocated

early neurosurgical intervention to optimise visual outcome.

A Polish study published the same year analysed 799 patients with pituitary adenoma, 14.4 % of whom had histological evidence of apoplexy and 5 % of whom presented with acute clinical apoplexy (Bonicki et al. 1993). Of the 39 patients with acute clinical apoplexy, 38 % reported blurred vision and 5 % sudden loss of vision. Visual loss and disturbance of consciousness were considered the main indications for surgery. Twenty-three patients were operated, 19 urgently. The authors reported full neurological recovery including visual deficits in 14/19. Two further patients made a partial recovery, one developed consecutive hypopituitarism and two patients died from cerebral oedema and hypothalamic damage. Sixteen patients without severe visual deficits were treated conservatively. The authors reported that some clinical improvement occurred in all members of this group but that a poor outcome resulted in several cases at long-term follow-up; this was not defined further.

A group from Oxford, UK studied 35 patients (Randeva et al. 1999). They reported a 66 % prevalence of reduced acuity. Four people were managed conservatively and none of these patients had ocular sequelae. Eighty-six percent of the surgically treated group improved, and outcome was found to be better in patients treated within 8 days, all of whom had complete resolution of acuity (defined as 6/6 or a return to premorbid acuity).

Another UK study is especially notable for pursuing a conservative management strategy in 40 % of the 45 patients studied (Sibal et al. 2004). In this series, decreased visual acuity was found in 46 % including four patients managed conservatively. Ninety-three percent of surgically treated patients had either complete or near-complete resolution of visual acuity but so did all four of the patients with visual loss in the conservative group. The authors advocated a conservative strategy in patients with mild neuro-ophthalmological signs.

Another British study supports this approach (Gruber et al. 2006). They reported complete blindness in 4 of their 30 patients, monocular blindness in 2 and reduced visual acuity in 12. Two-thirds of the patients were managed conservatively, including two of the six blind patients. Three of the blind patients regained partial vision, and this included the two in the conservative group.

The largest number of patients from a primary investigative study comes from a Chinese group (Mou et al. 2009). They reported 83 patients, of whom 81 % had visual loss. However, these patients were defined on the basis of histology at surgery and/or radiological features, rather than a clinical presentation with acute apoplexy, so is likely to have included patients with subclinical onset. For this reason, these patients have not been included in our prevalence estimate meta-analysis.

A fairly large joint South African-American clinical study of 62 patients found reduced visual acuity in 56 % of their patients overall (Semple et al. 2004). This figure rose to 61 % when patients were excluded if their vision could not be accurately assessed, for example, if comatose at presentation. The severity of visual dysfunction was graded by the authors. It was recorded as reduced but functional in 44 %, reduced and non-functional in 7 % and blind in 10 %. Ninety-five percent of these patients were treated surgically. Follow-up data was available for 55/62 patients at an average of 56 months. At this time, acuity was normal in 69 %, improved but not normal in 16 % and unchanged in 15 %. The six blind patients remained blind.

A Belgian group studied 24 patients (Dubuisson et al. 2007). Fifty percent of these patients had a visual deficit, which could have been either a reduction in acuity or a field defect. Twenty-one of the patients were operated, and 92 % of these patients' visual deficits resolved postoperatively.

A group from Taiwan studied the differences in patients presenting with clinical versus subclinical apoplexy (Liu et al. 2010). Sixty-five patients were identified with histopathological confirmation of pituitary haemorrhage at the time of surgery. Only 25 had symptoms consistent with acute pituitary apoplexy. In the other 40 there was radiological evidence of pituitary

haemorrhage. Visual impairment was defined as either a reduction in Snellen acuity or a field defect on automated perimetry performed by an ophthalmologist. This was present in 88 % of the clinical group and 70 % of the subclinical group. All patients were treated surgically. Vision improved in 64 % of the clinical group and 93 % of the subclinical group. Only the clinical group has been included in our meta-analysis.

Two studies have focused specifically on the neuro-ophthalmic manifestations of pituitary apoplexy, an early study by a Scottish group (McFadzean et al. 1991) and a recent study by an Australian group (Simon et al. 2011). McFadzean et al. (1991) quantified loss of vision in their group of 15 patients, 12 of whom had reduction in acuity. In four patients, it was mild (6/9–6/12), in one moderate (6/18–6/36), in one severe (6/60 to CF) and in four very severe (HM or less) emphasising the variability that is seen.

Simon et al. (2011) studied 23 patients. All except one presented as acute apoplexy. Reduced visual acuity was present in 55 % (11/20) of patients for whom data was available. Bilateral involvement was present in more than half (55 %). One patient was NPL. Eighteen patients were operated. After a median follow-up of 11 months, all of the patients with reduced acuity had made some visual improvement but this was complete in only 25 %.

A Turkish group focussed specifically on patients with severe visual impairment as a result of pituitary apoplexy and reviewed 186 cases published over the last century (Turgut et al. 2010). They selected patients with blindness, defined as NPL. In this group 69 % had monocular and 31 % bilateral blindness. Analysis of a surgically treated subgroup of 91 of these patients showed that vision improved in 75 % of eyes blind for less than a day prior to admission. The figure fell to 58 % for those blind for more than 1 day. However, the authors found no association between the time from symptom onset to surgery and the eventual visual outcome, suggesting that factors other than the absolute duration of visual loss may also be at play.

Other studies have reported conflicting results as to whether the duration of visual loss is associated with visual outcome; some have reported an association (Cohen et al. 1985; Maurer et al. 1999; Randeva et al. 1999) whilst others have not (McFadzean et al. 1991; Peter and de Tribolet 1995). One study reported that preserved light perception was a favourable prognostic factor (Parent 1990), and the authors of another small case series noted that complete blindness appeared a poor prognostic sign (Onesti et al. 1990). The optimal management of pituitary apoplexy remains controversial (Chanson et al. 2004), and it is apparent that visual acuity can sometimes improve following conservative management. Moreover, the timing of surgical intervention is still debated, as some authors reported that restoration of visual function may occur even when surgery is delayed (Onesti et al. 1990; Parent 1990). Based on several observational studies, it is clear that early surgical intervention, within 7 days of symptom onset, results in better visual outcomes (Randeva et al. 1999; Adams 2003; Agrawal and Mahapatra 2005; Sibal et al. 2004; Muthukumar et al. 2008; Nawar et al. 2008; Suri et al. 2008; Turgut et al. 2010). This suggests that significant damage to the chiasm and optic nerves occurs early and may be reversible if surgical decompression is performed within a week although further studies are needed to investigate this and its pathophysiological reasons. Nowadays, there is general agreement that the presence of severe visual symptoms is an indication for surgery, and this should be performed within the first week of apoplectic ictus in patients with sudden and severe visual deterioration (Cardoso and Peterson 1984; McFadzean et al. 1991; Bills et al. 1993; Randeva et al. 1999; Agrawal and Mahapatra 2005; Sibal et al. 2004; Muthukumar et al. 2008; Suri et al. 2008; Turgut et al. 2010).

Whilst reviewing the literature for this chapter, we performed a meta-analysis of the available data on prevalence of visual symptoms in patients with acute pituitary apoplexy (Table 10.1). Overall, 63 % percent of patients had some type of visual involvement. From the studies which distinguished between loss of acuity and peripheral field defects, 51 % had reduced acuity. This can be either monocular or binocular.

Therefore, it appears that whilst involvement of the afferent visual pathway is fairly common, it is by no means invariable in patients with acute apoplexy. It is clear that a prompt visual assessment should be performed when possible in all patients suspected of pituitary apoplexy as the presence of visual loss is a diagnostic clue, may directly influence early management and, to a degree, may inform prognosis.

10.4.2 Visual Field Defects

Examination: At the bedside, visual fields should be examined to confrontation using a red hat pin when possible. Peripheral red desaturation occurs before complete loss of the peripheral field. More detailed paraclinical assessment may be performed using static automated Humphrey perimetry or dynamic nonautomated Goldmann field analysis, which each offer a slightly different perspective. Goldmann perimetry tests peripheral vision to different size targets. Humphrey perimetry repetitively tests different points in the visual field with pinpoint light stimuli of varying luminance to determine a detection threshold. The latter technique produces quantitative data output including estimates of test reliability. Guidelines recommend formal visual field assessment using either Humphrey or Goldmann techniques within 24 h of suspected diagnosis of pituitary apoplexy in clinically stable patients (Rajasekaran et al. 2011).

A visual field defect may be central or peripheral. There are differences in how visual field defects are defined in the pituitary apoplexy literature. Some studies describe patients with "visual deficit" or "visual loss" as a composite measure that does not distinguish between reduced central acuity and peripheral field defects (Wakai et al. 1981; Dubuisson et al. 2007). Others report "partial loss of vision" (Bonicki et al. 1993), taken to imply a field defect. Other studies distinguish between loss of acuity and field defects, reporting them separately, and either define or imply that the term "visual field defect" applies to peripheral field defects, rather than loss of central acuity. For our meta-analysis, we differentiate between central acuity loss and visual field defects. We use the latter term synonymously with a peripheral field defect detected on confrontation or paraclinical testing and accepting that a peripheral field defect can, of course, occur together with central acuity loss in the same patient. This definition was chosen for pragmatic reasons in order to be consistent with most studies cited in the meta-analysis, but the resulting estimates may therefore include some heterogeneity in case definition.

A further caveat in interpreting the data on field defects is that, as with visual acuity, it is sometimes not easy to assess the fields in patients with apoplexy who present confused or comatose. When field defects are reported, their nature is not always clear. The "classical" defects resulting from extension of a pituitary mass encroaching on the optic chiasm from below are initially bitemporal superior quadrantanopia (Fig. 10.2) (Murad-Kejbou and Eggenberger 2009) and later bitemporal hemianopia. A minority of studies report the specific defects seen.

Semple et al. (2004) reported bitemporal hemianopia in 43 % of their 62 patients (in 13/62 the fields were not testable). Biousse et al. (2001) reported "chiasmatic field defects" in 47 %. Various other types of visual field defect are also seen. Simon et al. (2011) focussed on the neuro-ophthalmologic manifestations of apoplexy and reported that, when present, field defects were bilateral in 80 %. Bitemporal hemianopia was the commonest defect (50 %), homonymous hemianopia was seen in 20 %, and 10 % had generalised depression of the field. In a group of 16 patients with apoplexy, Onesti et al. (1990) reported five bitemporal hemianopias, one bilateral superior quadrantanopia, one unilateral temporal hemianopia and one right homonymous field defect.

McFadzean et al. (1991) provided a detailed description of the visual field defects present in 12/15 of their patients. Only 6/12 had a classical bitemporal hemianopia. Nine had central scotomata, five had nasal defects (three were bilateral), two had generalised constriction and two had a residual nasal island.

Of the larger studies reporting prevalence of field defects, Bills et al. (1993) found them in

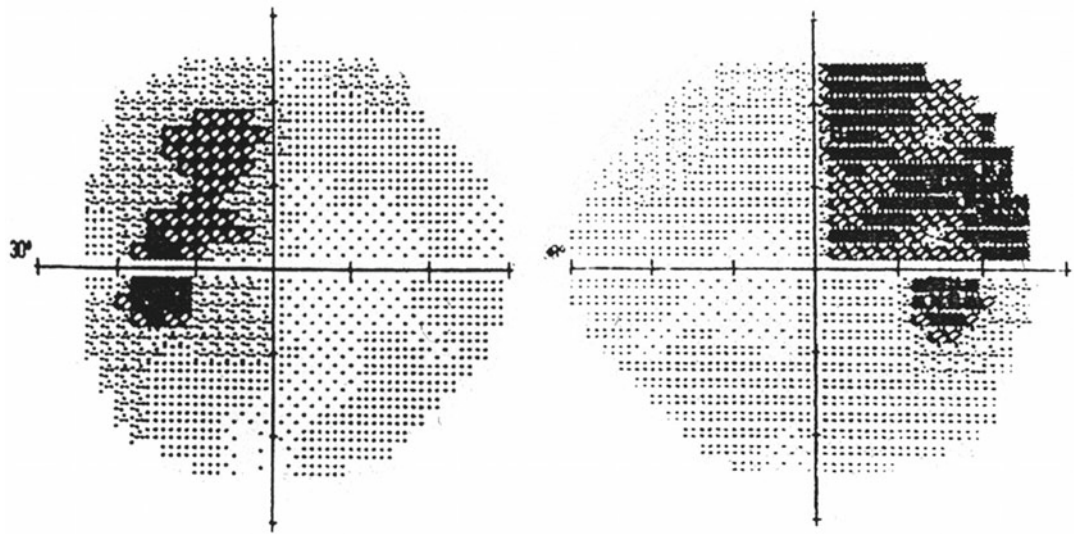

Fig. 10.2 Bitemporal superior quadrantanopia seen on Humphrey field examination (Image courtesy of James Acheson, University College London Hospital NHS Foundation Trust, United Kingdom)

64 % of their patients, Sibal et al. (2004) in 48 % and Mou et al. (2009) in 49 % (in this latter study, it should be noted that the patients were defined on radiological and pathological rather than clinical grounds); the nature of the field defects was not specified.

Improvement in field defects is frequently seen following decompressive surgery. Simon et al. reported field defects in 48 % of their 23 patients. Eighteen patients were operated. In the group of patients with field defects who were treated surgically, three recovered completely and five made a partial recovery. One patient got worse.

Randeva et al. (1999) found that 71 % of their 35 patients had visual field defects and 76 % of these improved following surgery. Improvement was more common if surgery was performed within 8 days (75 % versus 23 %). Onesti et al. (1990) reported field improvement following surgery in all of their 16 patients. Lubina et al. (2005) found field defects in 61 % of 40 patients, and improvement occurred following decompression in 81 %. Of six patients treated conservatively in this series, three had visual field defects and two people improved.

Sibal et al. (2004) studied a cohort with the highest rate of conservative treatment. They compared the outcome of visual field defects between surgically and conservatively treated patients in a group of 45 patients. Visual field data was available on 42 patients, of whom 20 (48 %) had a field defect. The authors noted that there was a statistically significant difference between the two treatment groups. Patients with significant field defects were more likely to be treated surgically. This is a bias common across the literature that makes assessment of the natural history of visual recovery following acute apoplexy difficult and complicates interpretation of surgical benefit. In the surgical group, eight patients had complete resolution of field defects (57 %), five had near-complete resolution (36 %) and one made no improvement (7 %). In the conservative group, three patients experienced complete resolution (75 %) and one patient near-complete resolution (25 %). It was unclear whether these differences were related to treatment effects or differences in the initial severity of visual loss.

In patients who undergo surgical intervention, guidelines recommend that visual fields, acuity and eye movements are assessed postoperatively within 48 h and should include Humphrey or Goldmann perimetry where possible (Rajasekaran et al. 2011).

Overall, the literature suggests that some improvement may be anticipated in visual field

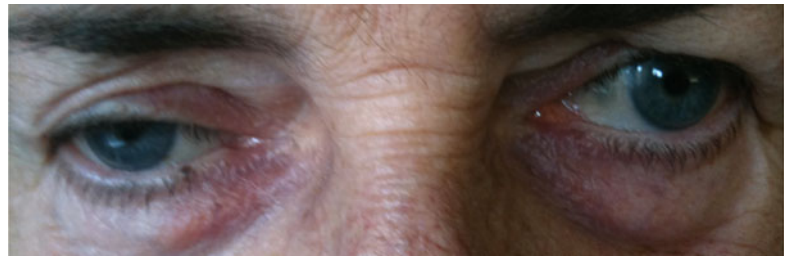

Fig. 10.3 Right oculomotor palsy in pituitary apoplexy (Reproduced with permission courtesy of Michael Powell)

defects following pituitary apoplexy but recovery may not be complete. Most patients with significant field defects are treated surgically and many improve. In the minority of patients with mild field defects treated conservatively, improvement occurs too but, because of surgical selection bias, it remains unknown whether this would be the case for more severely affected patients.

From our meta-analysis, 50 % of patients with acute pituitary apoplexy had some kind of visual field defect, a very similar prevalence to the number of patients who experienced loss of central acuity.

10.4.3 Optic Tract Involvement

Optic tract involvement can occur following pituitary apoplexy but appears relatively rare. Homonymous hemianopic field defects are certainly well recognised (Onesti et al. 1990; Simon et al. 2011), and theoretically the optic tracts could be compressed by superior extension of the intrasellar contents (Murad-Kejbou and Eggenberger 2009). However, surgical and pathological reports of direct optic tract damage are infrequent, and apparent homonymous field defects could also potentially be caused by bilateral damage to the anterior visual pathways. In case reports of optic tract damage following pituitary apoplexy, the field defects reported sometimes result from distinct haemorrhage within the optic tract of unclear mechanism, which could either be due to direct extension of blood from pituitary adenoma via the subarachnoid space or, alternatively, primary haemorrhage within an already ischaemic optic tract. Although on anatomical grounds one might expect incongruous homonymous field defects, the patients in these case reports usually have more extensive field defects implying more widespread visual pathway involvement. Examples include one patient with NPL acuity in one eye and temporal hemianopia with reduced visual acuity in the other (Kim and Cho 2007) and another patient with bilateral blindness to NPL in a patient with comorbid idiopathic thrombocytopenic purpura (Lenthall et al. 2001).

10.4.4 Ophthalmoparesis

Examination: The eyes should be observed in the primary position and eye movements examined to smooth pursuit, vergence and to rapidly alternating targets to assess saccades. The extraocular muscles work in pairs so, if one muscle of the pair is weak, deviation of the affected eye may be seen in the primary position. This deviation will be in the opposite direction to the action of the affected muscle and is called tropia. For example, if the right abducens nerve is damaged, the right lateral rectus muscle will be weak and the patient may have a right esotropia. This means that the right eye is deviated medially, pulled by the intact right medial rectus muscle. Conversely, in an exotropia the affected eye is deviated laterally and implies weakness of the medial muscles, for example, medial rectus weakness in oculomotor nerve palsy (Fig. 10.3). Hypertropia means the affected eye is deviated superiorly, for example, in trochlear nerve palsy as a result of a weak superior oblique muscle, when there may be also be a compensatory head tilt away from the side of the lesion. In hypotropia, the affected eye is deviated inferiorly, for example, due to weakness of superior rectus and inferior oblique in oculomotor palsy. Patients with subtle ophthalmoparesis may just manifest this deviation when the eye is

covered, detected clinically as a return to the primary position on uncovering the affected eye. If only evident on cover testing, this is known as exophoria if the deviation is lateral, esophoria if medial, hyperphoria if superior and hypophoria if inferior. However, in acute pituitary apoplexy the mechanism of injury to the nerves is such that any cranial nerve deficits involving eye movements are usually not so subtle. The compressive forces involved also suggest that, if oculomotor nerve palsy is present, pupillary involvement is likely, in contrast to "medical" causes of oculomotor nerve palsy in which the centrally located pupillomotor fibres are typically spared.

In their study of 37 patients, Bills et al. (1993) investigated the relative frequency of involvement of the cranial nerves. Seventy-eight percent of patients had ocular paresis. The oculomotor nerve was the most commonly affected nerve, seen in 57 %. The abducens nerve was involved in 30 % of patients, and the trochlear nerve was least frequently involved, seen in 13 %. It should be noted that this may reflect reporting bias as trochlear nerve palsy is the most difficult of these deficits to detect clinically, especially if a partial oculomotor palsy is also present (because downward gaze is a result of the action of both the superior oblique muscle, innervated by the trochlear nerve, and the inferior rectus muscle, innervated by the oculomotor nerve). In this study, all of the ocular pareses improved after surgery.

Semple et al. (2004) reported ocular palsy in 43 % of their 62 patients. Twenty percent had isolated oculomotor palsies, multiple cranial nerve palsies were found in 18 and 5 % had isolated abducens nerve palsies. It is well recognised that ophthalmoparesis may be unilateral or bilateral (Cardoso and Peterson 1984), but unilateral involvement appears more common from the reported case series when specified.

A Belgian group reported 54 % prevalence of ophthalmoparesis in their 24 patients (Dubuisson et al. 2007). Of these 13 patients, nine had a complete oculomotor palsy, seven had ptosis (presumably from partial involvement of the superior oculomotor fibres supplying the levator palpebrae superioris) and one had an abducens nerve palsy. Eighty-five percent of these deficits resolved following treatment.

Lubina et al. (2005) found that 40 % of their 40 patients had ocular paresis. Seventy-one percent improved following surgery. Of six patients in their series treated conservatively, two had ocular paresis and one recovered.

Simon et al. (2011) reported 61 % cranial nerve palsies from their series of 23 patients from Australia. There were a large number of different combinations of ophthalmoparesis, the most common of which was oculomotor palsy (29 %), then abducens palsy (21 %). All three nerves were involved in 14 %, and the oculomotor and trochlear together, oculomotor and abducens together and trochlear and abducens together each were seen in a single patient (7 %). All of these patients had made some improvement by a median of 11 months follow-up.

Randeva et al. (1999) reported ocular paresis in 69 % of their 35 patients. Sixty-seven percent had oculomotor nerve involvement, 29 % abducens and 4 % trochlear. Although this study found that early surgery within 8 days, performed in the majority of patients, was associated with improvement in acuity and field defects, no statistically significant difference in outcome of ocular paresis was found. Ninety-one percent of the surgically treated patients improved and so did 84 % of the conservative group.

Sibal et al. (2004) reported ophthalmoparesis in 51 % of their patients. They also found that an isolated oculomotor palsy was the commonest form of ophthalmoparesis – seen in 21 % – followed by combined oculomotor and abducens palsies (12 %), isolated abducens (9 %) and combined oculomotor, trochlear and abducens nerves (9 %). The presence of ocular palsy was no different in the surgical and nonsurgical groups. After a median follow-up of 49 months, complete resolution was seen in 75 % of the conservative group and 64 % of the surgical group, near-complete resolution in 25 and 36 %, respectively, and no improvement in 0 and 7 %. There were no statistically significant differences between the two groups.

A Brazilian group performed a rare prospective study of treatment in pituitary apoplexy

(MacCagnan et al. 1995). This was primarily aimed at evaluating medical treatment and 12 patients were included. All were treated with dexamethasone and surgery was performed if the patients failed to improve. Five of the 12 patients proceeded to surgery. Of the seven patients treated conservatively, two had blurred vision and all seven had ophthalmoparesis. Six of these patients had fully recovered within 6 weeks, and the remaining patient had partially recovered 12 months later. The authors concluded that isolated ophthalmoparesis is not an indication for surgery.

Mou et al. (2009) reported a surprisingly low prevalence of 11 % ophthalmoparesis in their large series of Chinese patients. Few of these patients had reduced consciousness and meningism too, and it appears likely that their definition of apoplexy on radiological and histopathological grounds resulted in patients with subclinical apoplexy being included. Acute extension into the cavernous sinuses may therefore have occurred less frequently in these patients. However, a low rate of ophthalmoparesis was also found by a Taiwanese group who compared clinical and subclinical presentations of apoplexy. In the clinical group, defined by a typical acute presentation, just 12 % had documented ophthalmoparesis. However, 20 % were reported to have ptosis and 28 % reported diplopia, suggesting that incomplete or more subtle deficits of ocular motor function were present. In their subclinical group, ophthalmoparesis was rare and the proportions of patients with ophthalmoparesis, ptosis and diplopia were 0, 2.5 and 2.5 %, respectively. This study illustrates another aspect of variability of reporting in the literature. Other groups have also classified their patients as having ptosis or diplopia, rather than further defining nerve involvement, for example, Bonicki et al. (1993) reported prevalence of these features of 38 and 28 %, respectively.

The frequent involvement of the oculomotor nerve in preference to the other nerves of ocular motility is a consistent finding across studies and maybe because the nerve is prone to compression against the interclinoid ligament (Verrees et al. 2004) and because its position in the lateral wall of the cavernous sinus makes it more susceptible to pressure effects from rapid lateral expansion (Piotin et al. 1999). The trochlear nerve also lies in the lateral wall, and it is conceivable that trochlear involvement is underreported because it is more subtle clinically. Odd patterns of patchy ocular paresis may occur, for example, bilateral oculomotor nerve lesions with complete sparing of the trochlear and abducens nerves (Lau et al. 2007).

From our meta-analysis, 52 % of patients with pituitary apoplexy had ophthalmoparesis. This is very similar to the prevalence of symptoms affecting the afferent visual pathway, consistent with the close neuroanatomical relationships in the parasellar region.

It appears that recovery of ophthalmoparesis following apoplexy is usually good and there is slightly stronger evidence that deficits of ocular motility can recover spontaneously compared to deficits of vision. For this reason, ophthalmoparesis in the absence of visual loss is sometimes managed conservatively (Verrees et al. 2004), and some guidelines advocate that ocular paresis in the absence of deficits of vision is not an indication for immediate surgery (Rajasekaran et al. 2011).

Conclusion

Pituitary apoplexy is an important diagnosis which is often missed. At presentation, patients often have no known preceding history of tumour. Deficits of visual acuity, fields and ophthalmoparesis are each present in around half of patients and, in someone presenting with a sudden-onset headache, should alert the clinician to the possibility of apoplexy. Conversely, the absence of neuro-ophthalmological signs certainly does not exclude a diagnosis of pituitary apoplexy. Considering the diagnosis when imaging patients with sudden-onset headache and other nonspecific features may help make the diagnosis in these cases.

The presence of significant neuro-ophthalmological signs prompts many clinicians to consider early neurosurgical decompression, but there remains controversy about what constitutes significant deficit. Severely reduced visual acuity and severe and persistent visual field defects are generally

considered a surgical indication; isolated ocular paresis is not (Rajasekaran et al. 2011). Patients with initially mild deficits can deteriorate rapidly and should be closely monitored. In the absence of a randomised controlled trial, there remains some controversy regarding the optimal management of visual deficits in patients with acute pituitary apoplexy. Guidelines advocate a case-by-case decision-making process involving neurosurgeons, neuroradiologists, ophthalmologists and endocrinologists. Visual outcome can be good even in patients with severe deficits, although is more guarded in those who are initially blind.

Therefore, it is obvious that an accurate assessment of visual acuity, visual fields and eye movements, ideally by an ophthalmologist or neuro-ophthalmologist, is crucial in patients presenting with possible pituitary apoplexy to help make the diagnosis, guide management decisions regarding early surgical intervention, assess postoperative recovery and, to some degree, predict prognosis.

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Visual Outcome Following Pituitary Apoplexy

11

Deepak Agrawal

Contents

11.1 Introduction

Pituitary apoplexy presenting with visual deterioration is an often misdiagnosed condition, presenting to the neurosurgeon after being treated by physicians, ophthalmologists and endocrinologists, causing avoidable delay in treatment, which could prove catastrophic for visual outcome. There is long delay in presentation to neurosurgeons due to this misdiagnosis, and the mean delay in the definitive diagnosis was 10 days in our study (Agrawal and Mahapatra 2005).

11.2 Clinical Presentation

Visual deterioration in pituitary apoplexy has been reported in 52–90 % of patients (Cardoso and Peterson 1984; Chuang et al. 2006). The incidence of blindness (absent perception of light) is 35–42 % amongst patients who present with visual deterioration (Maccagnan et al. 1995; Agrawal and Mahapatra 2005). In our study, eight cases (35 %) presented with visual deterioration to monocular ($n=2$) or binocular ($n=6$) blindness after apoplexy (Table 11.1). Visual field defects, specifically bitemporal hemianopia, are seen in nearly 75 % of the patients and are caused by upward enlargement of the intrasellar contents, leading to optic chiasmal compression (Onesti et al. 1990; Randeva et al. 1999; Sibal et al. 2004; Semple et al. 2007).

For reasons which are not clear, male sex is more predisposed to visual deterioration following pituitary apoplexy (Ebersold et al.

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1983; McFadzean et al. 1991; Agrawal and Mahapatra 2005; Seuk et al. 2011).

11.3 Assessment of a Patient with Visual Deterioration

As per UK guidelines (Rajasekaran et al. 2011), initial assessment of the patients presenting with symptoms consistent with pituitary apoplexy should include a detailed history focusing on symptoms of pituitary dysfunction, e.g. symptoms of hypogonadism, followed by a thorough physical examination including cranial nerves and visual fields to confrontation. A formal visual field assessment using Humphrey visual field analyzer or Goldmann perimeter must be undertaken when the patient is clinically stable, preferably within 24 h of the suspected diagnosis, and in patients with reduced visual acuity or defective visual fields, formal assessment of visual fields and acuity should be performed every day until a clear trend of improvement is observed. Importantly, the guidelines also state that the presence of a new or deteriorating visual deficit or neurological deterioration should prompt further imaging with a view to decompressive surgery (including external ventricular drain placement in the presence of hydrocephalus).

11.4 Visual Outcome

There are few studies assessing visual outcome after pituitary apoplexy. Of these, only five studies (Table 11.1) have specifically addressed the pattern of visual recovery following surgical decompression (da Motta et al. 1999; Randeva et al. 1999; Agrawal and Mahapatra 2005; Chuang et al. 2006; Zhang et al. 2007; Seuk et al. 2011). Surprisingly, there are only four studies documenting return of vision after surgical or conservative management in patients who became blind subsequent to pituitary apoplexy (Krueger et al. 1960; Robinson 1972; Maccagnan et al. 1995; Agrawal and Mahapatra 2005).

Visual field deficits improve to a greater extent than visual acuity with studies reporting improvement in 89–95 % of the patients operated (Cardoso and Peterson 1984; da Motta et al. 1999; Zhang et al. 2007).

Overall, surgery results in improvement of the visual acuity deficits in 82–88 % of patients (Cardoso and Peterson 1984; da Motta et al. 1999). Return of vision was noted within 24 h of surgery in all cases who had a good visual outcome, and the improvement continued for variable period (Agrawal and Mahapatra 2005).

Suri et al. (2008) analysed a mixed group of 79 suprasellar tumours who presented with blindness

Table 11.1 Summary of retrospective studies about visual outcomes after surgery of pituitary apoplexy

Authors	Total no. of patients	Patients in whom tumour decompression was done	Improvement
Peter et al. (1995)	53	53	Improvement of VA in 82 % and VF in 89 %
Cardeso et al. (1984)	37	37	Improvement of VA in 88 % and VF in 95 %. Improvement seen in those undergoing surgery within 7 days of apoplexy
da Motta et al. (1999)	16	10	Improvement of VA and VF in 6/8 patients
Randeva et al. (1999)	35	31	Improvement of VA and VF seen in those undergoing surgery within 8 days of apoplexy
Agrawal et al. (2004)	23	23	Improvement of VA and VF seen in those undergoing surgery within 7 days of apoplexy
Chuang et al. (2006)	13	13	Early decompression significantly improved outcomes
Zhang et al. (2007)	65	65	Improvement of VA in 88.4 % and VF in 92.7 and surgical decompression within 24 h after the hospitalization
Seuk et al. (2011)	21	21	Surgery within 60 h of apoplexy. Improvement of VA in 15/18 and VF in 15/17

and noted improvement in serviceable vision in 8.9 of eyes with preoperative blindness. However, the study group was very heterogenous with pre-existing blindness for variable periods as long as 7 years. Other studies have shown that surgery within a week of the apoplexy results in improved visual outcome. In our own study of 23 patients who underwent transsphenoidal surgery for pituitary apoplexy over a 5-year period, 8 (35 %) presented with visual deterioration to monocular ($n=2$) or binocular ($n=6$) blindness after the apoplectic episode. Postoperatively, four patients (50 %) had improvement in vision to greater than 2/60 (Snellen's), including two patients whose vision improved to 6/6. All patients in whom there was improvement in vision had been operated on within a week of the apoplectic episode (Agrawal and Mahapatra 2005). Muthukumar et al. (2005) analysed four patients who presented with blindness within 1 week after pituitary apoplexy and found that the patient who was operated on within the first week recovered from bilateral blindness to a visual acuity of 6/9 and 6/12 with superior quadrantic field defects. The two patients who were operated on 2 and 3 weeks after ictus improved to 6/60 in the affected eyes and the patient who was operated on after 2 months improved to 1/60 in the affected eye. The authors concluded that "early" surgery within the first week after ictus leads to excellent visual outcome when compared with surgery that is performed at a later stage.

In contrast to the general belief that optic nerves withstand ischaemia poorly, the good-to-excellent visual outcome attained in some studies points towards the ability of optic nerves to resist ischemia for prolonged periods. Interestingly, patients had relatively poor visual outcome if surgical intervention was delayed beyond a week. Our experience in treating more than 800 cases of traumatic optic nerve injuries has shown that "early" optic nerve decompression within the first 7 days of onset of symptoms is associated with the best visual outcome. Although these findings are not strictly comparable in view of the different aetiologies, we believe that the fundamental pathology, that is, the sudden compression of the optic nerves with resulting ischaemia, remains the same in most of the cases – traumatic or apoplectic.

11.5 Management of Visual Deterioration

The management of visual deterioration has remained controversial, with treatment protocols ranging from conservative management using steroids (Maccagnan et al. 1995), bromocriptine therapy, to early surgery by transcranial or transsphenoidal route (Ebersold et al. 1983; McFadzean et al. 1991).

11.5.1 Steroids

As per UK guidelines (Rajasekaran et al. 2011), indications for empirical steroid therapy in patients with pituitary apoplexy include reduced visual acuity and severe visual field defects. Dexamethasone was previously not favoured as glucocorticoid replacement in pituitary apoplexy. However, in patients with visual deterioration Dexamethasone may actually be the drug of choice. This is because dexamethasone has the maximum anti-inflammatory effect amongst all steroids and can rapidly reduce oedema as part of a nonsurgical strategy for the treatment of pituitary tumour apoplexy with chiasmatic compression. In patients without significant visual deterioration, hydrocortisone 100–200 mg as an intravenous bolus is appropriate followed either by 2–4 mg/h by continuous intravenous infusion or by 50–100 mg six hourly by intramuscular injection. Given the saturation kinetics of cortisol-binding globulin, intermittent intravenous injections of hydrocortisone are less favoured; much of the administered steroid will be filtered into the urine and not pharmacologically available.

11.5.2 Surgery

As our own study shows, conservative management may lead to avoidable delay in decompression of the optic apparatus, adversely affecting the visual outcome (Agrawal and Mahapatra 2005). We therefore advocate early transsphenoidal surgery as the modality of choice in view of its multifaceted benefits – surgical decompression

not only relieves the visual deficit but also provides tissue for histopathological examination and prevents a recurrent apoplectic episode and additional tumour growth (Brougham et al. 1950), besides being the definitive treatment for most patients. The UK guidelines (Rajasekaran et al. 2011) recommend that a decision regarding the timing of the decompression surgery should be based on the severity and the progression of the signs and symptoms, and surgical decompression should be performed preferably early timing, as soon as possible, within the first 7 days of onset of symptoms and semi-elective transsphenoidal surgery should be considered for patients who are clinically stable, but show no improvement or deterioration in the neuroophthalmic signs. Such an approach would enable the surgery to be performed by the pituitary surgeon, rather than by the on call neurosurgical team. Surgery should be performed by an experienced pituitary surgeon defined as an experience of five or more transsphenoidal pituitary operations per annum. Surgery for pituitary apoplexy is explained in greater detail in Chap. 17.

Conclusion

Even completely blind eyes may have significant improvement in vision if surgical decompression of the optic apparatus is undertaken early within the first 7 days of onset of symptoms. Awareness regarding pituitary apoplexy and reversibility of vision loss needs to be increased amongst the medical community, especially ophthalmologists and physicians so that timely neurosurgical intervention can supervene. Further research is needed to reveal the reasons behind the unique ability of the optic apparatus to withstand compression for a prolonged period.

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Preoperative Endocrine Function and Fluid Electrolyte Balance

12

Angus G. Jones and Bijay Vaidya

Contents

Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
FBC	Full blood count
FSH	Follicular stimulating hormone
GH	Growth hormone
IGF1	Insulin-like growth factor 1
IM	Intramuscular
IV	Intravenous
LH	Luteinising hormone
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
T4	Thyroxine
TSH	Thyrotrophin

12.1 Introduction

Endocrine dysfunction is present in the majority of patients presenting with pituitary apoplexy (Semple et al. 2005; Leyer et al. 2011). While endocrine abnormalities may be new or long-standing, the majority of patients will not be

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known to have pituitary or endocrine disease at presentation (Sibal et al. 2004; Leyer et al. 2011). Recognition and treatment of adrenal insufficiency is likely to be the most important acute nonsurgical intervention in a patient presenting with pituitary apoplexy. Fluid and electrolyte imbalance, principally hyponatraemia, is common and may contribute to neurological dysfunction. In this chapter we discuss prevalence, investigation and management of preoperative endocrine dysfunction and hyponatraemia.

12.2 Prevalence of Endocrine Dysfunction

12.2.1 Pituitary Hormone Excess

Nearly all patients presenting with pituitary apoplexy will have a pituitary macroadenoma, many of which are secretory. Preoperative prevalence of anterior pituitary hormone excess in case series reporting 15 or more cases of apoplexy is shown in Table 12.1. Prolactin excess is most common (20 % of cases of pituitary apoplexy) in line with the frequency of prolactinoma in the population with excess growth hormone (acromegaly) and adrenocorticotropic hormone (ACTH; Cushing's disease) occurring in approximately 7 and 3 % of cases, respectively. Co-secretion of more than one hormone may occur. This is important as the finding of one raised hormone should not prevent consideration of hypersecretion of other hormones. While apoplexy has been reported in a gonadotrophin-secreting adenoma (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) or thyrotrophin (TSH)-secreting adenoma, these tumours are rare (Sibal et al. 2004; Lubina et al. 2005; Beck-Peccoz et al. 2009; Zhang et al. 2011).

12.2.2 Pituitary Hormone Deficiency

The prevalence of preoperative deficiency of individual pituitary hormones in published case

Table 12.1 Prevalence of preoperative anterior pituitary hormone excess in pituitary apoplexy

Study	No. of participants	ACTH	Prolactin	GH	FSH or LH	TSH
Leyer et al. (2011)	40	2 (5 %)	4 (10 %)	3 (7.5 %)	0	0
Zhang et al. (2011)	52	1 (2 %)	13 (3 %)	6 (12 %)	0	1 (2 %)
Gruber et al. (2006)	30	0	4 (13 %)	2 (7 %)	0	0
Lubina et al. (2005)	40	0	12 (30 %)	1 (3 %)	1 (3 %)	0
Semple et al. (2005)	62	0/62	7/47 (15 %)	1/21 (5 %)	0/40	0
Sibal et al. (2004)	45	4 (9 %)	8 (18 %)	2 (4 %)	2 (4 %)	0
Ayuk et al. (2004)	33	NR	13 (39 %)	NR	NR	NR
Da Motta et al. (1999)	16	0	3 (19 %)	4 (25 %)	0	0
Randeva et al. (1999)	35	2 (6 %)	2 (6 %)	3 (9 %)	0	0
Onesti et al. (1990)	16	0	4 (25 %)	0	0	0
Total	369	9/336 (3 %)	70/354 (20 %)	21/295 (7 %)	3/347 (<1 %)	1/347 (<1 %)

Published case series of ≥15 participants
NR not reported, *ACTH* adrenocorticotropic hormone, *GH* growth hormone, *FSH* follicle-stimulating hormone, *LH* luteinising hormone

series (≥15 cases) is shown in Table 12.2. Approximately 70 % of patients presenting with pituitary apoplexy will have deficiency of at least one anterior pituitary hormone if tested, with deficiency of three hormones occurring in over half of cases. While growth hormone deficiency is rarely formerly assessed preoperatively (and therefore not reported in these series) where tested, it appears to be common with deficiency reported in 88 % (Veldhuis and Hammond 1980).

12.3 Pathogenesis of Endocrine Dysfunction

12.3.1 Pre-existing Endocrine Dysfunction

Many patients with pituitary apoplexy will have pre-existing pituitary insufficiency due to the presence of pituitary macroadenoma and resultant pressure effect (Arafah et al. 2000). Approximately half of patients with pituitary macroadenoma have partial hypopituitarism (Dekkers et al. 2007; Karavitaki et al. 2007). While this is often undiagnosed, patients presenting with apoplexy commonly report long-standing symptoms of pituitary insufficiency on questioning (Bills et al. 1993).

12.3.2 Endocrine Dysfunction as a Result of Pituitary Apoplexy

Pituitary apoplexy results in extreme elevation of intrasellar pressure due to the rapid increase in pituitary contents when haemorrhagic necrosis occurs (Zayour et al. 2004). High intrasellar pressure reduces blood flow to the anterior pituitary (Kruse et al. 1992; Arafah et al. 2000). While this may reversibly reduce anterior pituitary hormone secretion, ischaemia and cell necrosis occur leading to irreversible pituitary damage. The potential reversibility of pituitary dysfunction likely depends on the degree of pituitary necrosis (Arafah 1986). Zayour and colleagues (2004)

Table 12.2 Prevalence of preoperative endocrine deficiency in patients presenting with pituitary apoplexy

Study	No. of participants[a]	Any pituitary hormone deficiency	Panhypopituitary[b]	ACTH	FSH/LH	TSH
Leyer et al. (2011)	40	35 (88 %)	20 (50 %)	25 (70 %)	NR	NR
Zhang et al. (2011)	52	17 (33 %)	NR	NR	NR	NR
Dubuisson et al. (2007)	20	17 (85 %)	14 (70 %)	15 (75 %)	16 (80 %)	16 (80 %)
Lubina et al. (2005)	23	NR	NR	3/20 (15 %) (7/20 indeterminate)	NR	12/23 (52 %)
Semple et al. (2005)	62	45 (73 %)	NR	38(61 %)	25 (40 %)	34 (55 %)
Sibal et al. (2004)	45	34 (81 %)	NR	25 (60 %)	32 (76 %)	24 (57 %)
Ayuk et al. (2004)	33	NR	NR	17 (52 %)	22 (67 %)	12 (36 %)
Randeva et al. (1999)	35	NR	NR	27 (76 %)	28 (79 %)	17 (49 %)
Total	310	148/219 (68 %)	34/60 (57 %)	150/255 (59 %)	123/195 (63 %)	115/218 (53 %)

Case series including >15 participants with preoperative endocrine assessment
NR not reported, *ACTH* adrenocorticotropic hormone, *GH* growth hormone, *FSH* follicle-stimulating hormone, *LH* luteinising hormone
[a]Number with preoperative biochemical endocrine assessment
[b]ACTH, gonadotrophin (FSH/LH) and TSH deficiency

measured intrasellar pressure and prolactin in 13 patients undergoing pituitary surgery within a week of pituitary apoplexy. Pituitary pressure was inversely related to prolactin, high or normal prolactin (in non-prolactin-secreting adenomas) predicted recovery of anterior pituitary function. The six patients with prolactin level <2.5 mcg/L did not recover endocrine function after urgent surgery, whereas the seven patients with levels >3.5 mcg/L had at least partial preservation of pituitary function.

12.4 Presentation of Endocrine Dysfunction

The assessment of patients presenting with pituitary apoplexy should include detailed history and examination including assessment of symptoms and signs of pituitary hormone deficiency and excess (Rajasekaran et al. 2011). It is particularly important that the patient's haemodynamic status is promptly assessed so that supportive measures and presumptive corticosteroid treatment can be initiated without delay.

12.4.1 Features of Anterior Pituitary Hormone Excess

Clinical features of anterior pituitary hormone excess are detailed in Table 12.3. Biochemical investigation for acromegaly and Cushing's disease will be guided by clinical suspicion and may be missed by routinely performed investigations. Therefore it is essential that features of these conditions are specifically sought in the clinical assessment. In some cases a patient with clinical

Table 12.3 Clinical features of anterior pituitary endocrine dysfunction

Hormone	Deficiency	Excess
ACTH	Anorexia, weight loss, lethargy, generalised weakness, nausea, vomiting Hypotension, hypoglycaemia, hyponatraemia Adrenal crisis (shock) – confusion and coma can occur	'Cushing's disease': weight gain, truncal obesity, thin skin, striae, easy bruising, acne, hirsutism, proximal muscle weakness, hypertension, osteopenia, neuropsychological disturbance, glucose intolerance
Prolactin	Failure of lactation	Galactorrhoea, menstrual disturbance, low libido, erectile dysfunction
Gonadotrophins (LH/FSH)	Both sexes: low libido, infertility, lethargy, loss of secondary sexual hair Females: oligo-/amenorrhoea Males: erectile dysfunction, gynaecomastia, testicular atrophy	Rarely macroorchidism (males)
TSH	Hypothyroidism: lethargy, weight gain, cold intolerance, muscle aches/cramps, constipation, mental slowing, depression, dry skin, hair loss, hoarse voice, menstrual disturbance	Hyperthyroidism: weight loss, heat intolerance, sweating, palpitations, tremor, hyperactivity, altered mood, insomnia, lethargy, weakness, dyspnoea, menstrual disturbance, tachycardia, atrial fibrillation, congestive cardiac failure
GH	Impaired psychological well-being, reduced exercise capacity, reduced lean body mass, growth arrest (children)	Sweating, headaches, lethargy, joint pain, change in ring or shoe size, change in facial appearance, deepened voice, enlarged tongue, enlargement of hands and feet, osteoarthritis, carpal tunnel syndrome, goitre, hypertension, glucose intolerance, congestive cardiac failure, obstructive sleep apnoea

features of hormone excess will have deficiency on endocrine testing due to resolution associated with tumour infarction; this is particularly relevant to Cushing's syndrome where the presence of clinical features of cortisol excess does not exclude adrenal insufficiency following apoplexy (Alarifi et al. 2005; Fraser et al. 2009).

12.4.2 Features of Endocrine Deficiency

Clinical features of anterior pituitary hormone deficiency are detailed in Table 12.3. As clinical features of pituitary hormone deficiency are often vague and non-specific biochemical testing is required in all cases of apoplexy. The acutely life-threatening manifestation of pituitary hormone deficiency is hypoadrenal crisis secondary to ACTH deficiency. The key clinical feature of an adrenal crisis is shock; additional features include nausea, vomiting, abdominal pain, lethargy dehydration, confusion and coma. While severe thyroid deficiency (myxoedema coma) can be life threatening, this is rare, particularly unlikely acutely in the context of apoplexy (in part due to the long half-life of endogenous T4), and has not been reported.

12.5 Investigations

Recommended routine endocrine investigations for those presenting with pituitary apoplexy are described in Table 12.4. Many hormone deficiencies will not be detected by these investigations in the context of acute pituitary apoplexy, and more detailed investigation (e.g. an insulin tolerance test) may be needed postoperatively or following the acute episode if treated conservatively – the United Kingdom guidelines for the management of pituitary apoplexy recommend endocrine assessment at 4–8 weeks post event (Rajasekaran et al. 2011). Even where acute deficiency of a hormone is confirmed, repeat investigations after the acute period will be required as in some cases pituitary function may recover. Postoperative endocrine assessment is discussed in Chap. 13.

Adrenal insufficiency can be life threatening; lack of recognition is associated with a poor outcome (da Motta et al. 1999). It is therefore important that this is not missed; however, investigations will frequently not be able to exclude this in the acute context. To avoid delay where there is clinical suspicion, treatment should be given without waiting for laboratory confirmation. A random cortisol is only of value if levels are high (>550 nmol/L), making deficiency unlikely. In stable patients where acute corticosteroid treatment is not indicated, 9 am cortisol can be performed; this has the advantage that cortisol levels are likely to be higher than afternoon or evening samples (due to diurnal variation); cortisol above 500 nmol/L effectively excludes adrenal insufficiency, values below 100 nmol/L confirm adrenal insufficiency and intermediate values (100–500 nmol/L) do not exclude hypoadrenalism (Arlt and Allolio 2003). A Synacthen test will not detect adrenal insufficiency in the acute context (although pre-existing insufficiency would likely be detected) as prolonged ACTH deficiency is required before the adrenals develop diminished response to Synacthen (Grossman 2010).

12.6 Management

Conservative management of pituitary apoplexy is described in Chap. 17. We briefly address preoperative endocrine management in the context of the assessment described in this chapter.

12.6.1 Immediate Management and Steroid Replacement

The immediate medical management of pituitary apoplexy should include careful assessment of the patient's haemodynamic status and commencement of IV fluids and steroid therapy in those who are haemodynamically unstable or have symptoms and signs suggestive of adrenal insufficiency (Watt et al. 2008; Rajasekaran et al. 2011). Steroids can be discontinued should the initial (pretreatment) blood test show cortisol levels above 550 nmol/L. Hydrocortisone is

Table 12.4 Routine preoperative endocrine investigation in pituitary apoplexy

Pituitary hormone	Test(s)	Notes and interpretation
ACTH	Cortisol (random)	Should not delay corticosteroid treatment (give initial dose after phlebotomy where indicated). >550 nmol/L adrenal deficiency unlikely
	Cortisol (9 am)	If initial corticosteroid not indicated. >500 nmol/L deficiency unlikely. <500 nmol/L consider glucocorticoid replacement. <100 nmol/L confirms adrenal insufficiency
TSH	TSH, free T4	Low or normal TSH in the context of low T4 suggests deficiency but may represent 'sick euthyroidism' in the acutely unwell patient. Low T4 may not be apparent at presentation due to prolonged half-life
Prolactin	Prolactin	Below normal range associated with high intrasellar pressure and lack of recovery of pituitary function post surgery. High levels may indicate prolactinoma or stalk compression
GH	IGF-1	Low levels may indicate GH deficiency (normal levels do not exclude). High may indicate GH excess (acromegaly)
	GH	Low levels make acromegaly unlikely
Gonadotrophins (LH, FSH)	LH, FSH, testosterone (men), oestrogen (women)	Low levels of FSH/LH alongside low testosterone/oestradiol indicate deficiency
Other investigations	FBC (anaemia common in hypopituitarism), electrolytes (hyponatraemia), calcium (high calcium may indicate multiple endocrine neoplasia)	

Additional investigations for hormone excess are guided by clinical findings

generally recommended for glucocorticoid replacement (where haemodynamic instability 100–200 mg IV bolus followed by 2–4 mg/h IV infusion or 50–100 mg 6 hourly by IM or IV injection); dexamethasone may be used as part of a neurosurgical strategy to reduce cerebral oedema (Maccagnan et al. 1995; da Motta et al. 1999). The hydrocortisone dose should be quickly tapered to a physiological replacement dose of 20–30 mg per day following recovery from the acute episode (Rajasekaran et al. 2011).

12.6.2 Management of Other Anterior Pituitary Hormone Deficiency

Apparent secondary hypothyroidism (reduced T4 and TSH) in the acutely unwell patient may represent 'sick euthyroidism' and recover spontaneously. It has therefore been recommended that thyroid function tests are repeated at day 3–4 post surgery (or post presentation where conservatively managed) and treatment initiated where there is deficiency (Rajasekaran et al. 2011). Thyroid deficiency may not become apparent until weeks after the event; therefore further assessment will be required at 4–8 weeks in those with normal early investigations. Thyroid replacement therapy should be avoided in untreated corticosteroid deficiency (due to potential exacerbation and adrenal crisis).

Other hormone deficiencies do not require acute treatment and should be addressed at later stage following further assessment.

12.7 Outcome/Prognosis

A minority of patients will recover pituitary function after pituitary apoplexy (Leyer et al. 2011). Choice of surgical or conservative treatment does

not appear to affect endocrine outcome (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006; Leyer et al. 2011). Apoplexy may be associated with spontaneous resolution of previous pituitary hormone excess and improved rates of postsurgical remission (Alarifi et al. 2005; Fraser et al. 2009; Choudhry et al. 2012).

12.8 Special Considerations

12.8.1 Pregnancy

Although pregnancy may be a potential precipitant of apoplexy, apoplexy in pregnancy remains rare (Janssen et al. 2012). The assessment of pituitary function in pregnancy is complicated by the major physiological changes in anterior pituitary hormones in normal pregnancy, as a result of changes in pituitary secretion, placental hormones and changes in hormone binding globulins (Karaca et al. 2010).

The detection of adrenal insufficiency associated with apoplexy in pregnancy is important as unrecognised hypoadrenalism is associated with adverse outcome (Ambrosi et al. 2003); however, recognition may be particularly difficult. Mild hyponatraemia and many symptoms of adrenal insufficiency (such as vomiting and fatigue) are seen in normal in pregnancy. ACTH, free and total cortisol are increased and adrenal response to ACTH increased (Suri et al. 2006). Total cortisol increases two to three times by the third trimester of pregnancy so that cortisol may appear to be normal or above the normal reference range in a patient with adrenal insufficiency; usual diagnostic criteria cannot be used (Suri et al. 2006). At present due to the difficulties confirming adrenal insufficiency in pregnancy, we recommend a low threshold for treatment and would give initial presumptive steroid replacement in any case of pituitary apoplexy in pregnancy (Karaca et al. 2010).

Assessment of pituitary-thyroidal axis should be based on the levels of serum TSH and free T4; however, interpretation of free T4 level in pregnancy can be difficult and ideally each laboratory should have assay and trimester-specific reference ranges (De Groot et al. 2012). Likewise TSH levels are reduced (particularly in the first trimester), and trimester-specific reference ranges should be used to interpret TSH levels in pregnancy (De Groot et al. 2012). Prolactin levels in pregnancy are markedly elevated; pregnancy-specific reference ranges have been published (Abbassi-Ghanavati et al. 2009; Karaca et al. 2010).

Pituitary growth hormone is essentially replaced by placental growth hormone during pregnancy (Frankenne et al. 1988), assessment is likely to be helpful only where acromegaly is suspected, diagnosis of acromegaly in pregnancy is difficult and some authors have suggested waiting for delivery to confirm diagnosis (Cheng et al. 2012). Gonadotrophins (FSH and LH) are suppressed during pregnancy due to elevated levels of their target hormones.

12.8.2 Diabetes Insipidus

Deficiency of antidiuretic hormone (diabetes insipidus) appears rare preoperatively, with no cases reported in series of ≥15 cases (Table 12.5), with the exception of one study which reported a prevalence of 8 % (Semple et al. 2005). The presentation and management of diabetes insipidus are discussed in Chap. 13.

12.9 Fluid and Electrolyte Disturbance: Hyponatraemia

12.9.1 Prevalence

Hyponatraemia is a common electrolyte disturbance associated with pituitary apoplexy. Approximately 17 % (Table 12.5) of patients presenting with pituitary apoplexy will have hyponatraemia; although mostly mild, severe hyponatraemia can occur (Ebner et al. 2010; Krull et al. 2010).

12.9.2 Aetiology

The most likely aetiology of hyponatraemia in pituitary apoplexy is adrenal insufficiency. As

Table 12.5 Prevalence of preoperative hyponatraemia and diabetes insipidus

Study	No. of participants	Hyponatraemia (number and severity where reported)	Diabetes insipidus
Leyer et al. (2011)	44	NR	0
Zhang et al. (2011)	52	9 (17 %, 6 125–130 mmol/L, 3 105–124 mmol/L)	0
Dubuisson et al. (2007)	20	2 (10 %, 'mild')	0
Semple et al. (2005)	62	9 (15 %)	5 (8 %)
Sibal et al. (2004)	45	9 (20 %)	NR
Randeva et al. (1999)	35	15 (43 %), range 118–133 mmol/L	NR
Bills et al. (1993)	37	NR	0
Onesti et al. (1990)	16	3 (19 %)	0
Total	311	47/270 (17 %)	5/262 (2 %)

Case series of ≥15 participants reporting hyponatraemia or diabetes insipidus prevalence

NR not reported

patients with secondary hypoadrenalism are not deficient in mineralocorticoids (which is secreted in response to angiotensin 2 rather than ACTH), hyponatraemia (and hypotension) in secondary hypoadrenalism is less prominent than in primary hypoaldosteronism. However, marked hyponatraemia can occur, particularly in the presence of an acute stressor such as apoplexy.

The syndrome of inappropriate ADH secretion (SIADH) has been reported rarely in pituitary apoplexy, including as a cause of neurological deterioration late after initial presentation (Veldhuis and Hammond 1980; Agrawal and Mahapatra 2003; Ebner et al. 2010). Although little studied, it is likely that the cause of hyponatraemia in pituitary apoplexy is often multifactorial and will include other causes common to neurosurgical patients including dilutional hyponatraemia secondary to IV fluids and excess natriuretic peptide secretion ('cerebral salt wasting') (Hannon et al. 2012). Although cerebral salt wasting has not been reported in pituitary apoplexy, it is associated with subarachnoid haemorrhage, an established cause, and high levels of atrial natriuretic peptide (alongside high ADH) in hyponatraemic patients after pituitary apoplexy have been demonstrated (Agrawal and Mahapatra 2003). Hypothyroidism is common in pituitary apoplexy and may contribute to hyponatraemia; potential mechanisms include a reduction in glomerular filtration rate and elevated ADH secretion (Iglesias and Diez 2009).

12.9.3 Clinical Features

Symptoms of hyponatraemia are rare with sodium levels of over 125 mmol/L. Symptoms below this level depend on rate of onset as well as sodium level due to cerebral adaption – slow onset hyponatraemia may have few symptoms. Neurosurgical patients including those with pituitary apoplexy may be more prone to develop symptoms related to hyponatraemia due to the presence of additional cerebral irritation or raised intracranial pressure from their underlying diagnosis (Hannon et al. 2012).

Clinical features of hyponatraemia include nausea and vomiting, muscle weakness, headache, lethargy, ataxia, psychosis, seizures, coma, tentorial herniation and respiratory depression (Kumar and Berl 1998). Neurological deterioration due to hyponatraemia has been reported including at a late stage (7 days) after onset of apoplexy (Ebner et al. 2010). There is significant overlap with the symptoms and signs of pituitary apoplexy; therefore it is important that sodium is monitored and hyponatraemia is considered if there is a change in clinical condition of the patient.

12.9.4 Investigation

As late hyponatraemia has been reported, it is advisable to monitor electrolytes following apoplexy even if they are initially normal; electrolytes

should also be repeated should there be neurological deterioration (Ebner et al. 2010). If hyponatraemia occurs, corticosteroid deficiency must be excluded, through investigation or presumptive treatment. The fluid status of the patient should be carefully assessed, including measurement of serum urea, and monitoring of fluid balance initiated. Reduced plasma osmolarity should be confirmed – low sodium may be essentially physiological in the context of increased levels of another osmotically active substance (such as raised glucose or mannitol) in which case serum osmolarity will be normal (or raised) and treatment should be aimed at the underlying cause (Kumar and Berl 1998). The presence of dehydration excludes a diagnosis of SIADH; fluids (and glucocorticoid where appropriate) should be initiated. Where a patient is euvolaemic without corticosteroid deficiency, measure urine sodium and osmolarity on a single 'spot' sample. The presence of high urine sodium in a euvolaemic patient without corticosteroid deficiency or diuretic treatment is most likely to represent SIADH. Additional criteria for the diagnosis of SIADH include reduced plasma osmolarity, inappropriate urine concentration (osmolarity >100 mOsmol/kg H_2O) and the exclusion of glucocorticoid and thyroid deficiency (Hannon et al. 2012).

Differentiating between cerebral salt wasting and SIADH in a clinically euvolaemic patient can be challenging, although the latter appears to be far more common as a cause of neurosurgical hyponatraemia (Sherlock et al. 2009). Hyponatraemia in the context of increasing urine output, falling blood pressure and rising urea may suggest cerebral salt wasting rather than SIADH (where other causes such as corticosteroid deficiency have been excluded) (Hannon et al. 2012).

12.9.5 Management

12.9.5.1 Prevention

Given the high incidence and potential complications of hyponatraemia, steps should be taken to minimise its occurrence in apoplexy, including careful monitoring of electrolytes, early recognition and treatment of corticosteroid deficiency and careful fluid management. Fluid overload, particularly with dextrose, should be avoided.

12.9.5.2 Treatment

Whatever the underlying cause of hyponatraemia, it is important that both fluid balance and electrolytes are carefully monitored and underlying causes corrected. Failure of hyponatraemia to respond to the chosen treatment should prompt reassessment of the underlying cause. With the exception of those with hyponatraemia-associated acute neurological symptoms, the aim should be to restore normal sodium levels gradually, at less than 0.5 mmol/L/h (and <10 mmol/L in 24 h), to minimise the risk of osmotic demyelination. In those with acute neurological symptoms (regardless of the underlying aetiology of hyponatraemia), hypertonic saline (e.g. 3 % saline at 4–6 ml/kg/h in a fitting or obtunded patient) can be given to rapidly raise sodium to the point where life-threatening symptoms resolve (often as rise of 1–2 mmol/L is sufficient); hyponatraemia can then be corrected more gradually (Lauriat and Berl 1997). Risk of osmotic demyelination depends on chronicity of hyponatraemia and therefore be unlikely in those who have rapidly developed hyponatraemia in the context of apoplexy; however, in many cases hyponatraemia cannot be assumed to be acute and may have predated presentation.

SIADH is traditionally managed with fluid restriction to <1,200 ml/day per day. Intravenous normal saline may be effective in raising plasma sodium in patients who meet SIADH criteria but have urine osmolarity of <500 nmol/mOsm/kg; it may be a particularly appropriate initial therapy where there is diagnostic doubt. Where fluid restriction is inadequate or impractical, therapy with demeclocycline or vasopressin-2 receptor antagonists can be effective (Sherlock and Thompson 2010). Cerebral salt wasting is managed with IV normal saline; large volumes may be required (Hannon et al. 2012).

Conclusion

In conclusion both endocrine dysfunction and hyponatraemia are common in patients presenting with pituitary apoplexy. Detection and treatment of adrenal insufficiency is the key

nonsurgical intervention in managing pituitary apoplexy. Evaluation of preoperative endocrine function as well as fluid and electrolyte balance is necessary in all patients with pituitary apoplexy before an early surgical intervention to prevent a catastrophic outcome.

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Endocrinopathies and Other Biochemical Abnormalities in Pituitary Apoplexy

13

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Contents

Abbreviations

ACTH	Adrenocorticotrophic hormone
ADH	Antidiuretic hormone
DI	Diabetes insipidus
FSH	Follicle-stimulating hormone
IGF-1	Insulin-like growth factor-1
LH	Luteinising hormone
SIADH	Syndrome of inappropriate diuretic hormone
T4	Thyroid hormone-4
UK	United Kingdom

13.1 Introduction

Pituitary apoplexy, although a relatively uncommon condition, is important, as it may be potentially life threatening if not recognised and adequately treated. Pituitary apoplexy is a clinical syndrome caused by the sudden enlargement of a pituitary tumour, usually a pituitary macroadenoma, due to haemorrhage, infarction or a combination of both haemorrhage and infarction. The clinical features are typically of sudden onset, usually evolving in hours, and may be of varying severity, including headache, vomiting, visual disturbance ophthalmoplegia and altered consciousness.

Endocrinopathies in pituitary apoplexy result from the pituitary apoplexy per se causing destruction of the pituitary gland, or a previously undiagnosed pituitary tumour. Endocrinopathy, usually hormone deficiencies, if left untreated

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can contribute to the poor outcome. Endocrine evaluation, emergent treatment and long-term management of the endocrinopathy are an essential aspect of the treatment of the patient who presents with pituitary apoplexy. Adequate endocrine assessment and management is essential to prevent poor outcome or even death.

Although pituitary apoplexy typically occurs in pituitary macroadenomas and may involve functional or clinically non-functional tumours, it has also been described in microadenomas, the normal pituitary gland, craniopharyngiomas, Rathke's cleft cysts and lymphocytic hypophysitis. It appears that no specific subtype of adenoma confers a higher risk of apoplexy. Mou and colleagues (2009) showed that the proportion of patients with apoplexy was significantly higher in functional than non-functional adenomas. In contrast, there are studies that have reported a higher incidence of pituitary apoplexy among non-functioning tumours (Renabir and Baruah 2011). Semple et al. (2005) reported that 77 % of apoplexy occurred in non-functioning pituitary macroadenomas. Similarly, Randeva et al. (1999) reported 61 % of adenomas, where histological typing was possible in pituitary apoplexy, to be null-cell tumours. Bills et al. (1993) reported a 52 % predominance of null-cell tumours in pituitary apoplexy. A study by Dubuisson et al. (2007) showed equal prevalence among secreting and non-secreting tumours. Mou et al. (2009) in their series reported no difference in proportions of patients with apoplexy in pituitary tumours among the different hormone types. In 80 % of cases, pituitary apoplexy represents the first presentation of the pituitary tumour (Biousse et al. 2001; Semple et al. 2005).

The patient is also quite likely to have hypopituitarism (or occasionally hypersecretion) involving one or more hormones due to the pre-existing, usually undiagnosed macroadenoma. It is usually at the time of acute apoplexy that the hypopituitarism becomes apparent, as these patients are unable to adequately respond to the stress of the apoplexy as a result of the hypo-functioning pituitary gland.

13.2 Endocrinopathies and Other Biochemical Abnormalities in Pituitary Apoplexy

Endocrinopathies found at the time of presentation may manifest as a combination of abnormalities resulting from the previously undiagnosed macroadenoma and hypopituitarism, resulting from an apoplectic insult to the pituitary gland from compression by the expanding tumour or direct ischaemic or haemorrhagic injury to the gland. Surgery for pituitary apoplexy may also contribute to endocrine deficiency. A history compatible with hypopituitarism, fatigue, hypogonadism and constitutional changes that were unrecognised as being related to a pituitary tumour may have been present prior to the apoplexy.

The majority of patients (80 %) (Sibal et al. 2004; Semple et al. 2005; Rajasekaran et al. 2011; Renabir and Baruah 2011; Vanderpump et al. 2011) will manifest with at least one anterior pituitary hormone deficiency (Table 13.1). The inferior hypophyseal artery supplies both the pituitary gland and the tumour. The superior hypophyseal artery supplies the infundibulum and posterior pituitary gland. The differential blood supply of the anterior pituitary gland, tumour and posterior pituitary gland may explain the relative infrequency of posterior pituitary involvement (Bills et al. 1993).

The most important hormone deficiency is that of adrenocorticotrophic hormone (ACTH) and subsequently cortisol, which is one of the major causes of mortality in pituitary apoplexy (Lee et al. 2008). The percentage of patients reported with hypocortisolaemia following apoplexy varies from 50 to 83 % (da Motta et al. 1999; Randeva et al. 1999; Sibal et al. 2004; Semple et al. 2005; Kerr and Wierman 2011; Rajasekaran et al. 2011; Renabir and Baruah 2011). The possible reason for the variation in the reported incidence of cortisol deficiency may be different definitions of hypocortisolaemia as well as varying assays for the ACTH. The deficiency in ACTH may result in non-specific symptoms of shock and rapid deterioration of the patient's

Table 13.1 Hormonal deficiency requiring replacement therapy in pituitary apoplexy

Author	Hormone deficiency (%)		*N*
Ayuk et al. (2004)	Cortisol	72/87[a]	33
	Thyroid	60/72	
	Gonadotrophin	67/83	
Bills et al. (1993)	Cortisol	82	33
	Thyroid	89	
	Gonadotrophin	64	
	ADH	11	
Da Motta et al. (1999)	Cortisol	50	16
	Thyroid	55	
	Gonadotrophin	55	
Dubuisson et al. (2007)	Cortisol	80	24
	Thyroid	70	
	Gonadotrophin	40	
	Growth hormone	15	
	ADH	0	
Gruber et al. (2006)	Cortisol	72	36
	Thyroid	48	
	Gonadotrophin	18	
	ADH	7	
Lubina et al. (2005)	Cortisol	40	40
	Thyroid	54	
	Gonadotrophin	79	
	ADH	8	
Randeva et al. (1999)	Cortisol	58	35
	Thyroid	45	
	Gonadotrophin	45	
	ADH	6	
Sibal et al. (2004)	Cortisol	60	45
	Thyroid	57	
Semple et al. (2005)	Cortisol	61	62
	Thyroid	70	
	Gonadotrophin	40	
	Growth hormone	6	

N number of patients in series

[a]First number reflects percentage of patients who were surgically treated with hormonal deficiency and second number patients who were treated conservatively with hormone deficiency

condition, which may be fatal if left untreated (Mattke et al. 2002). In the severely stressed patient with pituitary apoplexy, the cortisol levels may fail to respond to adequate levels, due to a relative deficiency of ACTH. Dilutional hyponatraemia results from vasopressin release from the posterior pituitary, which has an inhibitory effect on water secretion (Renabir and Baruah 2011). A low cortisol also results in impaired vasoconstriction and haemodynamic instability.

Gonadotrophins were low in 75–85 % of patients. Hypothyroidism was reported in 42–55 % of patients, while thyroid-stimulating hormone (TSH) was documented as being low in 50–55.5 %. Growth hormone has been reported to be low in up to 88 % of patients (Cardoso and Peterson 1984; Randeva et al. 1999; da Motta et al. 1999; Sibal et al. 2004; Semple et al. 2005; Dubuisson et al. 2007; Renabir and Baruah 2011). Low prolactin levels have been associated with high intrasellar pressures and severe pituitary apoplexy (Rajasekaran et al. 2011). Severe ischaemic necrosis may give rise to low serum prolactin levels, whereas those individuals who have normal or elevated serum prolactin levels tend to have less severe hypopituitarism. In patients with functional tumours, remission of Cushing's disease and acromegaly has been reported following pituitary apoplexy (Dunn et al. 1975; Tamasawa et al. 1988; Kamiya et al. 2000; Fraser et al. 2009; Choudhry et al. 2011).

Long-term hormone replacement will be required in up to 80 % of patients with pituitary apoplexy. Dubuisson et al. (2007) reported that the majority of their series required replacement: adrenal 80 %, thyroid 70 %, gonadal 40 % and growth hormone 15 %. In general, long-term follow-up of patients with pituitary apoplexy replacement requirements will be corticosteroids in 40–85 %, thyroid hormone in 50–70 %, sex hormones in 40–80 % and growth hormone in 16 % of cases (Renabir et al. 2011). Some authors have suggested that early surgery may lead to better restoration or preservation of pituitary function, while others have not reported any difference between surgically and conservatively managed patients. Marouf and colleagues (2010) in their surgical series reported only 27 % of patients having normal pituitary function following apoplexy, while 42 % had panhypopituitarism, 31 % corticotrophic hypopituitarism. They also found that residual pituitary gland seen on MRI on follow-up did not correlate with pituitary function (Marouf et al. 2010). Leyer et al. (2011)

reported no significant difference in endocrine outcome after 21 months of follow-up between patients operated on and treated conservatively. Sibal et al. (2004) in their reported series found similar endocrine outcomes at follow-up between the surgically treated and conservatively managed patients. Ayuk and co-workers (2004) reported no difference in their series in cortisol and thyroid replacement in patients managed with surgery or conservatively.

The incidence of diabetes insipidus (DI) varies between 0 and 27 % of cases (Mauerhoff et al. 1991; Bills et al. 1993; Sweeney et al. 2004; Gruber et al. 2006; Dubuisson et al. 2007; Marouf et al. 2010; Renabir and Baruah 2011). DI may be a presenting feature of the pituitary apoplexy or it may occur postoperatively. Preoperative DI is rarely seen and in some series has not been reported at all (Duboisson et al. 2006). This may be attributable to the preservation of the posterior pituitary as a result of its different blood supply from the inferior hypophyseal artery rather than the superior hypophyseal artery that supplies the anterior pituitary and usually the tumour (Bills et al. 1993, Reid et al. 1985). However, postoperative DI appears to be more common and is described in 16 % of patients (Randeva et al. 1999; Rajasekaran et al. 2011). Postoperative DI is due to a lack of antidiuretic hormone (ADH) due to surgical manipulation of the neurohypophysis (Kristof et al. 2009). DI presents in the first two postoperative days in 86 % of cases and is transient in the majority of cases with half resolving in the first week (Bills et al. 1993; Kristof et al. 2009; Grant et al. 2012). Gruber et al. (2006) reported DI in 20 % who underwent surgery, compared to 0 % who was treated conservatively. On long-term follow-up ADH replacement therapy has been reported in 6–25 % of patients (Bills et al. 1993; Rajasekaran et al. 2011; Renabir and Baruah 2011).

Hyponatraemia following pituitary apoplexy has been described in up to 40 % of patients (Randeva et al. 1999). Hyponatraemia can occur as an early or late event, and it can be isolated. Alternatively, it can occur in the second phase of the triple response when there is ADH release (Grant et al. 2012). Hyponatraemia in the early phase of pituitary apoplexy may result from hypocortisolaemia and secondary activation of ADH, which has an inhibitory effect on water secretion (Diederich et al. 2003; Lee et al. 2008; Rajasekaran et al. 2011). Hyponatraemia may also result from surgery for the apoplexy (Kelly et al. 1995; Taylor et al. 1995). The syndrome of inappropriate antidiuretic hormone secretion (SIADH) rarely occurs in pituitary apoplexy except for a few case reports. SIADH may occur due to sparing of the neurohypophysis leading to hyponatraemia (Agrawal and Mahapatra 2003). Surgical removal of the apoplectic pituitary adenoma may distort the hypophyseal stalk resulting in a surge of antidiuretic hormone release ultimately resulting in fluid overload and dilutional hyponatraemia (Lee et al. 2008). It remains unknown whether cerebral salt wasting occurs in the setting of pituitary apoplexy.

13.3 Emergency Management

Awareness that ACTH deficiency leads to inadequate cortisol concentrations, particularly with acute coexistent stress is critical. Partial or complete hypopituitarism confers the morbidity and mortality associated with this condition (Laws et al 2008, Turgut et al. 2010). In the individual in whom apoplexy is suspected, it is critical to draw blood for electrolytes, glucose, cortisol, liver functions, renal function, clotting screen, full blood count, prolactin, TSH, free T4, insulin-like growth factor-1 (IGF-1), growth hormone, luteinising hormone (LH), follicle-stimulating hormone (FSH) and testosterone in men and oestradiol in women (Rajasekaran et al. 2011). As pituitary apoplexy is a life-threatening condition it warrants careful attention to fluid management, and in some instances, blood transfusions are required. Administration of hydrocortisone will have a dual effect of replacing endogenous cortisol deficiency, and to some degree to relieve oedema of the parasellar structures (Murad-Kejbou and Eggenberger 2009). The most notable improvement following glucocorticoid administration is the reduction of haemodynamic instability. Varying dosing regimens of hydro-

cortisone have been recommended in the setting of acute pituitary apoplexy, but there is insufficient evidence to recommend one versus another. Some sources recommend a dose of 50 mg intravenously every 6 h (Chanson et al. 2004; Nawar et al. 2008). Other centres recommend a bolus dose of between 100 and 200 mg of intravenous hydrocortisone, followed by 50–100 mg six hourly by intramuscular injection (Vanderpump et al. 2011). Hydrocortisone administered either intravenously or intramuscularly is favoured over dexamethasone (Vanderpump et al. 2011). One small study reports an increased mortality with dexamethasone use, but these findings have not been consistently found in other studies (da Motta et al. 1999). A deficiency of glucocorticoids can contribute to haemodynamic instability through its action on raising antidiuretic hormone and fluid retention as well as impaired vasoconstriction. There is concern that intermittent administration of intermittent intravenous hydrocortisone may result in rapid saturation of cortisol binding globulin, with resultant enhanced filtration in the urine and consequently continuous infusions of hydrocortisone is sometimes advised (Rajasekaran et al. 2011).

A random serum cortisol of greater than 550 nmol/L indicates that hydrocortisone may be withheld. Nevertheless, one should never delay administration of hydrocortisone, pending the serum cortisol results. Hyponatraemia is a frequent complication, occurring in up to 40 % of pituitary apoplexy (Randeva et al. 1999). The cause should be sought and it should be corrected as far as is possible prior to surgery (Chuang et al. 2006). The usual precipitants are those of hypocortisolaemia and syndrome of inappropriate antidiuretic hormone (SIADH). Hypothyroidism is not a contraindication to surgery unless it is severe, and the primary clinician should inform the anaesthetist in order to avoid central nervous system suppressants.

The patients in whom a conservative nonsurgical management approach is adopted, supraphysiological doses of glucocorticoids should be given along with other hormone replacement for several weeks. Some authors indicate that when dexamethasone was administered for 1 week and associated with a lack of neurological improvement, a surgical approach may be required (Maccagnan et al. 1995).

13.4 Timing of Surgery

While there is consensus in the use of hydrocortisone and careful management of fluids and electrolytes in the treatment of pituitary apoplexy, there is considerable debate on the use and timing of surgery. As pituitary apoplexy is a relatively rare entity, there are only published retrospective series, and the prospect of a prospective randomised study to establish the role of surgery versus conservative management may never be materialised. Consequently, the management of these patients may vary between different institutions. There are a number of studies suggesting that early decompressive surgery may improve the visual and endocrine outcome (Arafah et al. 1990; Bills et al. 1993; Bonicki et al. 1993; Randeva et al. 1999; Semple et al. 2005; Dubuisson et al. 2007). Randeva et al. (1999) has also suggested that surgery within the first week may result in an improved visual and endocrine outcome. da Motta and colleagues (1999) reported a higher mortality rate in patients not treated surgically. However, Ayuk and colleagues (2004) found no difference in the outcome whether surgery was performed before or after 8 days. In other published series the outcome in patients who were managed conservatively was the same as those operated on. However, there seems to be a consensus that patients with severe or deteriorating visual deficits or diminished levels of consciousness required surgery (Maccagnan et al. 1995; Sibal et al. 2004; Nawar et al. 2008; Shou et al. 2009; Leyer et al. 2011; Rajasekaran et al. 2011; Renabir and Baruah 2011). A reasonable approach to treatment for pituitary apoplexy is to perform surgical decompression in patients who have diminished level of consciousness and in those who have severe neuro-ophthalmological deficits, including blindness. In patients with less severe visual deficits, medical management can be undertaken for the first week and then surgery should be delayed. If there is marked

improvement, then conservative treatment can be continued. The major advantage of delaying the surgery for a week is that it allows for a complete endocrine assessment, and replacement, and correction of both fluid and electrolyte disturbances which are prevalent following an apoplexy, permitting safer surgery and an improved outcome.

13.5 Immediate Postoperative Phase

The hydrocortisone dose should be tapered gradually to replacement doses depending on the clinical response, which is about 5–10 mg/m^2. This equates to 15–25 mg/day divided in three doses for adults. About 50–75 % of the total dose is given in the morning on rising (Arlt 2008). In the immediate postoperative phase, the patient should be observed for the evolution of diabetes insipidus. The fluid balance, urea, electrolytes, urine osmolality and plasma osmolality should be requested if diabetes insipidus is suspected. If the clinical picture is complicated by diabetes insipidus, it may present with a triple response in which diabetes manifests, followed by temporary resolution and long-term diabetes insipidus (Sweeney et al. 2004). There is thus a critical need to be vigilant for this phenomenon and patients' fluid balance should be closely monitored.

One particular centre advocates the use of glucocorticoid therapy until at least 1 day postoperatively, when it is tapered or stopped abruptly. It is then suggested that serum cortisol concentrations are measured twice or three times daily (Hout et al. 1988). This method of assessing cortisol repleteness has the advantage that it may obviate the need for unnecessary long-term use of glucocorticoids and potentially limits side effects. While this approach may be reliable, our approach in this setting of pituitary apoplexy is somewhat different to exclude secondary hypoadrenalism and we advocate hydrocortisone cessation for 48 h, and the integrity of the hypothalamic-pituitary adrenal axis is then assessed with the 1 μg synthetic ACTH stimulation test. The 30 min cortisol should exceed 550 nmol/L in order to recommend complete withdrawal of hydrocortisone replacement therapy, with the proviso that it should only be performed at 3 months following recovery of apoplexy. The UK guidelines recommend checking the 9 am serum cortisol on days 2 and 3 after surgery in those individuals with no evidence of a preoperative cortisol deficiency. On the other hand, in those patients who are already on hydrocortisone replacement, omission of the previous evening and morning dose prior to being evaluated is warranted using the 9 am serum cortisol.

Some centres have adopted the insulin hypoglycaemia test to assess cortisol repleteness, defined by cortisol greater than 520 nmol/L following a blood glucose of less than 2.0 mmol/L, performed days or weeks following acute apoplexy (Sibal et al. 2004). Other centres utilise 250 μg ACTH stimulation test administered either intravenously or intramuscularly. A meta-analysis showed that the low dose 1 μg ACTH stimulation test and the 250 μg performed similarly, but the receiver operating curves using the 1 μg performed slightly superiorly in ruling out HPA insufficiency. However, the differences were clinically unimportant (Kazlauskaite et al. 2008). The adequacy or otherwise of hydrocortisone replacement should be assessed periodically, both clinically and biochemically by a specialist endocrinologist.

We tend to supplement thyroid hormone if there is biochemical evidence of secondary hypothyroidism, but only once 48 h of hydrocortisone replacement therapy has been administered, in order to avoid the possibility of precipitating an acute adrenal crisis. Consideration should be given to the possibility of the sick euthyroid state, which may be superimposed on the clinical picture, confounding the interpretation of the thyroid function tests (Rajasekaran et al. 2011). There are centres advocating a delay in initiating thyroxine therapy for 2–4 weeks in non-severe individuals in the event that recovery of the hypothalamic-pituitary-thyroid axis occurs, unless severe hypothyroidism exists in which case prompt therapy is initiated. Most centres, however, would recommend a TSH and free T4

to be performed on day 3 or 4 following surgery, and these tests should be repeated 4–8 weeks postoperatively.

13.6 Long-Term Endocrine Care

There are several reports indicating that either partial or complete recovery of pituitary function occurred in more than 50 % (Zayour et al. 2004). A study of 37 patients showed that 82 % required glucocorticoids, 89 % warranted thyroid hormone replacement, 64 % of males required testosterone replacement therapy and 11 % were using vasopressin in the long-term for central diabetes insipidus (Bills et al. 1993). The 1 μg synthetic ACTH test should be performed at 3 months as there is a risk that performing the test earlier may result in falsely normal results. Similarly, gonadal axis and growth hormone repleteness should be assessed several weeks after recovery. Adults do not inevitably receive growth hormone even if this is biochemically proven. There are arguments supporting and against its use in this setting (Nawar et al. 2008). Posterior pituitary gland deficiency following apoplexy manifests predominantly as transient diabetes insipidus in about 10 % of cases. However, permanent central diabetes insipidus was reported in 8 % (Lubina et al. 2005).

All patients with pituitary apoplexy require at least annual review to assess their endocrine status. This should include free T4, LH, FSH, testosterone in men, oestradiol in women, prolactin, IGF-I, cortisol and growth hormone (Rajasekaran et al. 2011).

Conclusion

Pituitary apoplexy may be life threatening. Part of the mortality and morbidity arises from endocrine and electrolyte disturbances that may be present due to a previously undiagnosed pituitary tumour, or develop secondary to the apoplexy. The urgent assessment of the endocrine status of the patient who presents with pituitary apoplexy is crucial in ensuring a favourable outcome. The initial emergency management includes the administration of high dose of hydrocortisone, the failure of which can result in a vascular collapse and death. Multiple endocrine deficiencies including thyroid hormone, sex hormones and growth hormone need to be assessed and if necessary replaced. Occasionally DI and hyponatraemia also need to be corrected. Cortisol replacement prior to surgery is mandatory and thyroid hormone should also be corrected prior to surgical decompression. This may mean delaying surgery until endocrine status is corrected, if vision is not threatened and the level of consciousness is not altered. In cases of pituitary apoplexy with progressive visual loss, early surgery, within the first 7–8 days of onset of apoplectic ictus, is indicated. Long-term follow-up and continued monitoring of the patient's endocrine status is necessary.

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Part VI

Mimicking Conditions

Carotid Artery Aneurysm

14

Alberto Torres-Diaz, Carlos Alarcon,
and Juan Jose Acebes

Contents

Abbreviations

ACoA	Anterior communicating artery
CCA	Cavernous carotid artery
CT	Computed tomography
ICA	Internal carotid artery
MRI	Magnetic resonance imaging
SAH	Subarachnoid hemorrhage

14.1 Introduction

Pituitary apoplexy is an uncommon syndrome resulting from infarction or hemorrhage of a pre-existing pituitary adenoma that sometimes can be massive with subarachnoid extravasation of blood and dural irritation (Torres et al. 2009). The coexistence of pituitary adenomas and intracranial aneurysms, specially arising from the internal carotid artery (ICA) and the anterior communicating artery (ACoA), has been previously reported in the literature (Handa et al. 1976; Weir 1992; Locatelli et al. 2008; Wang et al. 2009). ICA aneurysms with significant sellar/suprasellar extension can be misdiagnosed with pituitary macroadenoma (Arseni et al. 1970; Raymond and Tew 1978; Mangiardi et al. 1983; Mindel et al. 1983; Weir 1992; Borges et al. 2006) or even pituitary apoplexy (Laidlaw et al. 2003; Torres et al. 2009) by magnetic resonance imaging (MRI).

The relationship between pituitary apoplexy, subarachnoid hemorrhage (SAH), and ICA aneurysms is important to be taken into consideration

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in the management of pituitary apoplexy to avoid a possible life-threatening situation. In the present chapter special attention will be paid in the natural history, neuroradiological appearance, and treatment of giant ICA aneurysms as the most frequent and risky pathology misdiagnosed as pituitary apoplexy or pituitary tumors.

14.2 Pituitary Adenomas and Subarachnoid Hemorrhage

The relationship between SAH, intracranial aneurysms, and pituitary tumors is extensively described in the literature (Handa et al. 1976; Wakai et al. 1979; Mangiardi et al. 1983; Weir 1992; Borges et al. 2006; Locatelli et al. 2008; Wang et al. 2009). Pituitary apoplexy is an unusual clinical syndrome characterized by the sudden onset of headache, vomiting, visual impairment, and decreased consciousness caused by hemorrhage and/or infarction of the pituitary gland usually associated with a preexisting nonfunctional pituitary adenoma. When the necro/hemorrhagic contents extend into the subarachnoidal cisterns, the clinical syndrome can associate meningismus. All these constellation of symptoms can closely resemble those present in patients with spontaneous aneurysmal SAH.

Whereas coexistence between pituitary tumors and intracranial aneurysms is extensively described in the literature, the association between pituitary adenoma and pituitary apoplexy with SAH is very uncommon (Laidlaw et al. 2003). In a patient with a pituitary adenoma, SAH can present in two different scenarios: as a complication of a massive hemorrhagic pituitary apoplexy extending locally to the suprasellar arachnoidal cisterns (Fig. 14.1a, b) or a SAH secondary to a preexisting intracranial aneurysm (usually with more diffuse bleeding in the arachnoidal cisterns).

When SAH is secondary to a preexisting intracranial aneurysm, it can produce a pituitary apoplexy when the rupture of the aneurysm is into the pituitary tumor (Suzuki et al. 2001; Sasagawa et al. 2012); this condition can occur in large aneurysms of ICA and ACoA that extend into the pituitary gland. SAH is an uncommon complication in cases of cavernous carotid artery (CCA) aneurysms (German and Black 1965; Kupersmith et al. 1984; Vasconcellos et al. 2009).

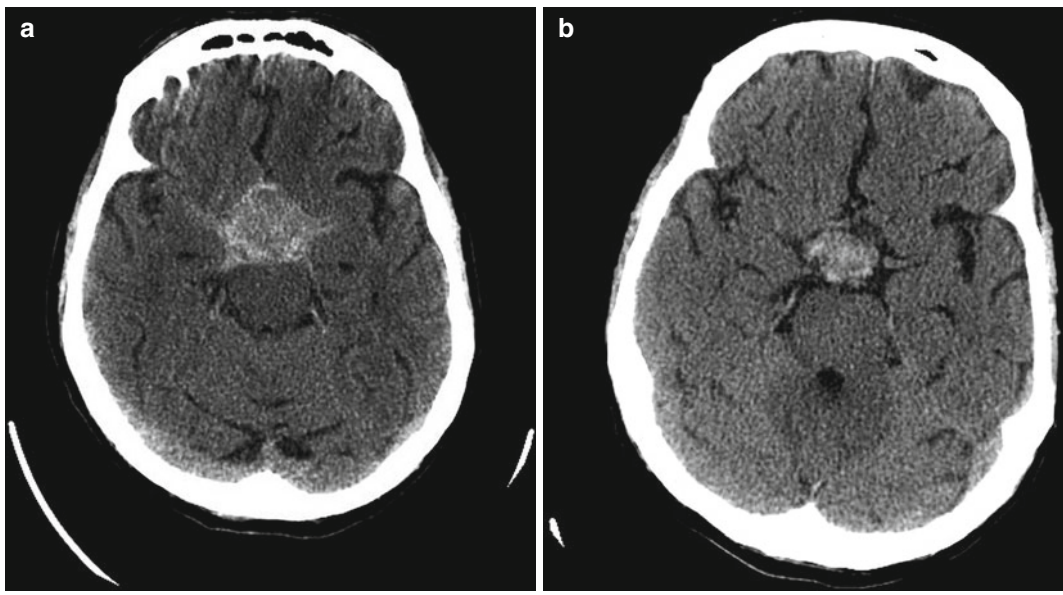

Fig. 14.1 (**a**) CT scan shows hemorrhagic PA extending locally to the suprasellar cisterns. (**b**) Postoperative CT scan after pituitary removal

Spontaneous thrombosis of ICA due to vascular compression is the most frequent complication in patients with aneurysm of CCA, most commonly in cases of giant aneurysms (Kupersmith 1993; Stiebel-Kalish et al. 2005). In the situation of a rupture of aneurysm of CCA it can present in different ways, as massive epistaxis (Davies et al. 2011) or as an acute cavernous sinus syndrome (Fernández-Real et al. 1994). In both cases an endovascular procedure is the best treatment option.

14.3 Pituitary Adenomas and Intracranial Aneurysms

In 1912, Dr. Harvey Cushing was the first to suggest a possible association between intrasellar aneurysms and pituitary neoplasms (Cushing 1912). This relationship is frequently described in the recent literature (Handa et al. 1976; Wakai et al. 1979; Mangiardi et al. 1983; Weir 1992; Borges et al. 2006; Locatelli et al. 2008; Wang et al. 2009). In the clinical series reported by Wakai et al. (1979), the incidence of aneurysms associated with 95 pituitary tumors was 7.4 %. In a more recent retrospective study (Pant et al. 1997) of 467 cases of pituitary adenomas, the incidence of associated intracranial aneurysms was 5.4 %. In general, the consensus is that the incidence of an intracranial aneurysm associated with pituitary adenomas is low (Nakagawa and Hashi 1994) from 3.7 to 7.4 % (Housepian and Pool 1958; Pant et al. 1997), and it is more common than with other intracranial tumors (1.1 %).

Regarding the location of intracranial aneurysms that coexists with a pituitary tumor, the ICA and the ACoA are the most frequent arteries affected because they supply the pituitary region (Locatelli et al. 2008). In one retrospective study (Pant et al. 1997), 48 % of intracranial aneurysms associated with pituitary adenoma were observed in the cavernous segment of the ICA artery followed by ICA-ophthalmic aneurysms in 19 % and ICA bifurcation in 13 %. Moreover, 60 % of aneurysms are near the parasellar region and 40 % at distant locations (Pant et al. 1997).

Several hypotheses to explain the association of aneurysm and pituitary adenoma have been proponed. A radiation-induced arterial damage, in cases where radiation was used to treat pituitary adenomas, has been suggested (Bulsara et al. 2007), which leads to loss of arterial muscle with necrosis and fibrosis of the tunica intima and media, thus causing dilation of the arterial walls. Different studies have also attempted to link the coexistence of pituitary adenomas and intracranial aneurysms to mechanical factors. In their study of 116 cases (Pia et al. 1972) reported that microanatomical changes in the cerebral circulation secondary to compression or traction might lead to increase in blood flow and aneurysmal formation. Recently, a series of 800 patients who underwent transsphenoidal surgery for pituitary apoplexy was reported and concluded that the existence of a cavernous sinus invasion was correlated with an increased incidence of intracranial aneurysms in patients with pituitary adenoma (Oh et al. 2012). Hormonal and microcirculatory influences have also been proposed as a major etiological factor. There have been many studies with growth hormone pituitary adenomas and intracranial aneurysms (Acqui et al. 1987). They studied 62 cases of pituitary adenomas and intracranial aneurysms and stated that mechanical, microcirculatory, and hormonal factors, especially growth hormone, play an important role in the formation of intracranial aneurysms (Acqui et al. 1987). In their review of the literature, they reported that 50 % of the pituitary adenomas associated with intracranial aneurysms were growth hormone secreting (Acqui et al. 1987).

Large or giant ICA aneurysms, in association or not with a pituitary adenoma, have been previously documented to mimic pituitary tumors and pituitary apoplexy (Arseni et al. 1970; Raymond and Tew 1978; Mangiardi et al. 1983; Mindel et al. 1983; Weir 1992; Borges et al. 2006), especially when they expand to the sellar and suprasellar area. This situation can suppose a tremendous risk to the patient, particularly when the aneurysm lies near the operative field (Pant et al. 1997). There is a recent review the literature regarding cerebral aneurysm with sellar extension (Hanak

et al. 2012). The most common artery of origin for intrasellar aneurysms was the ICA, which gave rise to 90 % of reported aneurysms, with the remaining 10 % originating from the ACoA.

14.4 Carotid Artery Aneurysms

14.4.1 Aneurysmal Classification

ICA aneurysms can expand to the sellar region mimicking a pituitary adenoma or pituitary apoplexy depending on their clinical presentation. There are two primary growth patterns by which aneurysms extend into the sellar region: (1) infradiaphragmatic, extends medially through the cavernous sinus dura and under the diaphragma sellae, and (2) supradiaphragmatic, extends inferomedially from above the diaphragma sellae (Hanak et al. 2012). The majority of infradiaphragmatic aneurysms are considered "cavernous segment" ICA aneurysms in the literature (Kupersmith et al. 1992; Hahn et al. 2000; Stiebel-Kalish et al. 2005; Kasliwal et al. 2008; Davies et al. 2011). Nevertheless, recent studies (Hanak et al. 2012) concluded that the clinoid ICA segment is the most frequent origin for these aneurysms, extending into the sella turcica through the thin medial cavernous sinus wall. These aneurysms tend to be smaller at the time of presentation than supradiaphragmatic ones (Fig. 14.2), because extensive growth is greatly limited by the dural and bony confines of the sella turcica (Table 14.1).

Supradiaphragmatic intrasellar aneurysms are typically large or giant superior hypophysial aneurysms that grow into the suprasellar space (Fig. 14.3a, b). With enlargement, they depress the diaphragma sellae into the pituitary fossa but do not generally erode through this membrane to contact the actual pituitary gland itself.

Occasionally, large inferiorly projecting ACoA aneurysms can extend anteriorly and inferiorly into the sella turcica, displacing the diaphragma sellae downwards. Whereas they do not originate in the ICA artery, they are considered supradiaphragmatic aneurysms with extension to the sella (Hanak et al. 2012), both the ICA and ACoA artery aneurysms. Aneurysms of CCA typically reach very large or giant proportions before extending into the sella turcica (Lemole et al. 2000; Wang et al. 2009; Szmuda and Sloniewski 2011).

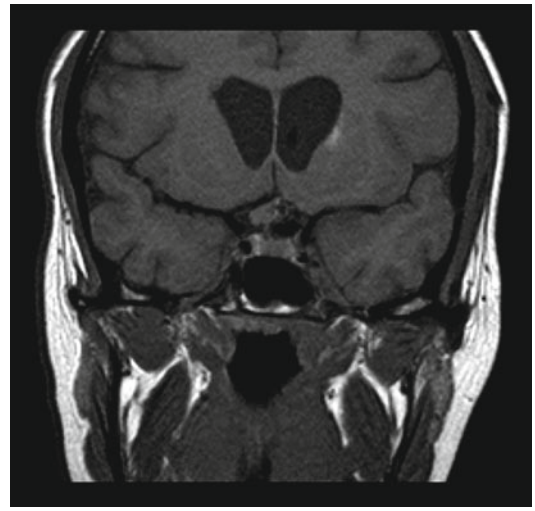

Fig. 14.2 MRI T1 sequence shows a small medial clinoid aneurysm compressing the pituitary stalk

Table 14.1 Sellar aneurysm classification

	Infradiaphragmatic	Supradiaphragmatic
Location	Cavernous or clinoidal	Sup. hypophysial or ACoA
Size	Small to large	Large to giant
Thrombosed wall	(++)	(+)
Rupture/ SAH	(−)	(+)
ICA thrombosis	(+)	(−)

14.4.2 Epidemiology and Clinical Presentation

14.4.2.1 Infradiaphragmatic Aneurysms

Infradiaphragmatic aneurysms represent approximately 3–5 % of all intracranial aneurysms and 15 % of those originated in the ICA (German and Black 1965). Aneurysms of CCA can arise from any segment of cavernous ICA, most commonly in the horizontal segment (Goldenberg-Cohen et al. 2004). Morbidity and mortality indices of

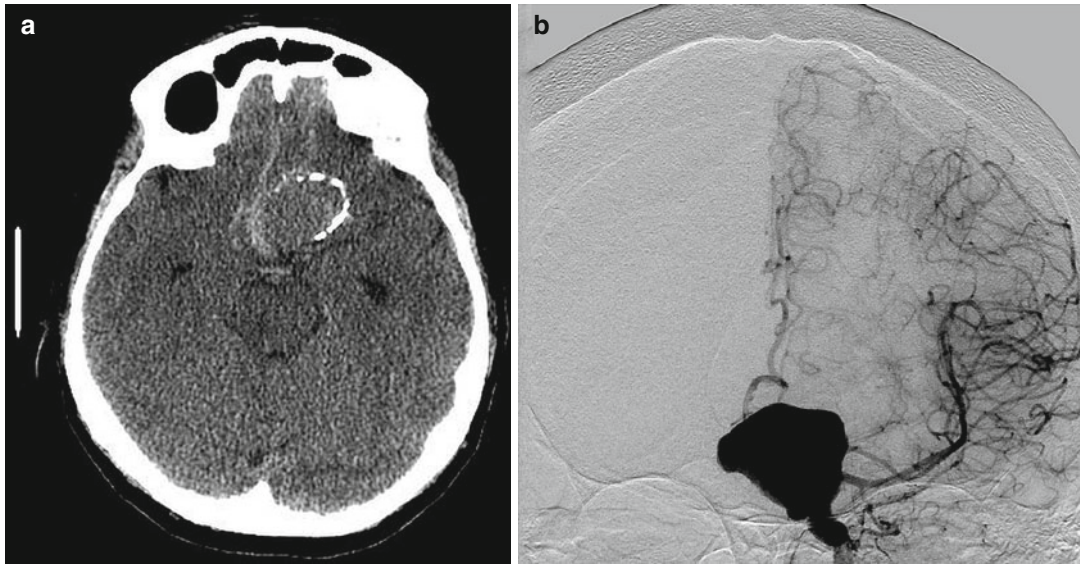

Fig. 14.3 (**a**) CT scan demonstrates a giant carotid aneurysm with sellar/suprasellar extension. Calcification is demonstrated on the aneurysm wall. (**b**) Carotid angiography shows a giant superior hypophysial artery aneurysm

aneurysms of CCA are low; however, pain and neuro-ophthalmologic deficits due to neurovascular compression are frequent (Roederer et al 1984; Seckhar and Heros 1981; Wiebers et al. 2003). Spontaneous thrombosis of ICA is a complication in patients with aneurysm of CCA, frequently associated with giant aneurysm (Kupersmith 1993; Barth and de Tribolet 1994; Stiebel-Kalish et al. 2005; Hahn et al. 1992; Krings et al. 2005), due to vascular compression (Fig. 14.4a–c). The occlusion of ICA can be a dangerous complication to patients without a patent collateral circulation (Autret et al. 1987; Linskey et al. 1990; Van der Zwan et al. 1992; Vasconcellos et al. 2009; Busuttil et al. 1981; Juvela et al. 2005; O'Donell et al. 1985; Reilly et al. 1983) manifested as an ischaemic scenario, with a devastating cerebrovascular accident, or results in spontaneous therapeutic with a patent collateral circulation.

In an uncommon event a giant and thrombosed sellar aneurysm of CCA can present an acute expansion causing a compression of the residual pituitary gland and the cavernous sinus. This situation can manifest as a pituitary apoplexy: acute hypopituitarism, headache, and ophthalmoplegia (Torres et al. 2009). The intrasellar compression might inflict direct tissue damage to the pituitary gland or stalk or instigate ischemic changes attributable to compression of the superior hypophysial arteries and/or meningohypophysial trunk, thereby presenting the symptoms of pituitary apoplexy.

Aneurysms of CCA rarely present with a SAH, due to the fact that cavernous sinus is composed by dural slices, which lay over the body of the sphenoid bone and are, infrequently, projected towards the subarachnoid space (German and Black 1965; Kupersmith et al. 1984). In the unfortunate situation of a rupture of aneurysm of CCA, it can present in different ways. A massive epistaxis can be the clinical manifestation of a rupture of aneurysm of CCA that can be managed with endovascular ablation technique of the feeding ICA (Davies et al. 2011). An atypical case was reported by Fernández-Real et al. (1994) of a patient harboring a giant ICA that presented with a SAH, left ophthalmoplegia, and left hemiparesis. The MRI showed a giant ICA aneurysm ruptured into the cavernous sinus. Again an endovascular procedure is the best option to treat this critical situation.

Symptoms of neurovascular compression are frequently associated to aneurysms of CCA

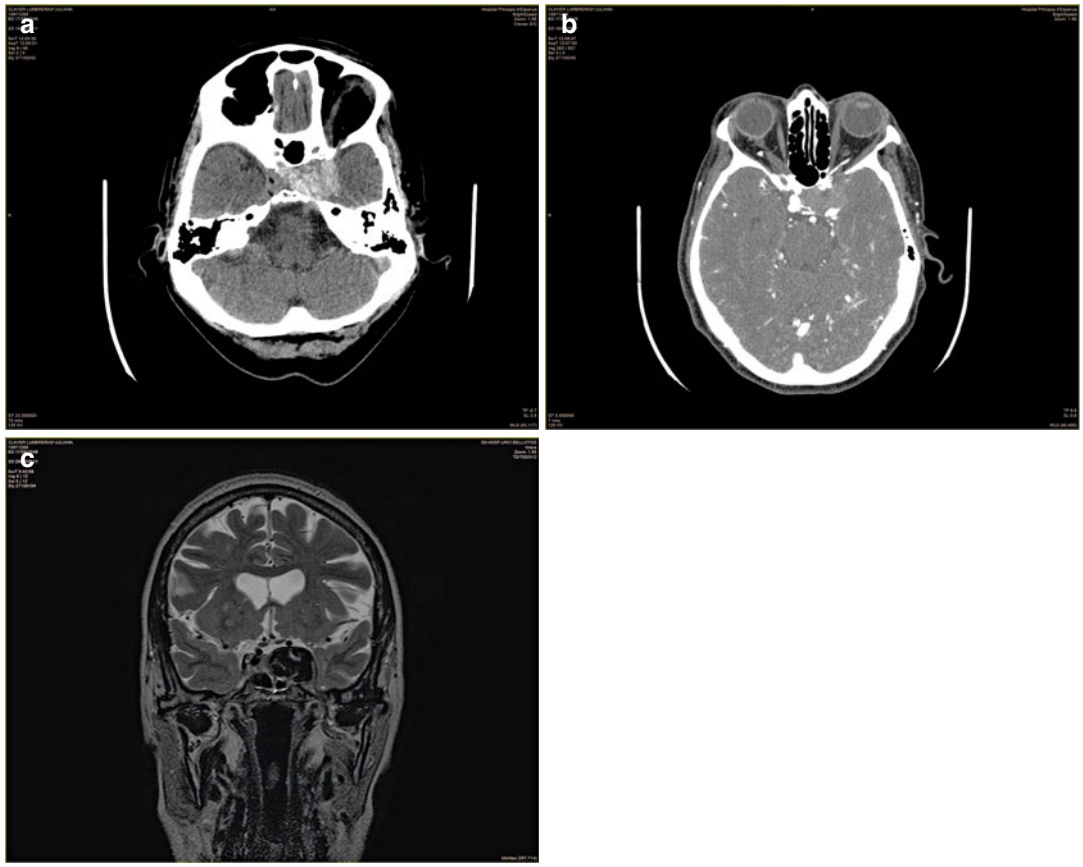

Fig. 14.4 (**a**) CT scan shows a large round hyperdense lesion centered in the left cavernous sinus. (**b**) Angio-CT demonstrates a giant partially thrombosed CCA with a small area of contrast enhancement. (**c**) MRI identifies a giant CCA complicated with an acute spontaneous thrombosis extending to the sellar area and compressing the pituitary gland

(Lees et al. 1984; Locksley 1966; McCormick and Acosta-Rua 1979), being the most prevalent diplopia due to the cranial nerve VI lesions (Vasconcellos et al. 2009). The association with other cranial nerves (III, IV, V1, and V2) located in the lateral wall of the cavernous sinus characterizes the complete cavernous sinus syndrome (Stiebel-Kalish et al. 2005).

Medial clinoid ICA aneurysms have been recently considered infradiaphragmatic aneurysms (Hanak et al. 2012). The clinoid ICA segment ascends beneath and just medial to the anterior clinoid process before passing through the dural ring to enter the subarachnoid space; this curvature places a hemodynamic vector on the medial surface of the carotid artery aimed toward the contents of the sella turcica. Aneurysms in this region presumably arise in association with small branches that supply the parasellar dura or pituitary gland. Termed "medial variant clinoid segment aneurysms," these lesions expand into the confines of the sella turcica normally occupied by the pituitary gland and, with sufficient enlargement, cause compression of the gland and resultant hypopituitarism. On rare occasions (similar to aneurysms of CCA), these lesions can rupture into the pituitary fossa, creating a clinical picture similar to pituitary apoplexy (Hanak et al. 2012).

14.4.2.2 Supradiaphragmatic Aneurysms

Supradiaphragmatic ICA aneurysms are typically giant superior hypophysial aneurysms that grow into the suprasellar area. They are a subset of ophthalmic segment aneurysms that arise from the ventromedial wall of the ICA just after it becomes intradural. Because the dural ring slants from lateral to medial (higher laterally), a small diverticulum of CSF is evident medially, termed the carotid cave, from which the most proximal superior hypophysial arteries originate.

Occasionally, large inferiorly projecting ACoA aneurysms can extend anteriorly into the sella turcica, usually in association with long optic nerves and postfixed chiasms, an anatomical situation that allows the aneurysm to reach the sella by displacing the diaphragma sellae downward.

Both superior hypophysial aneurysms and inferiorly projecting ACoA aneurysms are more likely to present with visual field cuts and/or decreased visual acuity than infradiaphragmatic aneurysms (Hanak et al. 2012). Hypopituitarism (due to mass effect on the hypothalamo-pituitary axis or the pituitary gland itself) is reported in the literature (Cartlidge and Shaw 1972; Heshmati et al. 2001; Tungaria et al. 2011; Lawson et al. 2008). Among 4,087 patients with hypopituitarism, an intrasellar aneurysm was observed in only seven patients (0.17 %) (Hanak et al. 2012). The patients reported in the literature usually have additional neurological/visual deficits secondary to brain or visual pathway compression (Cartlidge and Shaw 1972; Ooi and Russell 1986; Fernández-Real et al. 1994; Ray et al. 2002; Gondim et al. 2004; Fujii et al. 2008; Kasliwal et al. 2008). Pituitary dysfunction due to an ICA aneurysm involves the pituitary-gonadal axis, followed by the pituitary-adrenal and pituitary-thyroid axis (Tungaria et al. 2011). Diabetes insipidus and pituitary stalk compression causing elevated serum prolactin levels is a rare event (Heshmati et al. 2001). A detailed list of symptoms is shown in Table 14.2.

Table 14.2 Aneurysmal symptoms

Mass effect symptoms	Vascular symptoms
Hypopituitarism	Spontaneous thrombosis ICA
Diabetes insipidus	Embolic/ischemic events
Pituitary stalk effect	Rupture and SAH
Neuro-ophthalmologic deficit	Rupture and CSS
Visual pathway defect	Rupture and pituitary apoplexy

14.4.3 Neuroradiological Appearances

Aneurysms of the cavernous/medial clinoid and supraclinoid ICA make up nearly 5 and 15 %, respectively, of all intracranial aneurysms. When they are large to giant, they can present as masses in the sellar and parasellar region and may compress the contents of the cavernous sinus, optic chiasm, and pituitary gland.

Although the neuroradiological diagnosis is usually done with carotid arteriogram or computed tomography (CT) angiography, in cases where the patient presents a clinical syndrome of pituitary apoplexy (headache, vomit, and visual impairment), a CT scan or cranial MRI is the first radiological image obtained in order to rule out a pituitary tumor. Special attention has to be paid to the radiological findings on CT scan and cranial MRI not to misdiagnose an aneurysm as a pituitary apoplexy or a pituitary adenoma.

CT scan may show erosion of the adjacent bony wall around the cavernous sinus, with circumferential or lamellar calcification within the wall of the aneurysm. In a non-thrombosed giant aneurysm on CT, the mass intensely enhances following contrast administration, and this represents the true lumen of the aneurysm (Fig. 14.5a–d). This may simulate the appearance of other masses in the sellar/parasellar region as pituitary macroadenomas. If the aneurysm is partially thrombosed, a focal area on enhancement surrounded by a low-density area is shown (Eisenberg and Al-Mefty 2000).

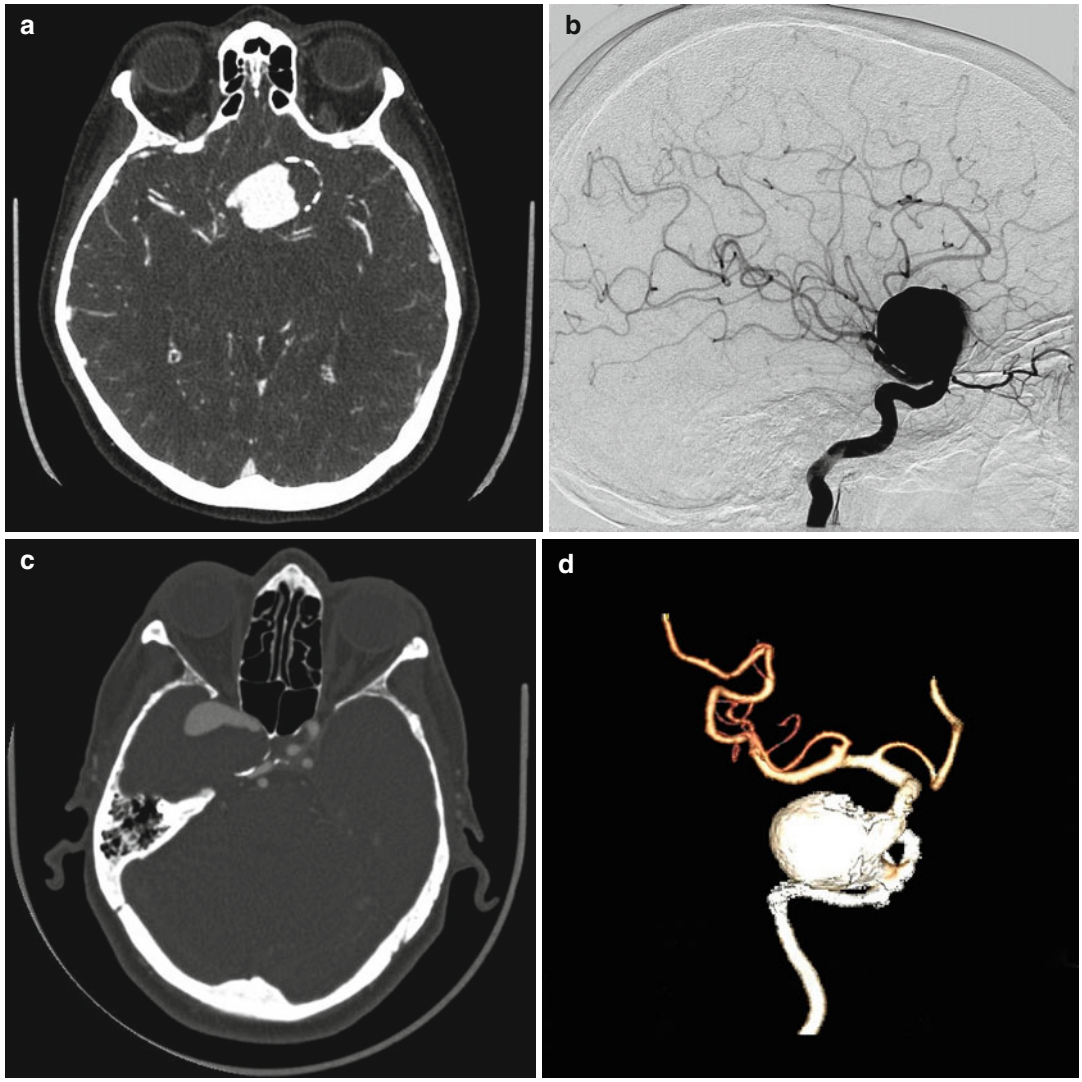

Fig. 14.5 (**a**) Angio-CT: left giant supradiaphragmatic aneurysm. The true lumen of the aneurysm is appreciated after contrast administration. (**b**) Carotid angiography demonstrates the giant supradiaphragmatic aneurysm corresponding to a superior hypophysial artery aneurysm. (**c**) Angio-CT: right giant partially thrombosed cavernous carotid aneurysm erosion and remodelation of adjacent bone is shown. (**d**) Cavernous carotid aneurysm 3D reconstruction

On MRI, the aneurysm typically presents a circumscribed area of flow void (Fig. 14.6a, b), with associated phase artifacts corresponding to the disturbed flow within the lumen. With partially thrombosed aneurysms, crescentic areas of intermediate to high signal intensity are seen in the wall of the aneurysm on MRI and represents methemoglobin in this location. This intramural hemorrhage of different ages is responsible for the onionskin appearance on non-contrast T1WI. In a recent report, the radiological features of giant intracranial aneurysms in MRI were studied, and it was found that the onionskin appearance showed only a sensitivity

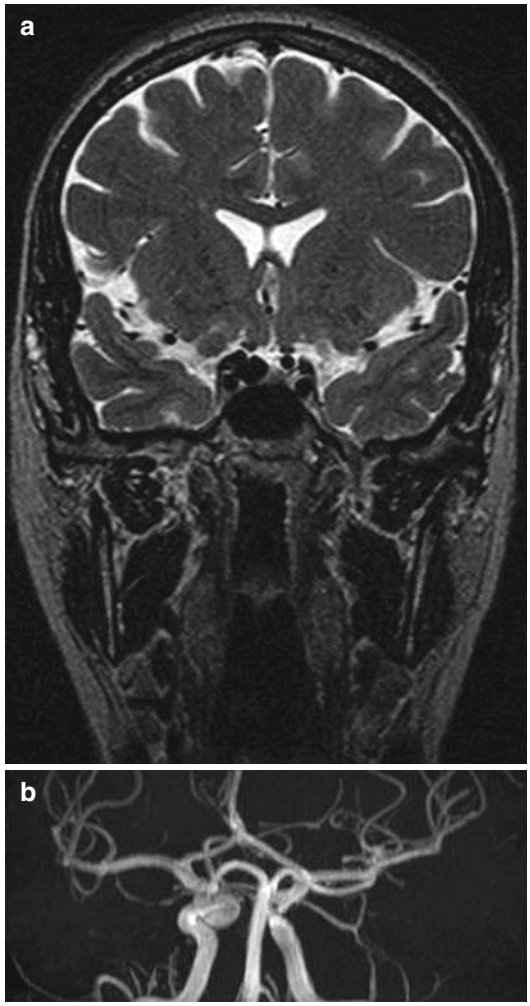

Fig. 14.6 (**a**) Cranial MRI: a circumscribed area of flow void adjacent to the right ICA correlates with a small CCA extending to the sellar region. (**b**) Angio-CT: small CCA confirmed

of 80 % (Teng et al. 2003). Furthermore, they demonstrated that the finding of flow voids is 100 % specific for aneurysms. However, the sensitivity of the presence of flow voids on noncontrast T1-weighted imaging, postcontrast T1-weighted imaging, and T2-weighted imaging was 88, 22, and 88 %, respectively.

Furthermore, in another study (Olsen et al. 1987) observed that only 12 of 15 giant aneurysms (80 %) showed signs of intraluminal blood flow. One explanation might be that the turbulent flow, frequently seen in giant aneurysms, leads to signal heterogeneity, even in the presence of a patent lumen, thereby not showing the classic finding of a flow void (Wilms et al. 1999). Recently, was reported the case of a bilateral carotid artery aneurysm simulating a pituitary apoplexy where no flow voids indicating the presence of an intracranial aneurysm could be identified on MRI (Torres et al. 2009).

Therefore, CT angiographic or carotid arteriogram imaging should be always performed preoperatively to rule out the slight possibility of vascular origin of the lesion. Carotid arteriogram will reveal the patent lumen of the aneurysm, with may be significantly smaller than the total size of the aneurysm in cases of partially thrombosed aneurysms (Atlas et al. 1987; Krisht and Tindall 1999; Hahn et al. 2000).

14.4.4 Aneurysmal Treatment

Conservative therapy may suffice for small and incidental aneurysms of CCA. Large and giant aneurysms or patients with embolic events, mass effect on cranial nerves, and subarachnoid hemorrhage unquestionably require a joint surgical/endovascular approach.

14.4.4.1 Surgical Management of Aneurysms with Intrasellar Extension

Most aneurysms of CCA are typically bound within the walls of the cavernous sinus. They are extradural and therefore carry little or no risk of SAH. They are almost always managed endovascularly. Only rare cases or large intracavernous clinoid segment aneurysms (infradiaphragmatic) with medial and superior projection expanding to and through the diaphragma sellae into the suprasellar space can result in the possibility of SAH from aneurysm rupture. The neck of these aneurysms is typically quite narrow and remains below the dura, making radical anterior clinoid process removal and wide opening of the dural

ring necessary to treat them with clipping. Nevertheless, most surgeons, however, would opt to treat these aneurysms endovascularly.

The majority of supradiaphragmatic aneurysms with sellar extension are ICA superior hypophysial aneurysms (a subset of ophthalmic segment aneurysms that arise from the ventromedial wall of the ICA just after it becomes intradural). Approximately 10 % are ACoA aneurysms project inferiorly.

Surgical treatment of large or giant superior hypophysial aneurysms typically requires exposure of the cervical ICA as a means of obtaining proximal vascular control. The pterional approach is typically augmented with an anterior clinoidectomy and unroofing of the optic canal to decompress the optic nerve and facilitate exposure of the proximal aneurysm neck. Surgical strategy focuses on reconstruction of the ICA with a series of fenestrated clips, after temporary trapping of the aneurysm.

14.4.4.2 Endovascular Management of Aneurysms with Intrasellar Extension

The field of endovascular neurosurgery is constantly evolving with new catheter technology, occlusion devices, and novel techniques. Despite advances in noninvasive diagnostic neuroimaging, catheter-based cerebral angiography remains the gold standard for the evaluation of patients with cerebrovascular disease and is the foundation for successful endovascular intervention (Hanak et al. 2012). According to the literature, although direct coil embolization has been reported for some aneurysms with intrasellar extension, no studies to date have reported more advanced endovascular techniques, such as balloon or stent-assisted coiling, or flow-diversion devices, specifically for intrasellar aneurysms (Fig. 14.7a–c). Whereas coiling might be feasible in narrow-necked aneurysms, stent-assisted coiling or telescoping flow-diversion stents may be more useful for wide-necked aneurysms. Self-expanding open cell stent designs allow navigation and stent deployment in the often-tortuous carotid siphon. In rare cases, parent artery coil occlusion may be used as a backup treatment option after successful balloon test occlusion. In cases of failed balloon test occlusion, Hunterian ligation in association with a bypass procedure is an alternative treatment option.

14.4.4.3 Association Between Sellar Aneurysms and Pituitary Adenomas

Although the possible association between intrasellar aneurysms and pituitary adenomas remains somewhat obscure, neurosurgeons must be aware that these lesions may coexist, resulting in potentially serious surgical complication (Suzuki et al. 2001; Torres et al. 2009). The presence of an aneurysm, possibly complicated by tumor invasion, makes surgery extremely hazardous and requires a cogent management strategy.

Sellar extended aneurysms can be classified as nonadjacent, adjacent, and intra-adenoma types (Sasagawa et al. 2012). In nonadjacent types, an aneurysm is located apart from the adenoma (supraclinoid aneurysm or ACoA aneurysm) and has less chance of exposure during transsphenoidal surgery. In adjacent types, an aneurysm is located adjacent to the adenoma and could be exposed during transsphenoidal surgery. In intra-adenoma types, an aneurysm is encased in the adenoma. In nonadjacent-type aneurysms, a resection of the pituitary adenoma can be carried out before aneurysm treatment due to the low risk of rupture during surgery. In adjacent types, a tumor resection can precede aneurysm treatment in cases of low-rupture-risk aneurysms and untreatable aneurysms. In intra-adenoma types, adenoma resection should be performed after coil embolization of the aneurysm.

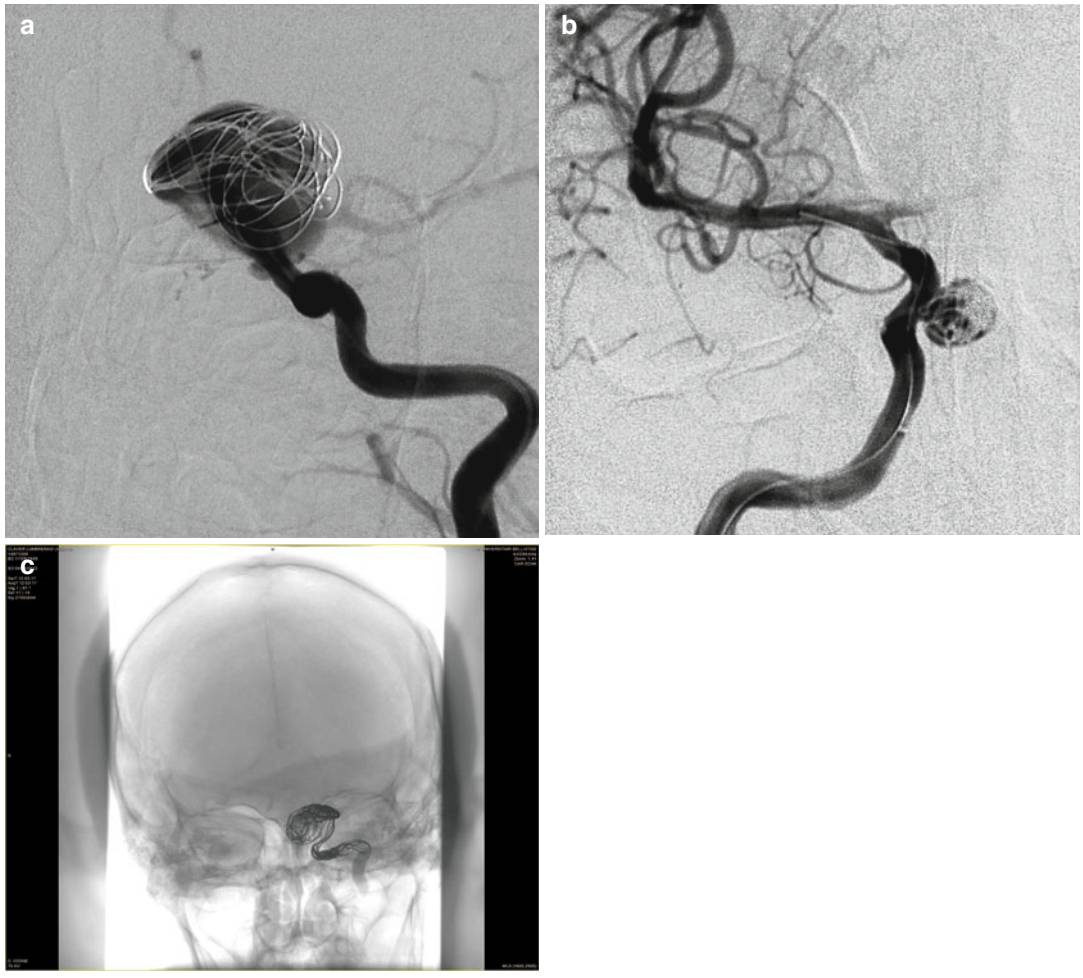

Fig. 14.7 (**a**) Carotid angiography: Balloon-assisted coiling of a giant CCA. (**b**) Carotid angiography: direct coil embolization of a small and narrow-necked CCA. (**c**) Carotid angiography: complete coil embolization of a giant CCA and occlusion of the left ICA (after the occlusion ICA test confirms collateral circulation)

Conclusion

ICA and ACoA aneurysms can extend to the sellar region and be misdiagnosed with pituitary macroadenoma or even pituitary apoplexy by MRI. Pituitary surgeon must to be prepared to identify this possible life-threatening situation, and CT or carotid arteriogram should be always performed preoperatively if there is a vascular origin suspicion of the pathology. The coexistence of ICA aneurysms and pituitary adenoma is a possible condition. Neurosurgeons should be able to identify the presence of aneurysms in preoperative images during transsphenoidal surgery planning and determine their locations and proximity to the adenoma. Such information, as well as the nature and acuity of clinical presentation, will be crucial in this decision-making process.

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Hypothalamic Lymphoma

15

Ali Akhaddar

Contents

Abbreviations

CNS	Central nervous system
CT scan	Computed tomography scan
MRI	Magnetic resonance imaging

15.1 Introduction

Central nervous system (CNS) lymphoma is an uncommon disease that accounts for less than 3 % of all intracranial tumours. It can appear in various anatomical locations, but only a few cases have been reported in hypothalamic region. To our knowledge, only 15 cases of hypothalamic lymphomas have been published until now. A variable natural history and a proximity to other central nervous structures make the management of these tumours both challenging and controversial especially with some clinical "apoplectic" presentations, making them indistinguishable from pituitary apoplexy. Effective treatment requires a multidisciplinary team to guide careful observation and judicious therapeutic intervention.

15.2 Literature Review

The literature used in the review was identified using the Medline database (PubMed, http//:www.ncbi.nlm.nih.gov/pubmed). The following English keywords were used: "lymphoma" and "hypothalamic". In addition, only three references

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(Lee et al. 2004; Akhaddar et al. 2009; Biasiotta et al. 2010) were found in English with the term "hypothalamic lymphoma", but bibliographies of all relevant articles were scanned to identify additional references from 1988 until April 2012. Only first-source information was analysed; second- or third-line references to original contributions were not taken into consideration. Abstracts were not included. For the sake of group homogeneity, patients with both intrasellar and suprasellar lymphomas were excluded (Wolfe et al. 2009; Li et al. 2012; Rizek et al. 2012). Finally, fifteen references were found which reported 15 cases during the last 25 years (Table 15.1).

15.3 Epidemiology

Lymphoma may involve the CNS either as a primary tumour or after spreading from an established systemic lymphoma (secondary tumour). This occurs in 5–29 % of patients with systemic lymphoma during the natural history of the disease and is usually associated with progressive widespread systemic disease (Fine and Mayer 1993). Primary CNS lymphoma is a less commonly encountered clinical entity (less than 2 % of all intracranial tumours) and is defined as lymphoma limited to the cranial-spinal axis without systemic disease.

Lymphomas originating in the hypothalamic region have been anedoctically reported to be among the most unusual causes of suprasellar masses. However, during the last decade there have been an increasing number of isolated reports describing new cases of hypothalamic lymphomas (Table 15.1).

In our review of 15 patients with hypothalamic lymphomas, there is an 8:7 male/female ratio. The mean age has been reported to be 48.4 years (range, 15–71 years). The peak incidence of the disease is younger than those described in patients with other CNS localizations (between the sixth and seventh decade in nonimmunocompetent subjects) (Pels et al. 2000). In these subjects the male to female ratio is 3:2. Primary hypothalamic lymphoma was seen in 11 patients (73 %) of our review and only in 4 patients (27 %) with secondary involvement. As others CNS lymphomas, hypothalamic ones may also be an incidental finding at necropsy (Patrick et al. 1989).

15.4 Clinical Presentation

Hypothalamic lymphomas may be concomitant to a secondary malignancy or inflammatory systemic diseases. The cases reported by Biasiotta et al. (2010) had a long past medical history of systemic lupus erythematosus. In addition, a possibly association with genetic predisposition may be occurred as suggested by Silfen et al. (2001).

Endocrine abnormalities were strongly associated with hypothalamic lymphoma, and pituitary hypofunction was the most common clinical presentation. More than 75 % of patients showed at the time of diagnosis clinical and/or laboratory evidence of pituitary hypofunction. In our review 11 patients (11/14, 78.5 %) exhibited anterior hypopituitarism and three had hyperprolactinemia (3/14, 21.4 %) pointing to a secondary hypopituitarism presumably due to pituitary stalk compression. Diabetes insipidus was seen in 12 patients (12/14, 85.7 %). Eight patients (8/14, 57.1 %) have both anterior and posterior pituitary failure (Table 15.1).

Together with hypopituitarism, some patients had some signs of hypothalamic dysfunction as eating disorders, sleep disturbances, mental status changes, behavioural disorders, memory loss and seizures. Headache, dysarthria, gait difficulty and cranial nerve abnormalities were less common presenting symptoms. Decreased visual acuity was seen in 2 patients (13.3 %), 2 patients (13.3 %) had diplopia due to the compression of the cranial nerves and 2 other cases (13.3 %) had visual field defects owing to optic chiasm involvement.

As far as we are aware, we report the only case presenting apoplectic symptoms similar to those of pituitary apoplexy with rapid impairment of consciousness level (Akhaddar et al. 2009; Turgut et al. 2010). This 30-year-old woman presented with 2 days of severe headaches, fever, dizziness and worsened vision. She was found to have polydipsia and polyuria with signs of dehydration.

Table 15.1 Summary of demographic data, clinical presentation, imaging characteristics, histopathologic findings, therapy and outcomes of the 15 cases with hypothalamic lymphoma reported in the literature since 1988

Author/year	Sex, age	Primary or secondary localization	Pituitary dysfunction	Neurological dysfunction	Affected sites	Histopathology findings	Treatment	Follow-up/ outcome
Patrick/1989	F, 30 y	Primary	Anterior and posterior	Ataxic with spasticity, hyperreflexia and diminished vibration sensation in the lower limbs	Normal CT scan Autopsy: cerebellum, thalamus, cingulated gyri and hypothalamus	Lymphoma (autopsy)	Corticosteroids	No clinical response. Died 26 months after onset
Balmaceda/1994	M, 65 y	Primary	Anterior	Declined cognitive function and urinary incontinence	Multiple lesions in lateral, third ventricles, right thalamus, hypothalamus and cerebellum	B-cell lymphoma Kappa light chain immunoglobulin (Stereotactic biopsy)	Intraventricular chemotherapy, systemic chemotherapy Radiotherapy	Clinical improvement Normal pressure hydrocephalus Recurrence 22 months later
Samuels/1994	M, 49 y	Primary	Anterior and posterior	Headache, diminished hearing, blurred vision, visual field defect, dysarthria, gait difficulty Cold intolerance	Hypothalamic lesion (20 mm) with extension to suprasellar cistern and optic chiasm	B-cell lymphoma Kappa light chain immunoglobulin (Stereotactic biopsy)	Chemotherapy (6 cycles of methotrexate) Hormonal therapy replacement	Clinical improvement Complete resolution of the mass

(continued)

Table 15.1 (continued)

Author/year	Sex, age	Primary or secondary localization	Pituitary dysfunction	Neurological dysfunction	Affected sites	Histopathology findings	Treatment	Follow-up/ outcome
Silfen/2001	M, 15 y	Primary (Family history of leukaemia, sarcoma and a brain tumour)	Anterior and posterior	–	Nine mm lesion in region of pituitary stalk	B-cell lymphoma suggestive of Burkitt's lymphoma	Intrathecal chemotherapy (methotrexate) and cytarabine, prednisone, vincristine, cyclophosphamide, doxorubicin and hydrocortisone Hormonal therapy replacement	Clinical improvement Complete mass resolution after 11 months Remission for 17 months
Lee/2004	M, 64 y	Primary	Anterior Hyperprolactinemia	Stiff-man syndrome and visual field defect	Hypothalamic tumour (18 mm) with optic chiasm involvement	B-cell lymphoma (Partial resection)	Radiotherapy Hormonal therapy replacement	Clinical improvement Complete mass resolution after 1 year No recurrence after 2 years
Chourmouzi/2005	M, 41 y	Primary	Anterior and posterior	–	Suprasellar hypothalamic mass (30 mm)	B-cell lymphoma	NA	NA
Akhaddar/2009	F, 30 y	Primary	Anterior and posterior Hyperprolactinemia	Severe headaches with worsening vision	Hypothalamic mass (36 mm) with optic chiasm infiltration	B-cell lymphoma (Stereotactic biopsy)	Patient refused any adjuvant treatment	Died two months after diagnosis
Chan/2010	F, 50 y	Secondary B-cell lymphoma: stage IIIB disease	Anterior and posterior	Altered mental status after 6 cycles of chemotherapy	Suprasellar mass (20×18 mm) arising from the floor of the third ventricle	B-cell lymphoma (Open cranial biopsy)	Chemotherapy (methotrexate, ifosfamide, carboplatin and etoposide regimen) Hormonal therapy replacement	NA

Fadoukhir/2010	F, 26 y	Primary	Anterior and posterior Hyperprolactinemia	Headache, leg weakness and diplopia	Suprasellar mass (9×6 mm) with pituitary stalk and paraventricular involvement	B-cell lymphoma (Stereotactic biopsy)	No treatment	The patient died of hydrocephalus before treatment two weeks after
Takasu/2010	M, 71 y	Primary	Posterior	Slightly disoriented and mild weakness of the right upper arm	Suprasellar lesion (28 mm) in hypothalamic and third ventricle region	Burkitt's lymphoma (Neuroendoscopic biopsy)	Radiotherapy Hormonal therapy replacement	Recovered Shrinkage of the lesion
Biasiotta/2010	F, 67 y	Primary (Systemic lupus erythematosus)	Posterior	Speech difficulty, disorientation, memory loss, seizures and tetraparesis	Hypothalamic lesion (10 mm)	B-cell lymphoma (Open cranial biopsy)	Chemotherapy (intravenous methotrexate)	Died of pneumonia during the second cycle
Layden/2011	M, 50 y	Primary	Anterior and posterior	Mental status change, severe confusion, hallucinations and paranoia	Bilateral hypothalamic lesion extending to the optic tract 3 months later: progression to cerebral hemisphere and thalamus	B-cell lymphoma (Open cranial biopsy) Lumbar puncture: kappa-restricted B cells	Chemotherapy (5 cycles of intravenous methotrexate, procarbazine, vincristine and rituximab) Radiotherapy, than : two cycles of cytarabine Hormonal therapy replacement	Clinical improvement Resolution of brain lesion at 6 months
Schwingel/2011	M, 51 y	Secondary (Axillary large-cell non-Hodgkin lymphoma treated with chemotherapy and radiotherapy 8 y early)	NA	Unilateral third nerve palsy	Hypothalamic (18 mm), pineal and spleen lesion	Non-Hodgkin lymphoma (Spleen histopathology)	Chemotherapy	Brain lesions disappeared 11 months later, but a new lesion appeared in the right lateral ventricle and died

(continued)

Table 15.1 (continued)

Author/year	Sex, age	Primary or secondary localization	Pituitary dysfunction	Neurological dysfunction	Affected sites	Histopathology findings	Treatment	Follow-up/ outcome
Brousallis/2011	F, 57 y	Secondary	Posterior	Diplopia, eating disorder and psychosis	Hypothalamic lesion (14×8×10 mm) extended into the mesencephalon, the anterior commissure and to the mammillary bodies Thoracic and abdominal lymph nodes	B-cell lymphoma (Biopsy of iliac lymph nodes)	Chemotherapy (3 cycles of cladribine therapy) Hormonal therapy replacement	Clinical improvement Brain lesions disappeared 2 months after
Antic/2012	F, 60 y	Secondary	Posterior	Headache, back and left leg pain and sleep disturbance	Lumbar spinal canal Hypothalamus and lateral ventricle	B-cell lymphoma (Spinal surgery)	Chemotherapy (Intravenous and intrathecal methotrexate) Radiotherapy Hormonal therapy replacement	Clinical improvement with intermittent febrile episodes Complete remission of the brain lesions and partial regression of the spinal tumour

F female, *M* man, *Y* years, *NA* no data available

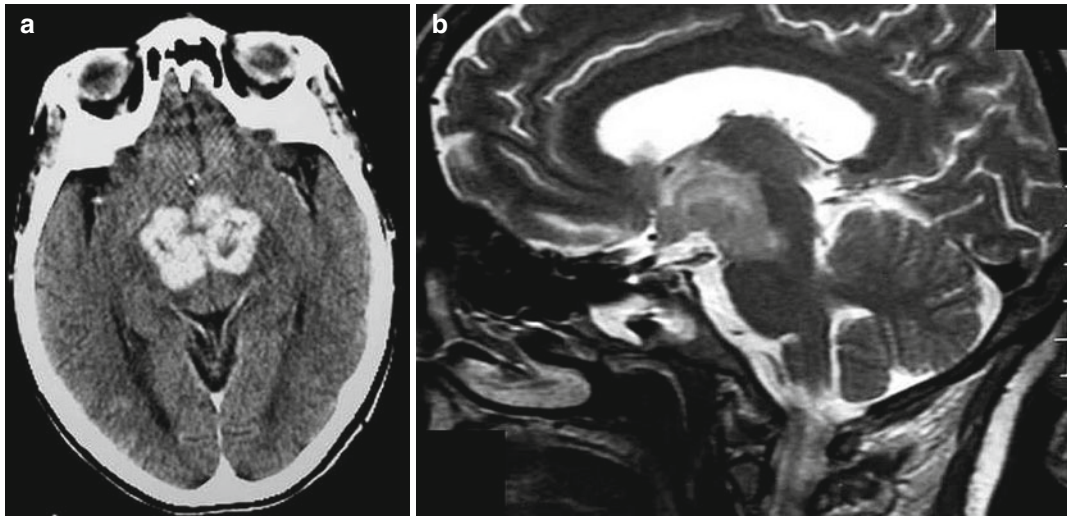

Fig. 15.1 Enhanced CT scan on axial view (**a**) and sagittal T2-weighted MRI (**b**) showing a bilateral hypothalamic lymphoma with suprasellar extension, optic chiasm infiltration and brainstem involvement

15.5 Diagnostic Studies

Lymphomas are rarely limited to the hypothalamic area (2/15, 13.3 %); in more cases the lesion may be extended to neighbouring regions (13/15, 86.7 %); the involved sites were suprasellar cistern, optic chiasm, pituitary stalk, pituitary gland, third and lateral ventricles, mammillary bodies, thalamus, brainstem, cerebellum and pineal area (Table 15.1).

Magnetic resonance imaging (MRI) provides anatomic details of the suprasellar and parasellar structures. It delineates the extent of tumour invasion and accurate assessment of tumour growth and response to treatment (Yasuda et al. 2010). Lymphoma in the hypothalamic region appeared to be iso- to hypointense on T1-weighted images and showed intense and homogeneous enhancement after contrast injection. On T2-weighted images, lesion may show hypointensity due to a high nucleus/cytoplasm ratio (Figs. 15.1 and 15.2).

It's well known that if a CNS lymphoma is suspected, administration of corticosteroids therapy should be delayed until a definitive biopsy has been performed.

The differential diagnosis of a hypothalamic mass includes craniopharyngioma, Rathke cleft cyst, germ cell tumour, granulomatous processes, glioma, hamartoma, germinoma and aneurysm (Samuels and de la Monte 1994; Akhaddar et al. 2001, 2011; Oweity et al. 2002; Chourmouzi et al. 2005; Binning et al. 2008; Rennert J and Doerfler 2007; Raoa et al. 2008; Fadoukhair et al. 2010; Belfquih et al. 2012).

Craniopharyngioma has a heterogeneous appearance with solid and cystic elements tumour in the suprasellar region. Rathke cleft cysts usually have the following imaging features: a sellar epicentre, smooth contour, lack of calcification, lack of internal enhancement and a homogeneous signal intensity within the lesion. The characteristic features of granulomatous diseases are thickening of the pituitary stalk and absence of a normal bright posterior pituitary signal. Imaging of germ cell tumour shows generally an infiltrative, solid, homogeneous mass in the midline with intense contrast enhancement. Hypothalamic glioma tends to be solid with microcyst formation and is iso- or hypointense on T1-weighted images, hyperintense on T2-weighted images and demonstrates enhancement with contrast. Hypothalamic hamartoma presents as precocious puberty in a young child with a nodular mass in the suprasellar cistern. The mass is isointense with normal brain on T1-weighted images and isointense or mild

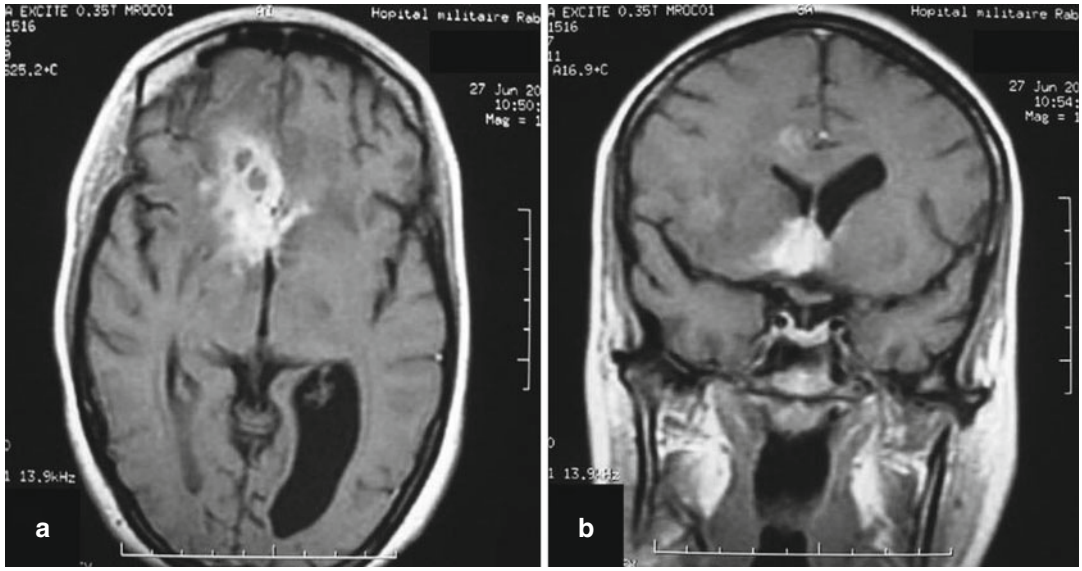

Fig. 15.2 Axial (**a**) and sagittal coronal (**b**) T1-weighted MRIs with gadolinium infusion demonstrate a suprasellar-hypothalamic lymphoma with bifrontal extension

hyperintense on T2-weighted images. These lesions usually do not enhance after contrast administration. Suprasellar germinoma appears as a well-marginated lobulated homogeneous tumour with prolonged T1 and T2 relaxation times which strongly enhances after gadolinium administration. The presence of these imaging findings along with the presence of diabetes insipidus and a suprasellar mass is a clue to the diagnosis of germinoma. Although metastatic tumour could not be ruled out, absence of any primary malignancy on chest, abdominal and pelvic computed tomography scan (CT scan) made it unlikely. Aneurysms of the sellar region usually originate from the cavernous or supraclinoid portions of the internal carotid artery and account for up to 10 % of all cerebral aneurysms. In selected cases, they can mimic other supra-, para- or intrasellar lesions. MRI or CT scan is useful in differentiating tumour from thrombosed and nonthrombosed aneurysms.

The differential diagnosis of primary versus secondary CNS lymphomas may include a complete neurological staging, including cerebrospinal fluid examination and ophthalmological evaluation with slit-lamp examination to exclude vitreous or retinal involvement. In addition, an abdominopelvic CT scan and bone marrow biopsy may be obtained to exclude systemic lymphoma (Giustina et al. 2001).

15.6 Pathology

Histologically, hypothalamic lymphomas are similar to other CNS lymphomas: predominant B-cell non-Hodgkin lymphoma. In our review of 15 reports of patients with hypothalamic lymphoma, 2 did not provide detailed histological description (Patrick et al. 1989; Schwingel et al. 2011), and 13 were B-cell immunophenotype which 2 patients had Burkitt's lymphoma (Table 15.1).

15.7 Treatment and Outcome

The management of hypothalamic lymphoma is multimodal requiring judicious use of observation, surgery, chemotherapy, radiotherapy and hormone substitution. The initial challenge is establishment of the diagnosis by surgical biopsy: open or stereotactic to differentiate from other suprasellar tumours. Most patients underwent surgical biopsy through stereotactic approach.

In our review, treatments were not observed in three cases, four received chemotherapy alone and one patient received radiotherapy alone. Chemotherapy followed by radiotherapy was performed in four cases. It seems that in immunocompetent patients treated with chemotherapy followed by radiotherapy have considerable improvements in survival (Hobson et al. 1986; Patrick et al. 1989; Jonkhoff et al. 1993; Pioltelli et al. 1996; Lee et al. 2004). Regimens used were different and were in the most cases extrapolated from the protocol used in CNS lymphoma. Despite the increasing number of studies published since a decade on CNS lymphoma and recent therapeutic advances, several questions still remain unanswered about the optimal management of these unusual tumours.

Treatment of immunocompromised patients is aimed at reversing the immunosuppression. If it is reversed, the tumour may regress. In patients with AIDS-associated primary CNS lymphoma, therapy of this type is not possible and the prognosis is very poor as with secondary CNS lymphoma (Samuels and de la Monte 1994).

We attempted to clarify the relationship between treatments and prognosis. However, the treatments varied case by case. In addition, in many reports, the description of clinical outcomes was limited (Matsuda et al. 1999).

Conclusion

Hypothalamic lymphoma is a rare but an increasing clinical entity in recent epidemiological data. It may be a primary tumour or after spreading from an established systemic lymphoma. The clinical presentations are always atypical. Acute presentation may mimic a pituitary apoplexy. MRI findings are largely nonspecific and the tumours are rarely limited to the hypothalamic area. The definite diagnosis depends on histopathologic description. The more common immunophenotype are B-cell non-Hodgkin lymphoma. The overall outcome is favourable with significant survival. Early diagnosis and prompt treatment combination of surgery, chemotherapy, radiation therapy and hormonal substitution can ensure maximal quality of life over the long term. Great attention must be paid to the lasting morbidity associated with pituitary/hypothalamic insufficiencies.

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Rathke's Cleft Cysts Mimicking Pituitary Apoplexy

16

Fuminari Komatsu

Contents

Abbreviations

MRI Magnetic resonance imaging
RCC Rathke's cleft cyst

16.1 Introduction

Rathke's cleft cyst (RCC) is an epithelial cell-lined cystic lesion of the pituitary that is thought to be derived from the remnants of Rathke's pouch, a dorsal invagination of the stomodeal ectoderm. Most remain asymptomatic throughout an individual's life. Occasionally, however, the cysts grow and compress surrounding structures, becoming symptomatic. Symptomatic RCC is usually accompanied by a long history of headache, visual disturbance, and hypopituitarism (Aho et al. 2005; Nishioka et al. 2006a, b). However, in rare cases, patients present with symptoms mimicking pituitary apoplexy. The incidence of acute presentation of RCC ranges from 11.3 to 20 % in the literature (Benveniste et al. 2004; Kim et al. 2004; Chaiban et al. 2011). From the pathological perspective, such cases are classified into haemorrhagic and non-haemorrhagic RCC apoplexy (Binning et al. 2008). Haemorrhagic RCC cases have haemorrhage on intraoperative or pathological findings (Binning et al. 2008; Chaiban et al. 2011). Non-haemorrhagic RCC apoplexy includes hypophysitis, aseptic meningitis, and abscess formation (Komatsu et al. 2010). RCC apoplexy from abscess formation is extremely rare (Komatsu et al. 2010).

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16.2 Clinical Features

The mean age of cases presenting with RCC apoplexy reported in the literature ranged from 32.0 to 56.8 years (Binning et al. 2008; Komatsu et al. 2010; Chaiban et al. 2011). The initial symptoms of RCC with apoplexy include headache, visual disturbance, general malaise, polyuria, dizziness, nausea, vomiting, and fever (Binning et al. 2008; Komatsu et al. 2010; Chaiban et al. 2011). The duration of headaches varies from sudden onset to a few days. Haemorrhagic RCC cases tend to have headache and visual disturbances, including loss of visual acuity, visual field defects, and diplopia, rather than hypopituitarism (Onesti et al. 1990; Kurisaka et al. 1998; Nishioka et al. 1999; Pawar et al. 2002; Binning et al. 2008; Komatsu et al. 2010; Chaiban et al. 2011). It is thought that the symptoms in haemorrhagic RCC are attributed to rapid increases in cystic volume by intracystic haemorrhage and compression of parasellar structures. In contrast, RCC cases with hypophysitis, which is a cause of non-haemorrhagic RCC apoplexy, often have symptoms related to adeno- and neurohypophyseal dysfunction, but they less often have visual disturbances (Komatsu et al. 2010). It is presumed that the symptoms of RCC with hypophysitis stem from chemical reactions to hypophyseal tissue following the rupture of the cyst contents rather than compression of the surrounding structures. Spillage of cyst contents into the subarachnoid space causes chemical aseptic meningitis, with the patient developing headache, fever, and nuchal rigidity (Sonnet et al. 2006; Koutourousiou and Seretis 2011).

16.3 Neuroimaging

An intrasellar cystic mass with or without parasellar extension is seen on MRI (Figs. 16.1 and 16.3). However, characteristic and consistent findings have not been identified for RCC apoplexy. The intensity of the cyst contents on T1- and T2-weighted image varies from case to case. Sphenoid mucosal thickening, which is seen in apoplexy due to pituitary adenoma, is also reported in RCC apoplexy (Binning et al. 2008; Chaiban et al. 2011). Cases that demonstrate rim enhancement following gadolinium injection have been described (Figs. 16.1 and 16.3) (Komatsu et al. 2010). Rim enhancement may contribute to distinguishing between RCC apoplexy and apoplexy due to pituitary adenoma, but it is difficult to diagnose RCC apoplexy preoperatively.

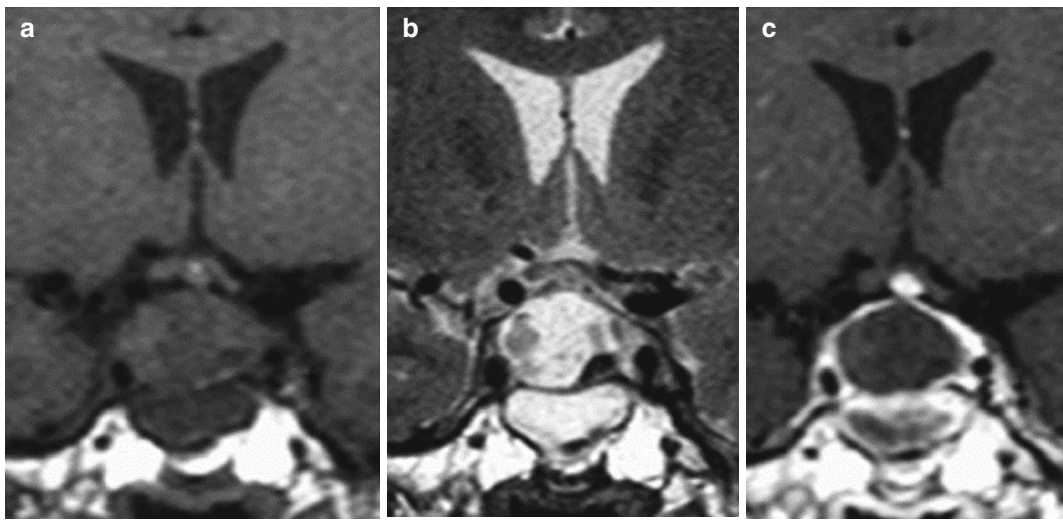

Fig. 16.1 An illustrative case of haemorrhagic RCC (Komatsu et al. 2010). A 46-year-old man had a 4-day history of severe headache. Neurological and endocrinological findings were normal. Coronal MR imaging show an intrasellar cystic mass with suprasellar extension, which is isointense on T1-weighted imaging (**a**) and mixed intensity on T2-weighted imaging (**b**). Rim enhancement is demonstrated along the cyst wall after gadolinium injection (**c**)

16.4 Pathological Findings

On pathological examination of haemorrhagic RCC, the wall of the cyst contains many thin blood vessels in granulation tissue with layers of haematoma, and it is hypothesized that the cause of haemorrhagic RCC is disruption of these small vessels (Fig. 16.2) (Nishioka et al. 1999). In RCC cases with hypophysitis, diffuse lymphocytic inflammation in the pituitary gland is seen (Fig. 16.4) (Komatsu et al. 2010).

16.5 Treatment

Hormonal replacement is important for cases with severe endocrinological deficits with acute onset. Drainage of cyst contents by a

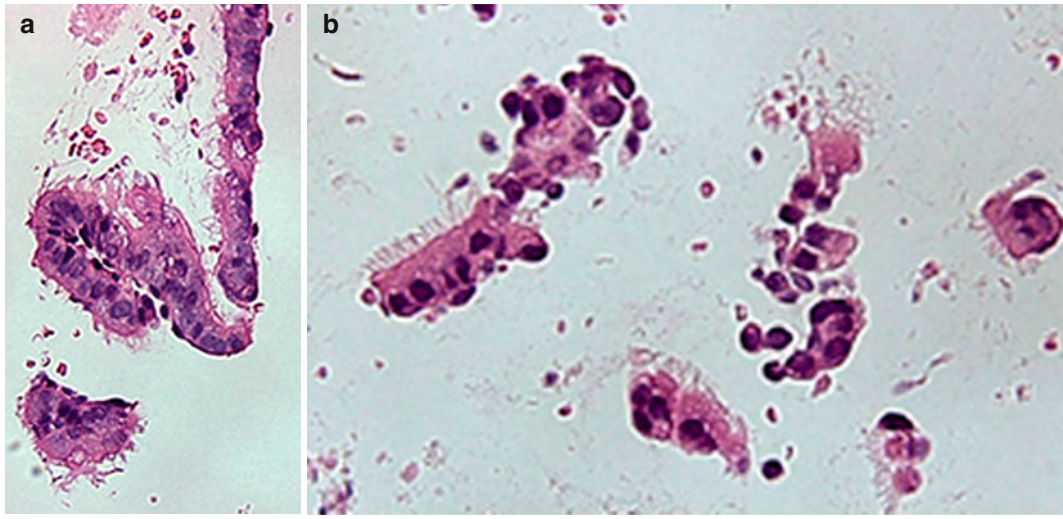

Fig. 16.2 Haematoxylin and eosin (H&E)-stained section of the case shown in Fig. 16.1 (Komatsu et al. 2010). Operative findings showed that the cyst was filled with haematoma. Pathologic examination shows that the RCC consists of ciliated columnar epithelium. The final diagnosis is RCC with haemorrhage (original magnification: **a** ×200, **b** ×400)

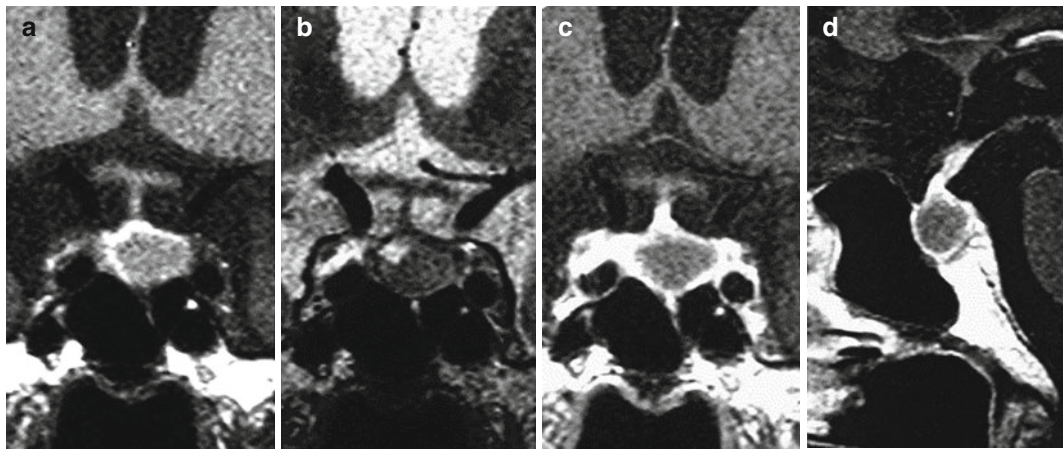

Fig. 16.3 Coronal and sagittal MRI of RCC with hypophysitis (Komatsu et al. 2010). A 77-year-old man developed a 2-day history of panhypopituitarism. MRI showed an intrasellar cyst with isointensity on T1-weighted imaging (**a**) and mixed intensity on T2-weighted imaging (**b**). Rim enhancement along the cyst wall is seen following gadolinium injection (**c** coronal view, **d** sagittal view)

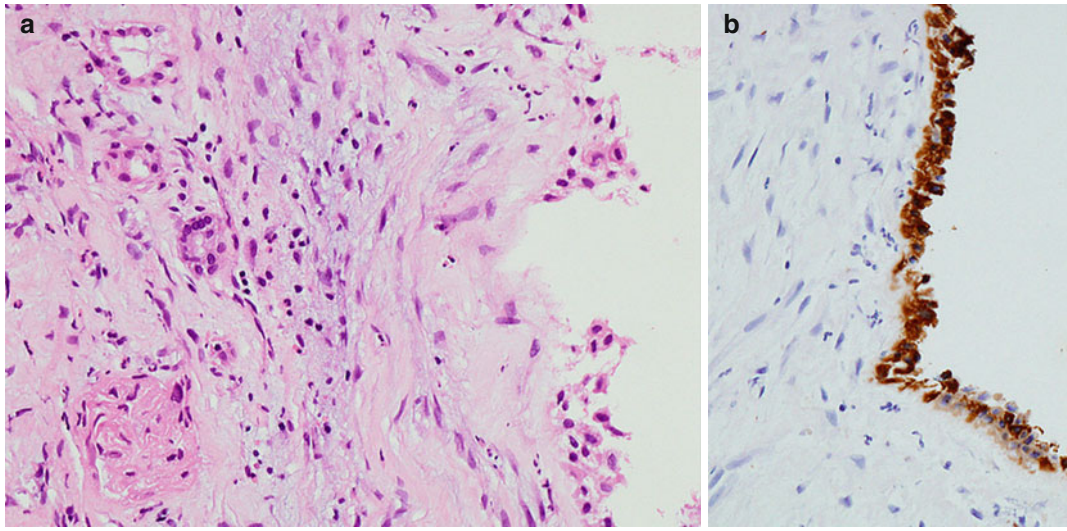

Fig. 16.4 Histology of the surgical specimen (H&E) of the case illustrated in Fig. 16.3 showing ciliated columnar epithelium and diffuse lymphocytic infiltration (**a**, original magnification ×200) (Komatsu et al. 2010). Immunohistological staining is positive for cytokeratin AE1/AE3, which is a marker for epithelium, on the cyst wall (**b**, original magnification ×200)

transsphenoidal approach is carried out as surgical treatment. There is a high rate of improvement of visual symptoms following surgery (Onesti et al. 1990; Kurisaka et al. 1998; Nishioka et al. 1999; Pawar et al. 2002; Binning et al. 2008; Komatsu et al. 2010; Chaiban et al. 2011). On the other hand, surgery can contribute to recovery from the endocrinological dysfunction, but the degree of endocrinological recovery varies (Binning et al. 2008; Komatsu et al. 2010; Chaiban et al. 2011). Further investigations regarding the effects of surgery on endocrine function are needed.

Conclusion

RCC rarely presents with an acute onset, and the presentation is quite consistent with the features of pituitary apoplexy caused by pituitary adenoma. Regarding the mechanism of RCC apoplexy, it is presumed that mucosal cyst contents in RCC trigger disruption of blood vessels in the cyst or cyst wall structure, leading to haemorrhage in the cysts, hypophysitis of the hypophyseal tissue, and chemical meningitis after spreading into the subarachnoid space. Although RCC apoplexy is difficult to diagnose preoperatively, RCC should be included in the differential diagnosis of pituitary apoplexy, and early surgical treatment, as for pituitary apoplexy caused by pituitary adenoma, is needed.

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Part VII

Management

Conservative Management of Pituitary Apoplexy

17

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Contents

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Abbreviations

ACTH	Adrenocorticotropic hormone
CSF	Cerebrospinal fluid
CT	Computed tomography
GH	Growth hormone
MRI	Magnetic resonance imaging

17.1 Introduction

Pituitary apoplexy is a rare, potentially life-threatening complication of pituitary adenomas. Survivors may have disabling visual and neurological sequelae. The pathophysiology of pituitary apoplexy is poorly understood but generally includes abrupt hemorrhage and/or infarction of a pituitary adenoma, leading to an increase in intrasellar pressure (Zayour et al. 2004). The outcome of pituitary adenoma apoplexy is highly variable and difficult to predict (Chanson et al. 2004).

Onset is often abrupt, with very severe headache, nausea-vomiting and, in 70 % of cases, ocular palsies due to the pressure elevation in the cavernous sinus injuring its content, but also decreased visual acuity and visual field defects through compression of the optic chiasm by the expanding intrasellar mass. This dramatic picture probably explains why pituitary apoplexy is considered a neurosurgical emergency by various authors and has almost always been treated surgically in the past (Epstein et al. 1971; Ebersold et al. 1983; Bills et al. 1993; Rolih and Ober

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1993). However, reports of spontaneous clinical improvement and shrinkage (or disappearance) of apoplectic pituitary adenomas suggest that a conservative approach may be appropriate in selected cases. Pelkonen et al. (1978) were among the first to propose a conservative approach, after observing not only spontaneous recoveries but also cases in which the pituitary apoplexy appeared to cure hormonal hypersecretion (GH, ACTH, etc.) (Pelkonen et al. 1978). Other authors also subsequently advocated a conservative approach (Jeffcoate and Birch 1986; McFadzean et al. 1991).

In 1995, Maccagnan et al. reported the results of a prospective study in which they treated pituitary apoplexy with high-dose steroids (Maccagnan et al. 1995). Only patients whose visual impairment or altered consciousness failed to improve underwent surgery. Conservative steroid treatment was possible in 7 of 12 patients, leaving only 5 patients who needed surgery. Visual defects resolved in 6 of the 7 patients and improved in the remaining patient. Importantly, the posttreatment prevalence of pituitary hormone deficiency and incidence of tumor regrowth were similar in conservatively and surgically treated patients.

17.2 Risk-Benefit Ratio of Conservative Treatment Versus Surgery

The risk-benefit ratio of conservative treatment must be carefully evaluated, in terms of not only visual outcome and pituitary function but also subsequent tumor growth. Indeed, what is the point of conservative treatment during the acute phase of pituitary apoplexy if surgery will ultimately be necessary? However, the potential serious complications of surgery also need to be taken into account.

Three large studies have compared the outcomes of conservatively and surgically treated patients with pituitary apoplexy (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006). As their authors acknowledged, these studies suffered from a selection bias due to their retrospective design: indeed, patients in the conservative group generally had less severe ocular defects than those in the surgical group (Table 17.1).

Guidelines were recently proposed in UK for the management of patients with pituitary apoplexy (Rajasekaran et al. 2011).

17.3 Outcome of Ocular Palsies After Conservative Treatment

Ocular palsies in this setting are due to acute pressure elevation in the cavernous sinus (Zayour et al. 2004). They are present in more than two-thirds of patients (Nawar et al. 2008) and generally improve within a few days or weeks, whether or not the patient undergoes surgery. In published series (Table 17.1), oculomotor palsies resolved completely in 64–100 % of patients without surgery and in 63–75 % of patients with surgery (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006). This lack of impact of surgery is not surprising, as ocular palsies are not associated with a poor prognosis.

17.4 Outcome of Ocular Defects After Conservative Treatment

Pituitary apoplexy can have neuro-ophthalmologic consequences when suprasellar extension of the adenoma compresses the optic chiasm, a complication found in three-quarters of patients enrolled in surgical series (Onesti et al. 1990; Randeva et al. 1999; Semple et al. 2005; Nawar et al. 2008). Decreased visual acuity and visual field defects (particularly bitemporal hemianopsia) are caused by upward enlargement of the intrasellar contents at the onset of apoplexy. Sudden-onset mono- or binocular blindness may occur. A degree of visual defect may preexist, while onset may reveal the disease in some cases.

Surgical decompression normalizes visual acuity in more than one-half of cases and improves it in another one-third of cases (Ayuk

Table 17.1 Main characteristics of patients with pituitary apoplexy at presentation and outcome after conservative or surgical management in three retrospective comparative studies

Author (years)	Ayuk et al. (2004)			Gruber et al. (2006)			Sibal et al. (2004)		
Type of management	Conservative	Surgery	P	Conservative	Surgery	P	Conservative	Surgery	P
N	18	15	–	20	10	–	18	27	–
Mean age (year) (range)	NA	NA	–	54 (23–84)	46 (17–70)	–	45.7 (25–72)	50.7 (25–72)	NS
Male/female	NA	NA	–	16/4	7/3	–	9/9	19/8	
At presentation									
Number (%) with decreased visual acuity	NA	NA	–	11 (55)	7 (70)	–	4/15 (26)	14/24 (58)	0.01
Number (%) with visual field defect	6 (33)	7 (46)	ns	4 (20)	6 (60)	–	4/17 (24)	16/25 (64)	0.01
Number (%) with ocular palsy	7 (39)	8 (53)	ns	12 (60)	3 (37)	–	8/17 (47)	14/26 (54)	NS
Number (%) with hypopituitarism	13 (87)	15 (83)	ns	15 (75)	9 (90)	–	13/18 (72)	21/24 (87)	NS
Outcome									
Decreased visual acuity									
Complete resolution	NA	NA	–	5/11 (45)	4/7 (57)	–	3/4 (75)	8/14 (57)	–
Partial/near-complete resolution	NA	NA	–	4/11 (36)	2/7 (28)	–	1/4 (25)	5/14 (36)	–
No improvement	NA	NA	–	2/11 (19)	1/7 (15)	–	0	1/14 (7)	–
Visual field defect									
Complete resolution	6/6 (100)	4/7 (57)	ns	2/4 (50)	2/6 (33)	–	3/4 (75)	7/16 (43)	–
Partial/near-complete resolution	0	NA	–	1/4 (25)	3/6 (50)	–	1/4 (25)	8/16 (50)	–
No improvement	0	NA	–	1/4 (25)	1/6 (17)	–	0	1/16 (7)	–
Ocular palsy									
Complete	7/7 (100)	5/8 (63)	ns	10/12 (83)	2/3 (66)	–	6/8 (75)	9/14 (64)	–
Partial/near-complete resolution	0	NA	–	2/12 (17)	1/3 (33)	–	2/8 (25)	4/14 (29)	–
No improvement	0	NA	–	0	0	–	0	1/14 (7)	–
Endocrine impairment									
Normal function	NA	NA	–	1 (5)	2 (20)	–	2 (11)	5 (19)	–
Corticotropic deficiency	13/18 (72)	13/15 (87)	ns	(68)	(60)	–	NA	NA	–
Thyrotropic deficiency	9/15 (60)	13/15 (87)	ns	(70)	(68)	–	NA	NA	–
Gonadotropic deficiency	15/18 (83)	10/15 (67)	ns	(80)	(86)	–	NA	NA	–
Tumor growth									
Recurrence of pituitary adenoma	1 (5)	1 (6)	–	0	6 (60)	–	4 (22)	1 (4)	–

NA non-available, *NS* non significant

et al. 2004; Sibal et al. 2004; Gruber et al. 2006). Visual field defects normalize after surgery in 30–40 % of cases and improve in another 50 % (Table 17.1). Unfortunately, visual outcome is poorer in patients with more severe forms such as monocular or binocular blindness, irrespective of the mode of management, conservative or surgery (Gruber et al. 2006; Muthukumar et al. 2008; Turgut et al. 2010).

The rate of recovery or improvement of visual acuity or the visual field is similar after conservative and surgical treatment: visual acuity normalized in 45–75 % of patients and improved in 25–36 % in studies comparing the two strategies (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006), while visual field defects normalized in 50–100 % of cases and improved in 25 % (Table 17.1). Even blindness was found to resolve at the same rate (~50 %) in patients treated with conservative and surgical approaches in one study (Gruber et al. 2006), in which patients with contraindications to surgery (anesthetic risk) were treated with steroids alone. Similar visual improvement was also found in a more recent study (Leyer et al. 2011).

It has been argued that conservatively treated patients may have less severe visual defects than surgically treated patients and that this might explain why the improvement is at least as good (Nawar et al. 2008; Rajasekaran et al. 2011). The number of patients with visual defects was effectively higher in the surgical groups (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006). Visual defects were also more severe, notably in Gruber's study, in which the proportions of patients with very poor visual acuity and >50 % field loss were clearly higher in the surgical group (Gruber et al. 2006). Nevertheless, the visual deficits either resolved or improved substantially in almost all the patients in both surgical and conservative groups (Table 17.1).

17.5 Outcome of Pituitary Function After Conservative Treatment

One of the main arguments in favor of the surgical approach is that surgical decompression can improve pituitary function, which is frequently impaired. Indeed, according to the review by Nawar et al. (2008), respectively, 67, 45, and 82 % of patients with pituitary apoplexy have adrenal deficiency, thyroid deficiency, and gonadal deficiency at presentation. After surgery, pituitary function recovers partially or completely in more than 50 % of cases (Arafah et al. 1990; Randeva et al. 1999; Nawar et al. 2008). Various series suggest that only about 20 % of patients do not require replacement therapy (Nawar et al. 2008) after surgery for pituitary adenoma apoplexy.

Is conservative treatment really less effective than surgery in terms of pituitary functional outcome? In the three studies which compared the two approaches, the proportions of patients with posttreatment hypocortisolism, hypothyroidism, and hypogonadism were roughly the same in both surgical and conservative groups (Ayuk et al. 2004; Sibal et al. 2004; Gruber et al. 2006). Similar results were found in a more recent study (Leyer et al. 2011): 16 % of patients had normal pituitary function after surgery versus 37 % of patients after conservative treatment (no statistically significant difference).

Whatever the management approach, the endocrine prognosis is poor in patients with pituitary apoplexy, with frequently irreversible damage. In our opinion, endocrine outcome is not an important criterion when choosing between surgical and conservative treatment, as the two approaches seem to have the same impact on pituitary functional recovery.

17.6 Tumor Outcome After Conservative Treatment

Another major argument in favor of the surgical approach is that surgery can not only relieve the symptoms of pituitary apoplexy but also remove the pituitary tumor. However, tumor shrinkage is frequent following apoplexy, many patients having no visible tumor remnant after the episode. Very few studies have examined the "completeness" of tumor removal between patients receiving surgery or conservative treatment for apoplexy. Recently, a long-term follow-up study showed a recurrence rate of 11.1 %, an average of 6.6 years after surgery (Pal et al. 2011). In one of the three

comparative studies (Table 17.1), the incidence of tumor regrowth was low (<5 %) and similar with the two approaches (Ayuk et al. 2004), while it was higher after surgery in another study (22 % versus 0 % with conservative treatment) (Gruber et al. 2006); only one of these three comparative studies has shown that surgery is associated with a lower rate of tumor regrowth (4 % versus 22 % after conservative treatment) (Sibal et al. 2004). Likewise, Leyer et al. (2011) found that tumor regrowth only occurred in the conservative treatment group (17 % versus 0 %). Thus, the respective merits of the two approaches in terms of tumor control are currently difficult to judge.

17.7 Conservative Treatment as a Means of Avoiding Surgical Complications

Even if surgical complications are rare, particularly in experienced hands, CSF leakage and diabetes insipidus (sometimes permanent) may occur (Dubuisson et al. 2007; Moller-Goede et al. 2011). Surgical papers rarely mention the rate of surgical complications in patients with apoplexy. Nevertheless, it seems that endocrine outcome after elective pituitary surgery is poorer in patients with pituitary apoplexy than in patients without apoplexy (Moller-Goede et al. 2011).

Another important point is that, in this acute setting, the operation may be performed by an on-call neurosurgeon rather than by a skilled pituitary neurosurgeon, as underlined in the UK guidelines (Rajasekaran et al. 2011).

17.8 Can Imaging Help to Choose Between Conservative and Surgical Treatment?

There are few data on the value of CT or MRI for prognostication or decision-making at the time of presentation. Compared to CT, MRI allows more precise evaluation of adjacent anatomical structures (optic apparatus, cavernous sinus, etc.) (L'Huillier et al. 1989; Piotin et al. 1999; Nawar et al. 2008) and provides earlier diagnosis (Rogg et al. 2002). In one study, the size of the adenoma and its extension were similar in surgically and conservatively treated patients (Ayuk et al. 2004). MRI did not predict the likelihood or severity of ocular paresis or field defects. Even when the tumor was very large, conservative management was followed by tumor shrinkage (Ayuk et al. 2004). A single large hypodense area within the tumor might be associated with better subsequent tumor shrinkage than several small hypodense areas (Maccagnan et al. 1995).

In another study, MRI findings were found to be associated with clinical status and outcome: patients with infarction had less severe clinical features and better outcomes than those with hemorrhagic infarction or hemorrhage (Semple et al. 2008).

Conclusion

Historically, being considered a neurosurgical emergency in the past, pituitary apoplexy was always treated surgically. However, a conservative approach is increasingly used in selected patients, as publications provide converging evidence that a wait-and-see approach is associated with similar outcomes in terms of oculomotor palsy, pituitary function, and subsequent tumor growth. Even visual acuity and visual field defects show similarly improvements with the two approaches. Owing to the uncontrolled design of retrospective studies comparing the two approaches, and the probable selection bias, the optimal management of acute pituitary apoplexy, conservative or surgery, still remains controversial. Ocular palsy is not, in itself, an indication for surgery and need not be taken in account when deciding between the two strategies. Whatever strategy is chosen, steroid therapy is mandatory to treat the possible adrenal insufficiency and its potentially life-threatening cardiovascular complications. Patients with reduced visual acuity and/or visual field defects must be closely monitored if a conservative approach is chosen, and surgery should be considered secondarily if no clear improvement is seen after a week or if the patient deteriorates. Long-term clinical and imaging follow-up is necessary to detect the recurrence of the adenoma or growth of a tumor remnant, which will require surgery or radiation therapy.

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Surgical Decompression for Pituitary Apoplexy

18

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Abbreviations

CSF	Cerebrospinal fluid
DI	Diabetes insipidus
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone

18.1 Introduction

Apoplexy in a pituitary adenoma is usually dramatic. Sudden severe headache, with prostration from a combination of loss of pituitary hormones and other factors, is a well-recognised feature and is discussed in the preceding chapters. Similarly, the accompanying ophthalmoplegias and chiasmal compression visual loss which occur in a significant percentage of these patients are also classic clinical signs. But, as the preceding chapters discuss, the presentation is not unique to apoplexy and the diagnosis may be obscured by other events, major surgery, travel and so forth, and the diagnosis may be delayed if the ictus is mistaken for a subarachnoid haemorrhage, other cerebrovascular events or a cardiac crisis.

Most clinicians are coming to realise that surgery for these tumours is not mandatory (Randeva et al. 1999; Gruber et al. 2006; Rajasekaran et al. 2011). By far the most important action is to stabilise the acutely ill patient, usually by correcting hormones and fluid balance, issues that will have been already covered.

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Mild eye signs, both double vision from cavernous sinus pressure on cranial nerves III, IV and IV which is rather more common than chiasmal compressive slight field loss, may well correct themselves without surgery. If the tumour shrinks of its own accord rather than through surgery, there is a slightly better chance that the remaining normal gland will be left undamaged. Surgery seems to put the remaining functioning gland at greater risk than in natural recovery according to large apoplexy series. This is contrary to what happens for the majority of surgery for pituitary adenomas.

18.2 Timing of Surgery

When surgery does become mandatory, it is seldom the case that this has to be carried out in emergency hours. There is no evidence supporting emergency surgery at the earliest opportunity, particularly by a non-pituitary specialist. What evidence there is would suggest that the procedure is carried out at the next available routine list by the unit's pituitary surgeon. In fact, there is no evidence supporting surgery as early as within 24–48 h and 'early' can be defined as within the first week, which many surgeons may not be aware of. These arguments with the evidence and the reasons for them are set out in detail in the guidelines on management paper (Rajasekaran et al. 2011).

The events that trigger this decision are almost always significant visual field loss, although some believe that double vision from ophthalmoplegias may correct themselves more rapidly – there is no clear evidence for this. It is also argued that the unremitting headache that can accompany apoplexy is relieved more quickly with surgery.

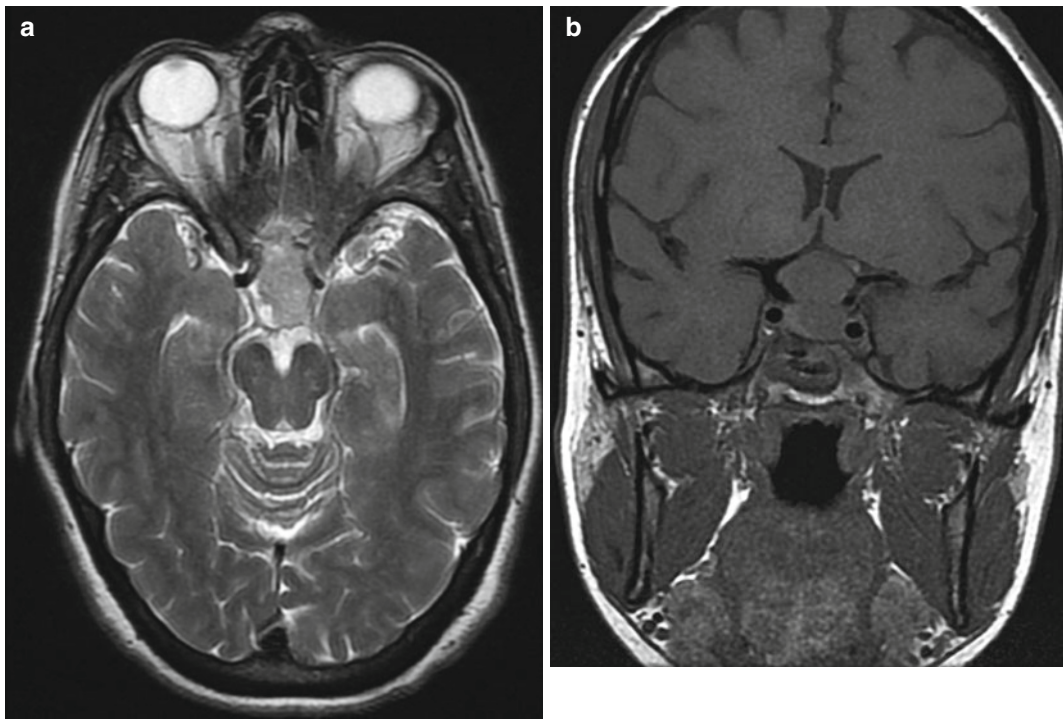

Fig. 18.1 (**a–f**) MRI sequence: (**a** axial T1, **b** coronal T1, **c** coronal enhanced T1 and **d** sagittal T1) of a 40-year-old woman presenting with classical apoplexy, who suffered sudden and worsening severe headache and new bitemporal visual field loss. Scans (**a–d**) show a mixed density lesion in and above the pituitary fossa compressing the chiasm. Note the multilobulated lesion with narrow waist and the prefixed chiasm pushing the adenoma back over the sella. This is a difficult surgical target. Operated by transsphenoidal approach by a reasonably experienced surgeon who was unable to remove any suprasellar component, the patient failed to wake from surgery, and an early postoperative CT scan (**e**) shows further haemorrhage in residual tumour and extension into caudate region. Following a further emergency craniotomy, the patient is left with an established infarct on CT some days later (**f**) and is completely blind

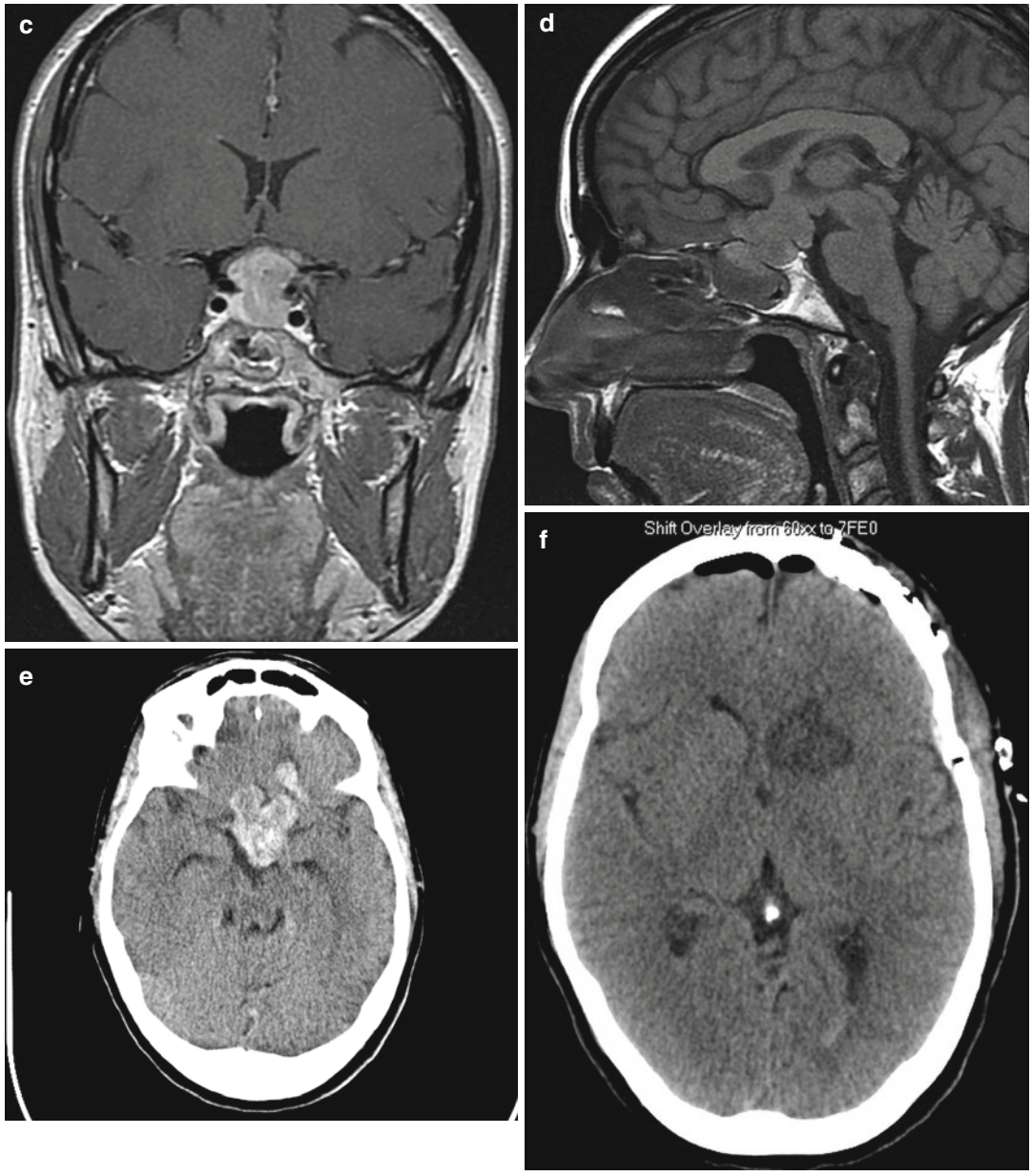

Fig. 18.1 (continued)

How severe the visual loss has to be before surgery is mandated is contentious. Full bitemporal hemianopias or worse field loss or significant visual acuity loss will certainly strongly advocate surgery. However, since the apoplexy usually occurs in an occult macroadenoma, the visual loss may predate the ictus. As is well known, patients often are unaware of quite significant impairment that because of optic atrophy was probably present for some time before the tumour was discovered.

If the visual fields worsen during the observation period, this would also trigger a decision to surgery. However, these patients are often too unwell to do formal testing and may well present at times when ophthalmologic services are not available.

Inexpertly done surgery may well threaten the chiasm to a greater extent than leaving the tumour to shrink in the natural course of the process of infarction. There is a mistaken belief that the apoplexy leads to immediate softening and liquidisation of the tumour. Whereas this may occur with time, more usually, the recently infarcted tumour will have a rather tougher texture. Unless the surgeon has some experience, there is more chance that significant tumour will be left in the suprasellar space. This residual, then, may actively bleed in the early postoperative period, leading to a dramatic worsening of the patient's condition (Fig. 18.1a–f).

18.3 Surgical Style: What Approach Should Be Used?

The majority of cases of apoplexy are only really suitable for transsphenoidal surgery and transcranial surgery should be avoided except in circumstances when the tumour is so far above the chiasm that it is unlikely to be removed by the nasal route. The brain in a patient who has suffered recent apoplexy may well behave like the swollen brain of a patient with severe subarachnoid haemorrhage, and the chance of vasospasm and its sequelae also seem to be much higher than in 'cold' transcranial pituitary surgery. This author's observation of emergency craniotomy in this situation would suggest that there is significant risk of severe morbidity (blindness and epilepsy) and even mortality.

The reader will be well aware that there is something of a revolution underway with regard to how the sphenoid is approached so that with more traditional and modern methods available; there is no 'one' correct way. Many surgeons are now adopting endoscopic approaches rather than the well-established microscope version, which is celebrating its fiftieth anniversary in 2012. There are many different minor variations of both techniques. None is wrong; it is only important that the surgeon uses a method with which he is comfortable.

Whichever is used, the essence of the approach is the same.

18.4 Anatomy

It is helpful to study a skull. From the nostril, along the septum, through to the area between the sphenoid ostia on the front face of the vomer, then through to the front face of the pituitary fossa up to its junction with the planum sphenoidale is a straight line. The nasal cavity is narrowed bilaterally on its lateral walls by the turbinates, the middle and inferior of which have to be pushed to one side on the approach regardless of the method used. In the microscope approach, this is done by the retractor, whereas in the endoscopic approach these have to be actively compressed or even resected.

By opening the rostrum of the vomer, access is gained to the sphenoid air sinus, lined with its mucosa. It is separated into compartments by sphenoid septi, usually just one and usually near the midline, separating the sinus into left and right halves. There are many variations to the position of these septi, so study of the patient's scans is imperative, as deviation from the midline into the carotids, which lie directly on either side of the pituitary fossa, is both dramatic and dangerous. If a very lateralised septum is mistaken for one in the midline and is removed from the carotid bulge, it is distressingly easy to damage the vessel and cause massive bleeding.

The pituitary fossa hangs in the space created by the sphenoid sinus (Fig. 18.3). In apoplexy, it is, almost by definition, harbouring a macroadenoma and therefore will usually have significantly expanded the fossa from its normal dimensions and thinned the anterior wall, to paper thin.

In the skull, seen from above, the pituitary fossa has no sides but which in life is filled in by the cavernous sinus containing both internal carotids and the cranial nerves III, IV and VI. Meckel's cave and the trigeminal nerves lie below, although are usually far enough away not to be involved. Only a thin single layer of dura forms the cavernous sinus pituitary interface lateral wall. The cavernous sinus has interconnections over the front of the fossa, sometimes referred to as the circular sinus. It lies at the junction of the fossa with the planum. Although this can be troublesome in Cushing's surgery and in

extended suprasellar approaches, it is not usually a limiting step in apoplexy surgery.

The tumour will have extended into the suprasellar space and may well be compressing the chiasm from below. The majority of physicians will recognise chiasmal compression visual loss. Equally, it may have pushed laterally and be compressing the contents of the cavernous sinus. It is of interest that cavernous invasion is common in adenomas but virtually never causes ophthalmoplegias, except in frankly malignant tumours. However, ophthalmoplegias are common in apoplexy, as mentioned above.

The posterior wall is the continuation of the clivus leading up to the posterior clinoids and the anterior wall, as previously described, the posterior, superior wall of the sphenoid. Continuation of the dura lines the whole structure. In places this has a double layer. The diaphragm sella is almost certainly thinned and stretched upwards by the previous growth of the tumour.

18.5 Surgery (Powell 2012)

As mentioned, both microscope and endoscopic approaches are acceptable. This description will focus on the endonasal/septal push over microscopic technique, but salient points in the endoscopic approach will also be mentioned. The difference between the two is that the latter enters the sphenoid directly through the ostia and does not utilise any nasal septal dissection, although, interestingly, the bone removal employed at the vomer is rather more than in the former technique. It is essentially the direct nasal approach described by Griffith and Veerapen (1987) for the microscope in 1987. The description will not cover those who prefer to use the sublabial approach. This author believes it to be an unnecessary extra dissection with no added value.

18.5.1 Surgical Position and Equipment

The patient is anaesthetised and placed supine on the table. Head up tilt is recommended as this aids venous drainage. Those employing the 'axilla' position for the surgeon will twist the head to suit their line of approach. Those, as this author, who prefer the 'head of table' (Fig. 18.2) approach will probably drop the head back for comfort.

It is likely that the patient is already on a cortisol replacement dose, excess to normal requirements; if not, it would be prudent to give the patient at least 50 mg hydrocortisone intravenously. It is also quite possible that there are protocols already in place regarding replacement. High doses of dexamethasone are frequently given, although there is no clear evidence that these influence outcome in any beneficial way and are more likely to promote diabetes mellitus. Equally, many neurosurgical units have a protocol for operative antibiotic prophylaxis. These may be employed if wished; again, there is little evidence that in transsphenoidal surgery, this has a useful place.

Ideally, the nose has been previously prepared with a nasal decongestant such as although this can be omitted.

If there is a very significant suprasellar component to the tumour, and particularly if the suprasellar part is much greater than that in the fossa, it can be very helpful to use a lumbar drain which should be put in at this point. The drain can be used to inject saline to bring the dome of the tumour down (see below), and if a cerebrospinal fluid (CSF) leak develops, it can also be used in the postoperative period to protect the repair.

The operation requires an array of specialised equipment, special retractors, dissectors, curettes and micro rongeurs. These are outlined in Figure 18.6 and their use will be described in the text. Microscope specialised tools tend to be 'bayoneted' to keep the holding hand out of sight, but for endoscopic approaches, this is not strictly necessary. Both can be used in either technique.

18.5.2 Endonasal Approach

The microscope is employed from the outset. Also, the fluoroscope is extremely helpful, to check orientation on the nasal approach and at

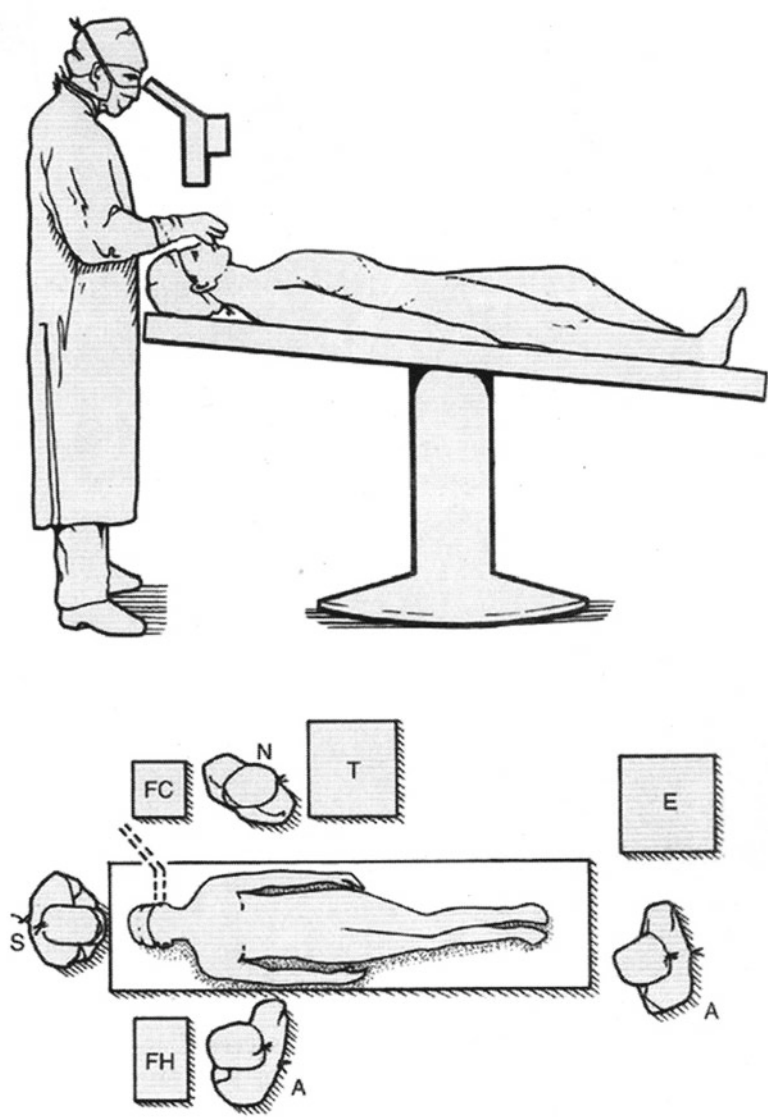

Fig. 18.2 Typical position of surgeon and patient for microscope transsphenoidal approach. *S* surgeon, *A* assistant, *N* nurse, *FH/FC* fluoroscope camera and head, *T* microscope base

the sella. It is put in place at the initial towelling up of the patient, hidden behind the drapes (Fig. 18.2).

The incision is made on the septum in one nostril (Fig. 18.3) (this surgeon always uses the right), approximately 5 mm long, well below the columella, which has small anchoring fibres that make this otherwise easy separation more tricky. The blue-grey nasal cartilage is seen and the mucosa separated from it over about 12–15 mm, ensuring the separation at the floor. This author uses a 'Hardy' dissector for this (Fig. 18.6, instrument 5). Following this avascular plane down deeper into the nose using a long handheld retractor, the junction of the cartilage with the bony septum is passed, onto the bony part. Here, the experienced will find the remnants of separate bones, and it will, in the correct trajectory, be extremely thin. At this point, twisting the retractor tips swiftly clockwise can crack the septum across. The blades of the retractor are placed on either side of the remains of the septum. A check X-ray can be taken at this point.

Ideally at this point, the surgeon will see the rostrum of the vomer. Some of the remaining septum can now be removed, if wished. The next key

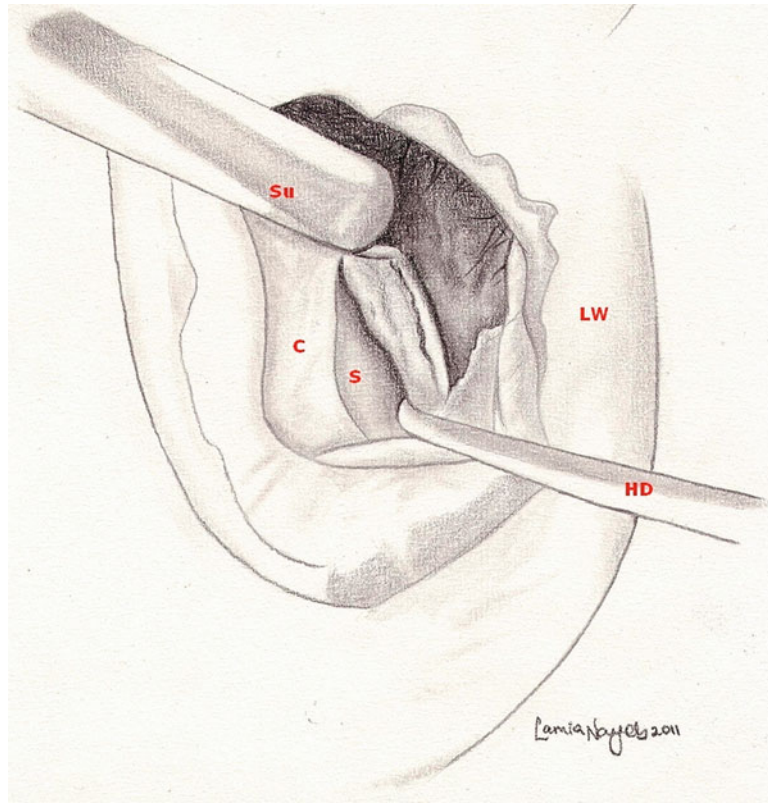

Fig. 18.3 Incision in septum. *C* columella, *S* septum, *HD* Hardy dissector, *LW* lateral wall of nostril, *Su* sucker

point is the identification of the sphenoid ostia. This is usually possible with the handheld retractor and, if seen, makes the use of the X-ray unnecessary.

The definitive retractor can now be deployed. There are many different options; all are based on the original 'Hardy–Cushing' design although this is rather heavy and more modern types much improve on it. This author uses the 'Papavero' (BBraun). The retractor is pushed into the nose though the blades of the handheld retractor, which is then slid out. The foot of the definitive retractor is then settled on the front face of the vomer and opened (Fig. 18.4).

The ostia are now more clearly defined, and entered, first with the Hardy's, and then further opened with 2 mm angled up-cut bone rongeurs, removing the front face of the vomer. Care is necessary here as too much bone removal inferiorly makes the next step impossible. However, the secret is to remember to remove bone mainly towards the skull base and not down towards the choana. Ideally, just enough is removed to allow the feet of the retractor to be placed within the sphenoid opening, which locks the blades in the ideal position. Some authorities decry this technique and actively forbid it, however.

18.5.3 Note for Endoscopic Use

In the endoscopic approach, the fluoroscope is considered unnecessary. The nose is prepared with a powerful decongestant, cocaine based being the most efficacious, e.g. Moffett's solution, although their use is proscribed in some countries. Once the endoscope has been set up, with orientation and white balance checks, the nasal cavity is entered. The left is used in our clinic.

The middle and inferior turbinates are identified and pushed aside with a flat dissector and the choana and left sphenoid ostium identified.

Once the latter is found, the mucosa is coagulated around it, and it is then widely opened up

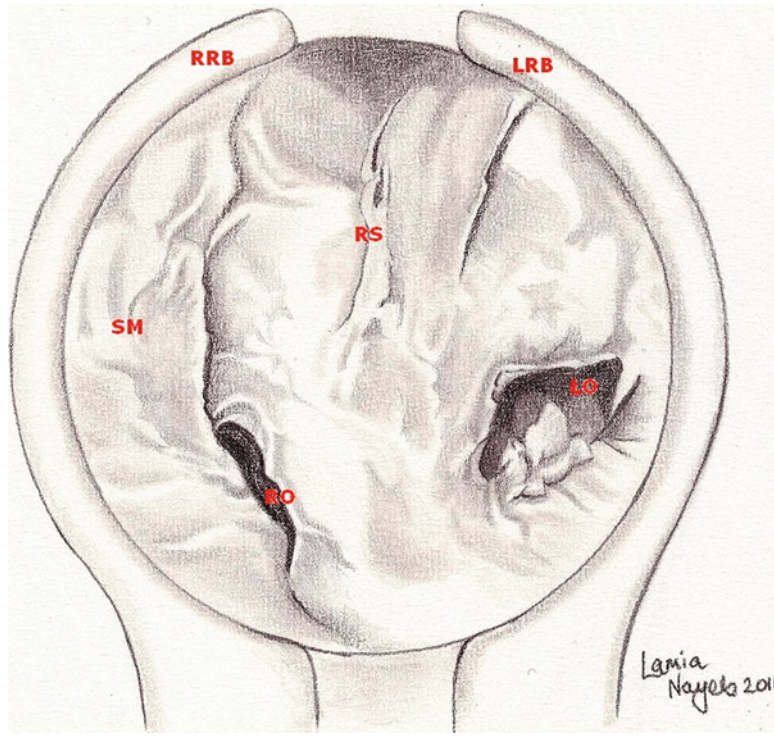

Fig. 18.4 Retractor placed on anterior wall of sphenoid vomer. *RRB*/*LRB* right and left retractor blade, *SM* septal mucosa, *RS* residual bony septum, *LO*/*RO* left and right sphenoid ostia

using either a Kerrison type or Stammberger punch. The root of the septum is dissected free, either directly or using the right nostril, so that a wide opening is made into the sphenoid (Cappabianca and de Divitiisis 2003).

18.5.4 Both Techniques: Continued

The interior of the sphenoid is then studied. The endoscope gives a much wider view than the microscope so that it should be possible to study both carotid bulges, the optico-carotid recesses and the clivus below the fossa. In the microscope approach, only the medial wall of the bulge will be seen and the recesses and clivus at best only just glimpsed. For safety, in this situation, a fluoroscope image should be taken delineating where the surgeon will enter next.

It should have now been possible to show the entire front face of the fossa and to strip it of its mucosa and any septation. The anterior wall will probably be very thin, so it is easy to enter the space between the bone and the dura, using a Hardy dissector (Fig. 18.5) or if necessary a small-toothed bone rongeur. The front bone face is then removed from carotid bulge to carotid bulge and up to the planum exposing the pituitary dura widely. There is seldom much more than a slight ooze at this point.

With the dura exposed, it should be widely opened. An 11 blade is probably the safest although some advocate cutting diathermy. Care should be taken not to stray into the small arachnoid recess at the junction of the fossa with the planum (de Tribolet's dangerous angle) as this will lead to a small CSF leak, evidenced by a wisp of clear fluid. This would need repair at closure to prevent a longer-term CSF leak.

The fossa part of the tumour is now exposed. The consistency of tumour in apoplexy is usually rather firmer than usual and may well have to be broken up. Although the fossa can be cleared in the usual way with small tumour rongeurs and curettes, it may well have to be fragmented first. The Hardy dissector is particularly helpful here (Fig. 18.6). It is important to clear the fossa first as once the arachnoid of the dome descends, it obscures pockets of residual tumour trapped in the fossa.

If the patient has an ophthalmoplegia from lateral extension, this can be chased laterally. Some

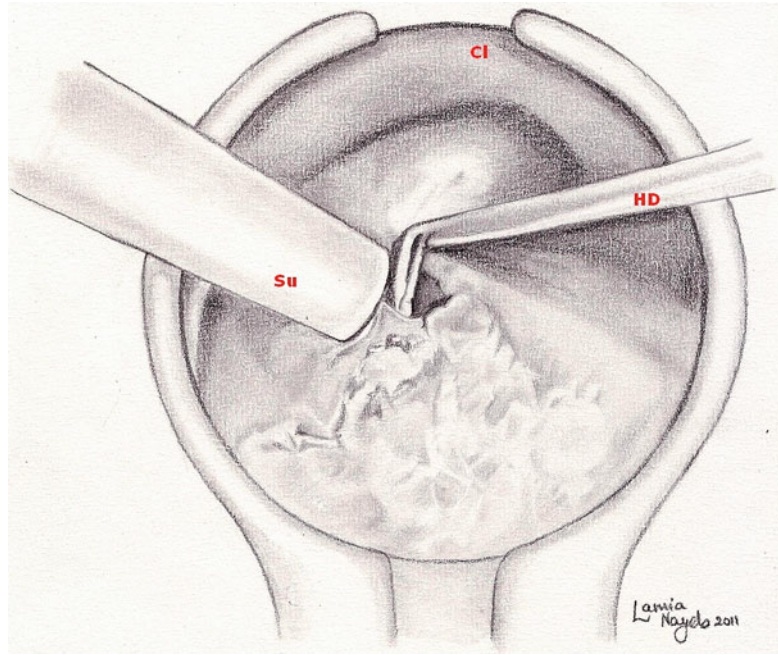

Fig. 18.5 Opening the pituitary fossa with Hardy dissector (*HD*). *Cl* clivus behind and beyond the pituitary fossa, *Su* sucker

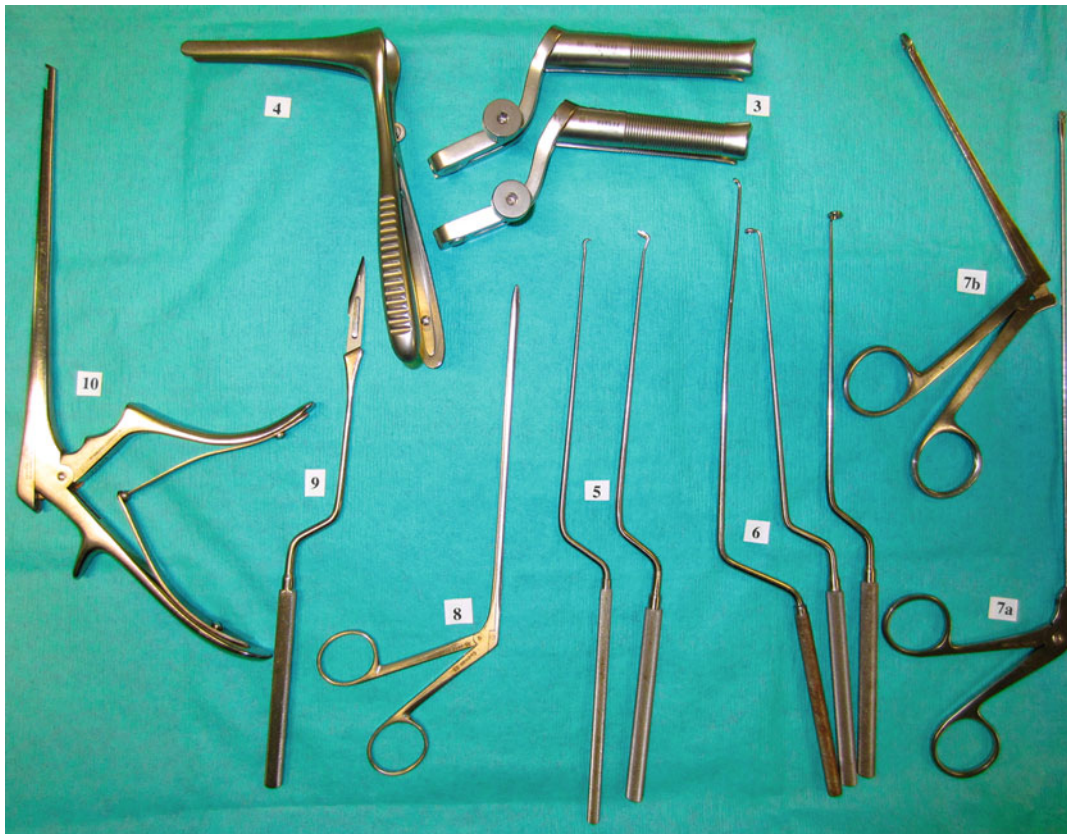

Fig. 18.6 Pituitary instruments: *3* Papavero retractors in 80 and 90 mm length, *4* Killian's handheld nasal retractor, *5* Hardy dissectors, *6* ring curettes in (L–R) micro-, medium and large sizes, *7* pituitary rongeurs, (*a*) Fahlbusch micro cups and (*b*) Angel James types, *8* toothed alligator micro rongeurs, *9* Hardy pituitary knife with 11 blade, *10* Kerrison 2 mm angled bone punch

authorities advise against attempts to remove cavernous extensions; however, if none is made, it is unlikely that recovery of an ophthalmoplegia will be swift. Obviously, care should be taken in pursuing tumour into the cavernous sinus as the carotids that lie within are less robust than in the neck. It should be noted, however, that this author has never seen carotid damage from use of the ring curettes in this situation. It is also prudent to warn the anaesthetist that this dissection is taking place as irritation of the carotid can lead to profound bradycardias.

Once cleared, the suprasellar portion can now be tackled. If the surgeon is lucky, this component may descend into the fossa of its own accord; however, it may have to be tackled in the same way as the fossa part. Curettes and dissectors break up the tumour which then falls down into the fossa and is removed. Eventually, the dome will descend as a translucent grey layer.

The surgeon may find that as the anterior dome descends, it obscures residual tumour in the posterior part. This part of the dome can be held up with cottonoid patties whilst the posterior part is removed.

If employed, a lumbar drain infusion of saline can assist in bringing the dome down. Our unit uses 20 cc aliquots injected over a short space whilst the injector calls the volumes in 5 cc quantities. This can be stopped if sudden descent occurs and it is even helpful on occasions to remove some of the injected fluid to slacken the dome. 20 cc is usually sufficient, but occasionally a second aliquot is required. The slight rise in intracranial pressure brought about by this method is both more prolonged and higher than using Valsalva. Consequently, it is more successful, although its use is restricted to patients with small fossa component to larger suprasellar tumour volume ratios.

With the tumour removed, closure can begin. If there is no leak, then very little repair of the fossa floor is necessary. However, what is used is very variable. Our unit would simply place some gelatin sponge across the fossa face, although others will use a variety of methods. These include fat, fascia lata, cartilage, bone compounded muscle and any number of artificial repairs, glues and sealants. There is no evidence that more complex repairs are beneficial. Although this author believes that simplest is quicker and therefore better, it is unlikely that this chapter will influence a change in individual unit style.

If a CSF leak has occurred, then some repair is mandatory. In the majority of cases, we use fat harvested from the lower abdominal wall. This may be sealed in place and there are many useful compounds now on the market to aid this. Again, others will have their own preferences, as before.

The retractor, if used, is removed and the nose repaired in the preferred method. The mucosal incision needs no sutures.

Endonasal approaches seldom need packing at all, and we now find that it is also true of the microscope approach as well, and apart from a small strip of gelatin sponge at the floor, we do not put packs in place. Nasal packing is a major contributor to postoperative pain and the patient will be thankful if nothing is placed at the end in the nasal cavity. However, if there is significant postoperative bleeding, then dehydrated nasal sponges are employed for 24 h or less.

18.6 Early Postoperative Management

In our unit it is most unusual to use intensive care facilities for our postoperative transsphenoidal patients. We do not use urinary catheters and the majority will spend only 30–60 min in a recovery suite before returning to the ward. They can be mobilised the same day if well.

Here, standard postoperative neurological observations are continued on a two-hourly basis with strict charting of fluid balance, oxygen saturation and drugs carried out as is normal in the otherwise well postoperative patient. Once stable, they can have the observations extended to four hourly and sat out of bed if wished.

It goes almost without saying that a patient sufficiently unwell to have already been on the intensive care unit prior to surgery will need to return there.

18.7 Vision and Steroid Cover

Since vision has been the driving reason for the patient's surgery, vision check is a standard part of postoperative management checks. Bitemporal field cuts often improve as soon as the patient is awake enough to be tested, although simple confrontation tests are all that is appropriate in the first and sometimes second postoperative day. The patient will often record that colours are brighter and simple objects such as the wall clock are clearer. Ophthalmoplegias will usually start to recover within a couple of days but may take rather longer. Initial double vision may be very troublesome as the eye opens and an eye patch may give the patient some relief in the early phase of recovery.

Steroid cover is a contentious issue. Many units will have protocols to follow and the post-apoplectic patient may well need long-term replacement. How much hydrocortisone is needed? The simple answer is 'as little as can be got away with'. However, many of these patients will have been acutely ill, so increasing the dose of normal replacement is prudent for a day or two. Hydrocortisone 20/10/10 mg should be sufficient, and the patient's dose reduced as soon as well. Normal replacement is 15/5/5 mg or even less – many patients manage on 10/5 mg. These tasks can, of course, be left to the endocrine team.

18.8 Fluid Balance

Apoplexy causing diabetes insipidus (DI) is almost unique as an occasional presentation of a pituitary adenoma. Otherwise, DI is virtually never caused by a simple adenoma, however big. Presumably, it is sudden swelling compressing the posterior lobe that causes it to occur. Clearly, fluid and electrolyte imbalance must be corrected prior to surgery, but equally, post-surgery, these parameters must continue to be carefully monitored.

DI is, unfortunately, rather over-diagnosed. The fluid load that the patient inevitably receives during surgery needs to be excreted. Only too often, this physiological diuresis is interpreted incorrectly and desmopressin (DDAVP) given.

One litre of urine in 4 h does not make DI. Stringent parameters would include osmolarity changes in blood and urine, but quite simply, a check of the patient's sodium will clarify the picture in the short term. Sodium of >150 will be sufficient to aid management and trigger DDAVP administration. Below 140, it is physiological in the majority of cases. In the grey area between 140 and 145, it is better to watch, wait and recheck.

The other risk is of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) from the damaged posterior lobe. This usually occurs 7–10 days post-surgery. Very occasionally, it occurs within 1 or 2 days of surgery. It does so to some extent in 20–25 % of all cases. It seldom causes symptoms until below 125 Meq/L (headaches, lassitude and some mild confusion) but below 120 Meq/L may lead to epileptic seizures. It is simply treated in the majority of cases by strict fluid restriction to 600 mL/day.

Sometimes, SIADH is part of the triple response. Once corrected, the patient slips back into mild DI.

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Timing of Surgery and Outcome in Pituitary Apoplexy

19

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Contents

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19.1 Introduction

Pituitary apoplexy is a relatively uncommon yet potentially life-threatening/vision-threatening clinical event caused by the rapid enlargement of a pituitary adenoma due to haemorrhage/infarction (Semple et al. 2005; Onesti et al. 1990). Pituitary apoplexy is often heralded by one or more of the following: sudden onset of headache, decreased visual acuity, restriction of visual fields, disorders of ocular motility and altered sensorium. Most often (≈ 80 %), it occurs in patients with no previous history of pituitary tumour, and in most cases (≈ 96 %), no precipitating factors could be identified (Semple et al. 2005). The outcome of pituitary apoplexy depends upon the correct diagnosis and early appropriate treatment. This chapter will deal with the outcome of surgery for pituitary apoplexy, especially, with special reference to the timing of surgery.

19.2 Visual Outcome and Timing of Surgery in Pituitary Apoplexy

The incidence of visual impairment in pituitary apoplexy is variable. In a large series of pituitary apoplexy reported by Semple and colleagues, impairment of visual acuity was found in 56 % of patients, visual field defects were found in 34 % of patients and 10 % of patients presented with bilateral blindness (Semple et al. 2005).

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Woo and colleagues studied the visual outcome in patients with pituitary apoplexy (Woo et al. 2010). In their study of 359 patients with pituitary tumours, pituitary apoplexy occurred in 3.3 % (Woo et al. 2010). Visual acuity improved in 91.6 % of patients and visual field defects improved in 54.5 % of patients at 3 months following transsphenoidal surgery. Complete recovery or partial recovery of visual acuity was seen in all patients who underwent surgery within the first 3 days of presentation as compared to 83.3 % of patients who underwent surgery beyond 3 days (Woo et al. 2010). Similarly, complete or partial recovery of visual field defects was seen in 66.6 % in patients who underwent surgery within 3 days as compared to 40 % of patients who underwent surgery after 3 days (Woo et al. 2010). Two of their patients had complete blindness following pituitary apoplexy and both patients underwent surgery 18 and 24 h following the apoplectic event and both showed improvement in vision 3 months following surgery. Dubuisson and colleagues (2007) studied 24 patients with pituitary apoplexy among their series of 1,540 pituitary lesions and found that visual field deficits were present in 50 % of patients at the time of presentation and all except two patients noted improvement in vision. Semple and colleagues (2005) reported improvement in visual acuity in 76 % and visual field defects in 79 % of patients. However, they did not analyse the influence of timing of surgery on the outcome. Bill and colleagues (1993) studied 37 patients with pituitary apoplexy and noted that there was improvement in visual acuity in 88 % and visual field defects in 95 % of patients, and improvement in visual acuity was significantly better in those who underwent surgery within the first week of onset of symptoms with all patients improving when operated within the first week. When subgroup analysis was made for patients operated within the first 3 days and those operated between 4 and 7 days, there was no difference (Bill et al. 1993). Three of their patients had unilateral blindness before surgery, and in two of them operated within the first week, there was complete recovery, and in the third patient who was operated 2 weeks after the onset, the visual acuity improved to 20/80 (Bill et al. 1993). Randeva and colleagues (1999) reported 35 patients with classical pituitary apoplexy and noted that complete resolution of impaired visual acuity occurred in all patients operated within 8 days of onset but only in 46 % of patients operated after 8 days, and complete restoration of visual field deficits occurred in 75 % of patients operated within 8 days versus 23 % of patients operated after 8 days. Takeda et al. studied the visual outcome in 12 patients with pituitary apoplexy and noted recovery of visual acuity in all patients with complete or near-complete visual recovery in 75 % of patients (Takeda et al. 2010). Based on their experience, they recommended that decompressive surgery is preferable within 7 days of symptom onset (Takeda et al. 2010). Muthukumar and colleagues (2008) studied the influence of the timing of surgery on the neuro-ophthalmic outcome in patients with unilateral or bilateral blindness due to pituitary apoplexy and found that patients who were operated within the first week showed good visual improvement even when they had bilateral blindness where as the visual outcome was suboptimal when the surgery was delayed beyond 1 week. Agrawal and Mahapatra (2005) reported 8 patients with unilateral or bilateral blindness following pituitary apoplexy and noted that 50 % of patients improved when surgery was done within 7 days of the apoplexy. Sibal and colleagues (2004) reported 45 patients with pituitary apoplexy among whom 60 % were operated; the median time to surgical intervention in their series was 6 days. In their series, complete or near-complete resolution of visual acuity and visual field defects occurred in 93 and 94 % of cases, respectively. Seuk and colleagues (2011) reported 32 patients with pituitary apoplexy and they compared the outcome of patients who were operated within 48 h with those who were operated after 48 h. In their series, they noted improvement of visual acuity and visual fields in 83.3 and 88.2 %, respectively, of patients operated within the first 48 h when compared to 62% and 50 % in patients who were operated after 48 h, thus emphasizing the importance of early surgical intervention in the visual outcome (Seuk et al. 2011). Chuang and colleagues (2006) studied 13 patients with severe

visual compromise after pituitary apoplexy and divided them into two groups: those who underwent surgery within 3.5 days and those who underwent surgery after a mean delay of 8.7 days because of associated medical illnesses; they found that 100 % of patients operated within 3.5 days showed visual improvement, whereas only 50 % of patients operated after a delay of 8.5 days showed visual improvement.

19.3 Outcome of Extraocular Palsy and Timing of Surgery

Woo and colleagues (2010) studied the outcome of cranial neuropathy in their 12 patients with pituitary apoplexy among their 359 patients with pituitary apoplexy. They noticed either a complete or partial recovery of extraocular palsies in all their patients with pituitary apoplexy. This improvement was not associated with the timing of surgery, i.e. irrespective of the timing of surgery recovery of extraocular palsy was the rule (Woo et al. 2010). They also noted that recovery of sixth cranial nerve palsy always occurred earlier than third cranial nerve palsy (Woo et al. 2010). The earliest beginning of recovery was within 4 days and the latest was 56 days. The recovery of extraocular palsies reached a plateau at 3 months following intervention (Woo et al. 2010). Dubuisson and colleagues (2007) found an incidence of 54 % of extraocular palsies in their series of 24 patients with pituitary apoplexy and 85 % of them improved during follow-up. In the series by Bill and colleagues (1993), all patients with extraocular palsies improved and the improvement was irrespective of the timing of surgery. In Randeva and colleagues' (1999) series of 35 patients with classical pituitary apoplexy, there was no statistically significant difference in the outcome of extraocular palsies in patients operated within the first 8 days and thereafter. Randeva et al. (1999) noted that ophthalmoplegia tends to recover, albeit partially, even when the surgical decompression is delayed due to factors such as the existence of medical co-morbidities. Among the 12 patients with pituitary apoplexy reported by Takeda et al. (2010), all the patients with extraocular palsy improved, but no mention was made regarding the timing of surgery and outcome. Muthukumar and colleagues (2008) studied the neuro-ophthalmic outcome in patients with pituitary apoplexy and found that the timing of surgery had no influence on the outcome of extraocular palsy, i.e. even patients who were operated after 1 week showed improvement in their extraocular palsy. In Sibal et al.'s (2004) series of 45 patients with pituitary apoplexy, 93 % of surgically treated patients recovered from the extraocular palsy. In the series reported by Semple and colleagues (2005), there was an incidence of 45 % of extraocular palsy, and among these, 91 % of patients showed improvement. However, there was no mention about the influence of timing of surgery on the outcome of extraocular palsy.

19.4 Endocrine Outcome and Timing of Surgery

In the series by Bill and colleagues (1993), out of 37 patients, long-term thyroid and steroid replacement therapy was necessary in 89 and 82 % of patients, and among male patients, 64 % required testosterone replacement therapy, while long-term desmopressin therapy was required in 11 %. In this study, there was no mention about the impact of the timing of surgery on the endocrine outcome. In the series reported by Randeva et al. (1999), long-term thyroid and steroid replacement therapy was required for 45 and 58 % of patients, and among male patients, testosterone replacement was required in 43 %, while desmopressin therapy was required in 6 %. Randeva and colleagues (1999) recommended early transsphenoidal surgery for better endocrine outcome in the long term. Verees et al. (2004) reported 15 patients with pituitary apoplexy in whom surgical intervention was done within 2.2 days after symptom onset, and they noted return of endocrine function in 11 of the 15 patients. They also noted that the return of endocrine function occurred as early as 3 days as evidenced by the return of endogenous adrenocorticotrophin hormone secretion (Verees et al. 2004). As the pituitary gland is capable of secreting hormones in sufficient quantities if as little as 10 % of the glandular tissue

remains, on the basis of their experience, they suggested that at least in some cases of pituitary apoplexy, the source of endocrine dysfunction is compression rather than destruction, and hence, early surgical decompression might be useful in restitution of pituitary function (Verees et al. 2004). In Takeda et al.'s (2010) series, preoperative panhypopituitarism improved in 2 of 5 patients, and among 3 patients with preoperative diabetes insipidus, two improved. Zayour and colleagues (2004) studied 13 patients with pituitary apoplexy by monitoring the intrasellar pressure and correlated the outcome with preoperative prolactin levels. In their series, all patients had surgery within 1 week of symptom onset. They noted that partial recovery or maintenance of pituitary function in 7 of 13 patients. In the series of 45 patients reported by Sibal and colleagues (2004), 19 % of the surgically treated patients with a median time to surgical intervention of 6 days had normal pituitary function. Chuang and colleagues (2006) reported 13 patients, six of whom underwent surgery with a mean delay of 3.5 days and 7 patients who underwent surgery with a mean delay of 8.7 days; they noted that patients in whom surgical intervention was delayed had three times higher chance of long-term endocrine replacement therapy. Harrington and colleagues also reported improved endocrine function when surgery was done on an emergency basis (Harrington et al. 1989).

19.5 Mortality and Morbidity of Pituitary Apoplexy

In a large series of 66 patients reported by Semple and colleagues (2005), there was a mortality rate of 5 and 6 % of patients were severely disabled.

19.6 Recurrent Pituitary Apoplexy

Recurrent pituitary apoplexy in a patient who has already suffered pituitary apoplexy is a rare event. However, few cases of recurrent pituitary apoplexy have been reported and the incidence of recurrent pituitary apoplexy is more common in patients managed conservatively (Brougham et al. 1950; Conomy et al. 1975; Weisberg 1977) during the first episode than in those treated surgically during the first episode (Randeva et al. 1999).

19.7 Tumour Recurrence After Pituitary Apoplexy

Randeva et al. (1999) reported a 6 % incidence of recurrent pituitary adenomas after pituitary apoplexy and cautioned that long-term follow-up of patients who suffer pituitary apoplexy is warranted not only for endocrine follow-up but also for the rare occurrence of recurrent pituitary adenoma. In the series of 45 patients with pituitary apoplexy reported by Sibal and colleagues (2004), 4 % of patients in the surgical group and 22 % of patients in the conservatively treated group had recurrence of pituitary adenoma. This implies that surgical treatment of pituitary apoplexy is associated with a significantly decreased chance of tumour recurrence when compared to conservative treatment. Pal and colleagues (2011) studied 32 patients with nonfunctioning pituitary adenomas presenting with classical pituitary apoplexy and followed them for a median of 81 months. They found a tumour recurrence rate of 11.1 % at a mean follow-up of 6.6 years and therefore recommended long-term follow-up of patients who suffer pituitary apoplexy as there is a small but significant risk of such patients developing tumour recurrences (Pal et al. 2011). In view of these findings, the recent UK guidelines for the management of pituitary apoplexy have recommended an MRI scan 3–6 months after the apoplectic event and annually thereafter for 5 years and then two yearly (Rajasekaran et al. 2011).

19.8 Influence of Precipitating Factors on Outcome of Pituitary Apoplexy

Precipitating factors for pituitary apoplexy is found in 24–40 % of patients with pituitary adenoma (Biousse et al. 2001, Semple et al. 2007,

Rajasekaran et al. 2011). Biousse and colleagues (2001) studied 30 patients with pituitary apoplexy and found that 30 % of patients had known precipitating factors for pituitary apoplexy. In their series, the mean time to surgery was 2.2 days (Biousse et al. 2001). They found that the outcome was worse in patients with known precipitating factors; the neuro-ophthalmic sequelae were present in 71.4 % of patients with known precipitating factors when compared to 14.3 % in patients without precipitating factors (Biousse et al. 2001). In a more recent series, Semple and colleagues (2007) analysed the influence of precipitating factors on the outcome of pituitary apoplexy and found that the overall neuro-ophthalmic and endocrine outcome was worse in patients with known precipitating factors than in those without. In their series, 50 % of patients with precipitating factors had residual visual defects and 37.5 % had residual ophthalmoplegia compared to patients without precipitating factors in whom 76 % had improved visual function and only 21 % had residual ophthalmoplegia (Semple et al. 2007). Likewise, the endocrine outcome was also worse in patients with precipitating factors for pituitary apoplexy: 100 % of patients with precipitating factors had hypopituitarism, whereas 83 % of those without precipitating factors had hypopituitarism (Semple et al. 2007).

19.9 Histopathological Findings and Outcome of Pituitary Apoplexy

Semple and colleagues (2006) studied 59 patients with pituitary apoplexy and divided them into two groups on the basis of their histopathological findings: those with infarction alone and another group with haemorrhagic infarction or frank haemorrhage. They noticed that those patients with infarction alone in their histopathological examination had less severe clinical presentation, longer course prior to presentation and better outcome than those presenting with haemorrhagic infarction or haemorrhage alone (Semple et al. 2006). They noted that in the group with infarction alone, 95 % of patients had normal vision during follow-up when compared to 45.9 % of patients who had normal vision in the group with haemorrhagic infarction. Similarly, in the infarction-alone group, 86 % had no ophthalmoplegia during follow-up when compared to 59 % of patients in the haemorrhagic infarction group (Semple et al. 2006). However, there was only a marginal difference in the endocrine outcome between both the groups: 82 % of the infarction group and 86.5 % of the haemorrhage group required long-term hormone replacement therapy (Semple et al. 2006). In another study, Semple and colleagues (2008) noted that no patient in the infarction group was blind when compared to 16 % of patients in the haemorrhagic infarction group (Semple et al. 2008).

19.10 Pituitary Apoplexy and Incidentalomas

In autopsy studies, the incidence of pituitary microadenomas (<10 mms) and macroadenomas (>10 mms) has ranged from 1.5 to 26.7 % (Molitch and Russel 1990; Teramoto et al. 1994, Feldkamp et al. 1999). Studies have shown that macroadenomas are found in 0.11 % and microadenomas in 10 % of healthy volunteers who undergo MRI examination (Arita et al. 2006). A recent study by Arita and colleagues (2006) has shown that pituitary apoplexy develops in 9.5 % of incidentalomas, and all these patients who suffered apoplexy developed persistent panhypopituitarism and 25 % developed persistent visual disturbance. However, in their study, there was no mention about the timing of surgery, and hence, the impact of timing of surgery in incidentalomas which undergo apoplexy cannot be determined with certainty.

19.11 Pituitary Apoplexy in Microadenomas

Most cases of pituitary apoplexy occur in patients with macroadenomas. Nevertheless, there have been four cases reported in the literature where pituitary apoplexy occurred in patients with

microadenomas (Corkill et al. 1981; Randall and Couldwell 2010). One of these four patients underwent surgery with good visual and endocrine outcome (Randall and Couldwell 2010).

Conclusion

There is overwhelming evidence in the literature that early surgical intervention within the first week after the onset of pituitary apoplexy leads to good improvement in both visual acuity and visual field defects. Even patients rendered blind by pituitary apoplexy can regain useful vision if surgical intervention is undertaken early. However, extraocular palsy has a good prognosis irrespective of the timing of surgery. There is some evidence in the literature that the endocrine outcome is better in patients who undergo early surgery, even though many patients require long-term hormone replacement therapy after pituitary apoplexy. Patients with known precipitating factors for pituitary apoplexy have a worse outcome when compared to patients who have no known precipitating factors. Patients who have only infarction on histopathological examination have a better outcome than those with haemorrhagic infarction. Tumour recurrence after pituitary apoplexy can occur and the incidence is of such recurrence is more in patients who are treated conservatively during the apoplectic episode than in those who are treated surgically. Therefore, long-term follow-up of such patients is required. Rarely, recurrent apoplexy can occur. Mortality after pituitary apoplexy is rare in recent series.

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Part VIII

Complications

Subarachnoid Haemorrhage After Transsphenoidal Surgery

20

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Contents

Abbreviations

CSF	Cerebrospinal fluid
SAH	Subarachnoid haemorrhage
TSS	Transsphenoidal surgery

20.1 Introduction

Transsphenoidal surgery is commonly performed for sellar region tumours. Compared with traditional transcranial surgery, transsphenoidal surgery is a less invasive approach to the sellar region, reducing the damage related to operation (Kuroyanagi et al. 1994). Since the advent of modern microneurosurgical techniques, transsphenoidal surgery is widely practised for the management of pituitary tumours and is considered to be a relatively safe procedure (Kuroyanagi et al. 1994). However, this relatively "blind" procedure is often fraught with complications. There are many reports about complications in transsphenoidal surgery (Wilson and Dempsey 1978, Laws and Kern 1979, Lister and Sypert 1979, Zervas 1984, Black and Sypert 1987). Black and Sypert (1987) reported cerebrospinal fluid (CSF) leakage, diabetes insipidus, paranasal sinusitis, delayed epistaxis, meningitis and so on, as major complications, but there were no mortality in their 255 cases. The mortality rate of Laws and Kern's 505 cases was also low, being 1.43 % (Laws and Kern 1979). According to Zervas' international survey, the mortality rate of 2,606 microadenomas was 0.27 % and that

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of 2,677 macroadenomas was 0.86 % (Zervas 1984). There were also some reported cases of cerebrovascular complications after transsphenoidal surgery (Wilson and Dempsey 1978; Lister and Sypert 1979). Wilson and Dempsey (1978) reported a case of pseudoaneurysm of the internal carotid artery due to its intraoperative injury. Lister and Sypert (1979) reported a case of carotid-cavernous fistula caused by injury of the internal carotid artery; however, subarachnoid haemorrhage (SAH) following transsphenoidal surgery is very rare with very few studies published in literature till date (Tsuchida et al. 1983; Matsuno et al. 1993; Zhou and Yang 2009; Goyal et al. 2012). In the opinion of the authors, the occurrence of SAH is rare, albeit more common than what has been reported in the literature. An extensive search of the literature yielded only four such case reports including one by the authors (Matsuno et al. 1993; Tsuchida et al. 1983; Zhou and Yang 2009; Goyal et al. 2012). The very few cases in the literature may be a reflection of the under-reporting of this unsightly, avoidable complication by the operating surgeons.

20.2 Pathogenesis and Clinical Features

Tsuchida et al. (1983) reported a case of a 55-year-old male, who had a nonfunctioning pituitary adenoma associated with a previously undetected anterior communicating artery aneurysm that ruptured during transsphenoidal surgery. The authors state that during the transsphenoidal surgery, the tumour capsule collapsed abruptly into the sella turcica as the bulk of the tumour was reduced (Tsuchida et al. 1983). This might have exerted traction on the anterior communicating aneurysm. This small aneurysm was not detected on bilateral angiography of the carotid artery, performed prior to the surgery, leaving a possibility that this aneurysm developed during the surgical procedure. The patient underwent surgical clipping for the aneurysm and did well after the surgery (Tsuchida et al. 1983).

Matsuno et al. (1993) reported a patient who suffered severe SAH after transsphenoidal surgery for pituitary adenoma (prolactinoma). The patient's condition continued to deteriorate and he died on postoperative day 21 (Matsuno et al. 1993). Kuroyanagi et al. (1994) reported a 59-year-old patient in whom, following a transsphenoidal resection of a nonfunctioning pituitary adenoma, SAH occurred along with midbrain haemorrhage and thalamic infarction. The patient suffered from Weber's syndrome, when followed up, at the end of 1 year after the surgery (Kuroyanagi et al. 1994).

It is noteworthy that in both the above-mentioned reported cases, there was no evidence of intraoperative CSF leak or direct injury to any blood vessels, and the operative procedure was limited within the sella turcica. Postoperative angiograms in both the cases failed to show any aneurysm. Both these authors proposed that an indirect injury to an artery caused by traction due to descent of the capsule during tumour debulking might have been the possible cause (Matsuno et al. 1993, Kuroyanagi et al. 1994). A small branch of the intradural internal carotid artery, which was adherent to the tumour capsule, might have been pulled down as the tumour capsule fell downward during the intracapsular removal of the tumour and caused SAH (Matsuno et al. 1993; Tsuchida et al. 1983).

The authors have also previously reported a 56-year-old female, who developed SAH following transsphenoidal pituitary tumour surgery (Goyal et al. 2012). The tumour in the reported case had a suprasellar and subfrontal extensions (Figs. 20.1 and 20.2). Intra-arterial angiography done on postoperative day 4 did not reveal any pathology such as aneurysm or arteriovenous malformation. Her transcranial Doppler study showed normal velocities and no evidence of

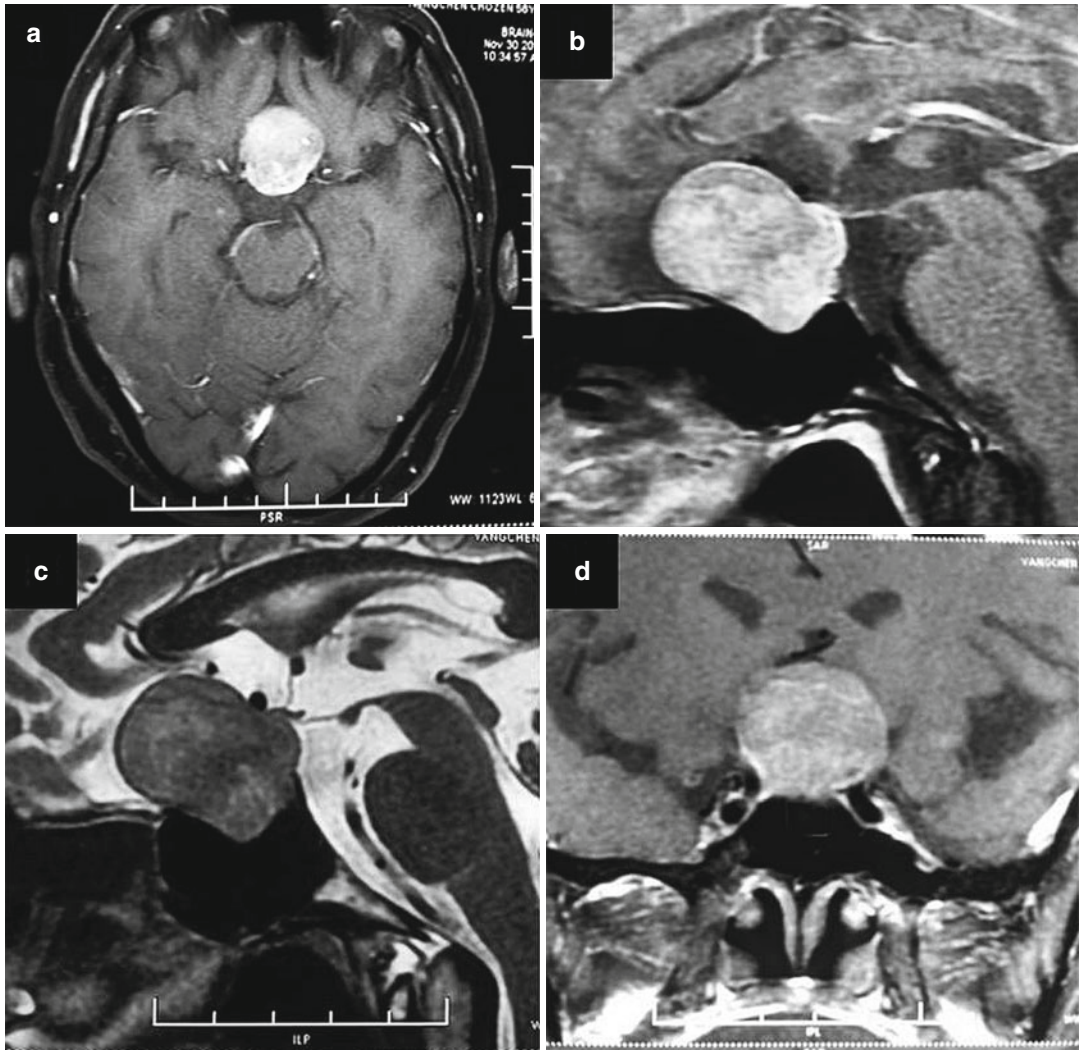

Fig. 20.1 Preoperative Contrast MRI of the Brain reveal a sellar surprasellar mass lesion with significant subfrontal extension Lowerate bulging into Sphenoid Sinus: (**a**) Axial, (**b**, **c**) Sagittal and (**d**) Coronal slices

vasospasm. The patient had a normal postoperative course and was discharged on the ninth postoperative day. In our case, there was intraoperative CSF leak. Also, there was subfrontal extension of the tumour, which might have led to the traction effect on the smaller vessels, while debulking the tumour. Therefore, the possibility arises that blood from the residual tumour or these smaller avulsed vessels might have trickled through the defect in the arachnoid and led to SAH (Goyal et al. 2012).

Zhou and Yang (2009) had also reported 8 cases of SAH following transsphenoidal surgery out of their 400 cases of transsphenoidal surgery, performed over a 40-year period, from 1964 to 2004 (Zhou and Yang 2009).

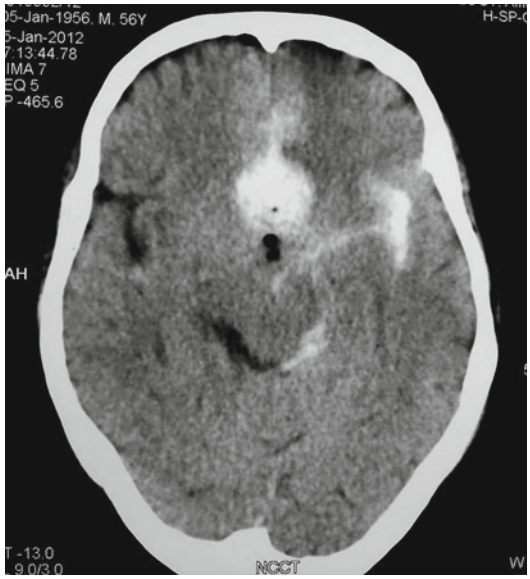

Fig. 20.2 Postoperative CT scan of the patient reveals residual tumour with haematoma and subarachnoid haemorrhage in the right sylvian, perimesencephalic and interhemispheric fissures

20.3 Prevention and Management of Subarachnoid Haemorrhage Following Transsphenoidal Surgery

The most important thing to prevent SAH following transsphenoidal surgery is to protect arachnoid membrane which locates between pituitary adenoma and intracranial tissues. Once obvious leakage of CSF occurs, which implies arachnoid membrane is breached, more attention should be paid and cause of the leakage should be found. Instant repair and complete haemostasis should be done, especially in case of haemorrhage from the residual tumour (Zhou and Yang 2009). For bleeding from anterior intercavernous sinuses, bleeding could be stopped by local gelatin sponge compression.

Pituitary tumour should never be pulled by force. Two-stage operation or transcranial approach might be adopted if necessary. Microsurgical procedure or endoscopic transsphenoidal surgery should be performed by skilled surgeons who are familiar with topography of sellar area and transsphenoidal procedures. Previous researchers suggested that experience is vital to avoid complications of transsphenoidal surgery (Ni et al. 1994; Long et al. 1996; Kitano and Taneda 2008).

While residual tumour bleed is confirmed, intrasellar haematoma might be removed by transsphenoidal reoperation. For suspected SAH, early diagnosis and early treatment are important. Cerebral vasodilator, neuronal protectors, antivasospasm treatment should be instituted as early as possible (Kasliwal et al. 2008). Antiepileptics should be given to prevent seizure in patients with SAH. For those with severe SAH, calcium-channel blockers, such as nimodipine, should be given via intravenous transfusion for 7–10 days (using micropump). Continuous CSF drainage might be adopted in those patients without obviously increased intracranial pressure. Drainage may be performed by ventricular or lumbar puncture by inserting an indwelling catheter for 3–5 days (drain 70–100 ml/day). Once severe vasospasm is caused by SAH, leading to extensive cerebral infarction, craniotomy and decompression procedures may be necessary. If blood enters the ventricular system and causes acute obstructive hydrocephalus, instant ventricular drainage should be performed to lower the intracranial pressure (Zhou and Yang 2009).

Conclusion

The rare possibility of an SAH should be kept in mind in patients undergoing transsphenoidal surgery for pituitary tumours. As the consequences of such a complication would be disastrous, it is important to prevent SAH. Early detection and management holds the key to success in such cases. A four vessel angiogram is indicated to rule in or out an associated aneurysm, which is reported in literature in 5 % cases.

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