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**Pituitary Apoplexy: Can Histopathology,  
Radiological Imaging and Predisposing Factors be  
used in Predicting Outcome?**

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**Doctor of Philosophy**

**In the Division of Neurosurgery**

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## **DECLARATION**

I, Patrick Lyle Semple, hereby declare that this thesis is my own unaided work, and that neither the whole or any part thereof has been, or is to be submitted for any other degree at this or any other university.

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## **PUBLICATIONS AND PRESENTATIONS**

The following publications and presentations have either been utilized in this thesis or have arisen from it:

1. Semple PL, Webb MK, De Villiers JC, Laws ER Jr.: Pituitary apoplexy. *Neurosurgery* 2005; 37:65-73.
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3. Semple PL, Jane JA Jr., Laws ER Jr.: Clinical relevance of precipitating factors in pituitary apoplexy. *Neurosurgery* 2007;61:956-962.
4. Semple PL, Jane JA Jr., Lopes MBS, Laws ER Jr.: Pituitary apoplexy: correlation between magnetic resonance imaging and histopathological results. *J Neurosurg* 2008;108:909-915.
5. Pituitary apoplexy: the correlation between MRI and histopathology. International Society of Pituitary Surgeons Congress, Bariloche, Argentina, September 2006. PL Semple, JA Jane Jr., Lopes MBS, Laws ER Jr.

6. Pituitary apoplexy: can we predict outcome? (Invited Speaker). Society of Endocrinology, Metabolism and Diabetes of South Africa, Annual Congress, Cape Town, South Africa May 2008.
  
7. Pituitary Apoplexy. South African Society of Neurosurgeons, 20<sup>th</sup> Biennial Congress, Durban South Africa, August 2008. PL Semple.

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## **PREFACE**

The research described in this thesis was based on two groups of patients. The first cohort of patients (62) was from a combined University of Virginia – Groote Schuur Hospital Pituitary Apoplexy Database, on an Internet website, set up by myself and the Department of Neurosurgery, University of Virginia. I did the analysis of data from the combined database. The research on the second cohort of patients (38) was undertaken by myself in the Department of Neurosurgery at University of Virginia. I traveled to the University of Virginia, Charlottesville, Virginia, USA, with the express purpose of doing the research. The concept of using histopathology to predict outcome, comparing Magnetic Resonance Imaging (MRI) to histopathology findings and using precipitating factors to predict outcome were all my original thoughts. Professor Laws gave me support, advice and encouragement during my research and facilitated my trip to Charlottesville.

## ABSTRACT

Pituitary apoplexy is an uncommon, yet potentially fatal illness, usually the result of infarction, hemorrhage or a combination of both in a pituitary tumor. The management of pituitary apoplexy consists of replacement therapy and in the majority of patients, surgical decompression, although some cases may be treated conservatively. Up to now no study has attempted to separate the two histopathological types of pituitary apoplexy or to analyze their clinical and radiological significance on presentation and outcome.

The University of Virginia – Groote Schuur Hospital Pituitary Apoplexy Database (UVA-GSH Pituitary Apoplexy Database), an Internet website, was set up and 62 patients entered to combine both centers experience. The presentation, clinical features, endocrine status, management and outcome were reviewed retrospectively. The 59 patients in whom histopathology reports were available were then divided into two groups: 1. those in whom infarction alone was present (22 patients) and; 2. those in who hemorrhage alone or mixed hemorrhage and infarction were found (37 patients) at histopathological examination. The time to presentation, severity of clinical presentation, outcome and endocrine status between the two histopathological groups were compared. The patients in whom infarction alone was found on histopathological examination had a longer course prior to presentation, significantly less severe clinical features on presentation and

a significantly better outcome than those presenting with hemorrhage or hemorrhagic infarction. The endocrine requirements were similar in both groups.

The discriminative ability of MRI to distinguish infarction alone from hemorrhage or hemorrhagic infarction was analyzed in an attempt to prognosticate outcome. A group of 36 consecutive patients from UVA (1996-2006), in whom pre-operative MRI was carried out, were divided into the two histopathological groupings. The MRI findings were reviewed blindly and divided into pituitary tumor alone, infarction alone and hemorrhage or hemorrhagic infarction, and were then correlated with the histopathological groups. The MRI scans were able to predict the histopathology accurately in the majority of cases (CI = 95%). The MRI was therefore able to predict the histopathological findings and consequently the severity of presentation and outcome.

In the same cohort of patients those (9 patients) in whom precipitating factors were identified were investigated to assess whether the presence of precipitating factors had an influence on outcome. The majority of patients in whom precipitating factors were identified (8 / 9 patients), were 13.1 times more likely to have hemorrhage or hemorrhagic infarction on histopathology.

In conclusion patients in whom the histopathological studies show infarction only have a longer presentation period, less severe clinical features and better outcome than those with hemorrhage or hemorrhagic infarction. The histopathology and consequently the severity of clinical findings and outcome may be predicted in the majority of patients on the MRI. In addition the presence of a precipitating factor

appears to make the likelihood of a histopathological finding hemorrhage or hemorrhagic infarction greater. These findings may prove useful in managing patients and predicting outcome for patients and families, as well as facilitating a decision on surgery or conservative management.

## CHAPTER 1

### INTRODUCTION

#### 1.1 Historical perspective of pituitary apoplexy.

In 1898 Bailey, a neurologist from New York City described the first clinical case of pituitary apoplexy when he documented the catastrophic results of a hemorrhage in a pituitary adenoma in a patient with acromegaly [Bailey 1898]. In 1905 Bleibtreu found old hemorrhage in a pituitary adenoma at post mortem in a young man with acromegaly [Bleibtreu 1905]. In 1913 Munro described a patient who clinically appeared to have had a pituitary apoplexy, resulting in rapid demise, and at post mortem was found to have a large pituitary adenoma that, although it had no hemorrhage, was described as edematous and necrotic [Munro 1913]. Dingley and Lond published, in 1932, a report of a patient previously well who suddenly collapsed and died and who at post-mortem examination was found to have a large pituitary adenoma with old hemorrhage as well as a considerable amount of fresh hemorrhage within it [Dingley & Lond 1933]. However, it was only in 1950 that Brougham et al first coined the phrase “pituitary apoplexy”. They published a series of 5 patients who had died and at post-mortem findings of hemorrhage and / or extensive necrosis of a pituitary adenoma were found. These patients had presented with a fairly uniform

syndrome consisting of drowsiness, coma, headache, neck stiffness, ocular palsies and sometimes hemiparesis [Brougham et al 1950].

Subsequent to these early reports there have been numerous case reports and series published on patients with pituitary apoplexy resulting in an improved understanding of the clinical syndrome and the associated pathological features. Rovitt et al reported 9 patients in whom pituitary apoplexy was the presenting feature of their pituitary adenoma [Rovitt & Fein 1972]. In 1981 Wakai et al reported 51 cases of pituitary apoplexy that were symptomatic and had been treated in their department [Wakai et al 1981]. Mohr and Hardy reported 4 patients with pituitary apoplexy that were treated by them between 1962 and 1979 [Mohr & Hardy 1982]. Ebersold and co-workers managed 11 patients with pituitary apoplexy at the Mayo Clinic in a busy neuroendocrine service where 940 pituitary tumors were operated on between 1972 and 1982 [Ebersold et al 1983]. Sixteen patients were diagnosed and treated for pituitary apoplexy over a 10-year period by Onesti [Onesti et al 1990]. Between 1975 and 1991 38 patients were managed surgically by Bills et al [Bills et al 1993]. Randeva and co-workers reported on 35 patients treated at the Radcliffe Infirmary, Oxford over an 11-year period [Randeva et al 1999].

Transsphenoidal surgery and corticosteroid replacement is generally accepted as the optimal management, although there is a body of opinion in the literature favoring conservative management in carefully selected patients [Rovitt & Fine 1972, Wakai et al 1981, Mohr & Hardy 1982, Ebersold et al 1983, Onesti et al 1990, Bills et al 1993, Randeva et al 1999]. Despite the improvements in both the medical and surgical

management of this condition it remains a poorly understood and frequently undiagnosed with potentially fatal implications.

## **1.2 Definition and incidence of pituitary apoplexy**

The term “apoplexy” is derived from the Greek apo – from, off – and plessein – to strike, to disable by stroke [Cardoso & Peterson 1984]. The reported incidence of pituitary apoplexy varies from 0.6% - 25.7%. The reason for this wide variation is largely related to the lack of uniformity in the definition of pituitary apoplexy.

Moharty and co-workers reviewed the histopathology of 70 resected pituitary tumors. They found in 18 of these tumors (25.7%) there was evidence of hemorrhage on histopathological examination, but 11 of these patients did not have any clinical apoplectic event [Moharty et al 1977]. Findling noted that spontaneous infarction of microadenomas may be subclinical resulting in improvement of pituitary hormone hyperscretion without impairment of other anterior pituitary hormone secretion [Findling et al 1981]. Mohr and Hardy attempted to assess the significance of necrosis and hemorrhage in patients with pituitary adenomas operated on by them from 1962 to 1979. They found that the clinical picture of pituitary apoplexy was present in only 4 (0.6%) of the 663 cases but necrosis or hemorrhage was found on histopathological examination in 9.5% of cases [Mohr & Hardy 1982]. In 1981 Wakai et al published at that time the largest series of patients presenting with pituitary apoplexy. In a series of 560 patients operated on for pituitary adenomas they found hemorrhage, old or new, visualized at operation in 90 (16.6%). Thirty eight patients (6.8%) were described as having a “major attack” – history and clinical findings consistent with pituitary

apoplexy; 13 (2.3%) a “minor attack” with symptoms but no clinical findings consistent with apoplexy; and 42 patients (7.5%) were found to have asymptomatic hemorrhage [Wakai et al 1981]. Ebershold and colleagues reporting on their experience with 940 pituitary adenomas operated on found only 11 of these to have presented with pituitary apoplexy. Their criteria for inclusion were sudden onset of neurological symptoms and signs in a patient previously asymptomatic or with prior signs of a pituitary adenoma associated with hemorrhage or necrosis within a surgically removed pituitary adenoma [Ebersold et al 1983]. Ostrov et al reviewed the clinical presentations, Computed Tomography (CT) scans, Magnetic Resonance Imaging (MRI) scans and findings at surgery to determine the clinical significance of suspected intratumoral hemorrhage in pituitary adenomas. They concluded that intratumoral hemorrhage is not synonymous with pituitary apoplexy and only 3 of their patients with intrasellar hemorrhage had clinical apoplexy [Ostrov et al, 1989]. Onesti and colleagues reported on 16 patients over a 10-year period with clinical pituitary apoplexy that had hemorrhage confirmed at surgery and on histopathological examination. During the same period 5 patients were operated on who had large hemorrhages into the pituitary tumors, but had no clinical symptoms of pituitary apoplexy. They described these patients as having subclinical pituitary apoplexy [Onesti et al, 1990]. Thirty-seven patients were treated neurosurgically by Bills and colleagues between 1975 and 1991 for pituitary apoplexy. They defined pituitary apoplexy as a patient who had an abrupt onset of severe headache or visual disturbances in the presence of a pituitary adenoma. During the same period 2034 pituitary adenomas were treated surgically, therefore the incidence of apoplexy in their series was 1.6% [Bills et al 1993]. Randeva et al used the same inclusion criteria

as Bills et al for patients with pituitary apoplexy in their series and published an incidence of 3.2% [Randeve et al 1999].

The highly variable incidence of pituitary apoplexy reported is therefore related to the unclear definition of pituitary apoplexy. The term pituitary apoplexy has also been used to describe the sudden infarction of nontumorous pituitary glands initially described by Simmonds as well as Sheehan and Summers [Simmonds 1914, Sheehan & Summers 1949, Conomy et al 1974, Reid et al 1985]. The term subclinical pituitary apoplexy has been used to describe asymptomatic hemorrhage or infarction in a pituitary tumor [David et al 1975, Findling et al 1981]. However this is not descriptive of a clinical syndrome at all, is potentially confusing and may best be discarded. The term tumor “burn-out” has been used to describe the event of a secreting tumor spontaneously being cured by a hemorrhage or necrosis occurring within that pituitary adenoma [Males & Townsend 1972, Laws 1979, Mohr & Hardy 1982].

The definition now most universally agreed upon is that pituitary apoplexy is a clinical syndrome resulting from hemorrhage, infarction, or hemorrhagic infarction of a pituitary tumor that results in its sudden and fulminant expansion. Apoplexy is of sudden onset and may be characterized by sudden headache, visual disturbance, ophthalmoplegia, pituitary hypofunction, physical collapse, impaired level of consciousness, and death [Cardoso & Petersen 1984, Dubuisson et al 2006, Nawar et al 2008, Randeve et al 1999, Verrees et al 2004]. Using this definition of pituitary apoplexy the incidence is 0.6% - 3.2% making pituitary apoplexy an uncommon

occurrence [Mohr & Hardy 1982, Wakai et al 1981, Ebershold et al 1983, Onesti et al 1990, Bills et al 1993, Randeva et al 1999, Dubuisson et al 2006].

### **1.3 Age and gender distribution**

The age of patients in which pituitary apoplexy occurs does not appear to differ from that in which pituitary adenomas are diagnosed. Reid et al described an even distribution between 20 and 70 years [Reid et al 1985]. Wakai et al reported a mean age of 35.5 years with a range from 16 to 63 years, however their series of patients appears to be younger than other reported series [Wakai et al 1981]. The most commonly reported mean age is in the 5<sup>th</sup> and 6<sup>th</sup> decades: Bills reported a mean age of 56.6 years; Duboisson 56 years; Onesti 49 years and Randeva 49.8 years [Bills et al 1993, Duboisson et al 2006, Onesti et al 1990, Randeva et al 1999]. The series of Wakai and colleagues and Onesti and co-workers described pituitary apoplexy occurring with equal frequency in both sexes. However in the majority of published series there is a preponderance of males to female in the approximate ratio of 2:1 [Bills et al 1993, Duboisson et al 2006, Ebersold et al 1983, Randeva et al 1999, Reid et al 1985, Rovit & Fein 1972].

### **1.4 The vascular supply of the pituitary stalk and gland**

The arterial blood supply to the pituitary stalk and gland arise from the supraclinoid and cavernous portions of the internal carotid artery bilaterally. The superior hypophyseal artery arises from the supraclinoid internal carotid artery just as it emerges from the dura mater covering the cavernous sinus. The superior hypophyseal

artery usually arises as two or three small trunks on the medial aspect of the internal carotid artery and run upwards and medially to the tuber cinereum where it joins its contralateral fellow and forms a plexus around the hypophyseal stalk – the circuminfundibular network [Baker 1971, Pribram et al 1966] Each superior hypophyseal artery sends branches to the optic nerve, optic chiasm, the ventral hypothalamus and upper portion of the pituitary stalk before giving off a major branch, the trabecular artery that descends alongside the infundibulum to supply the lower infundibulum and pierce the substance of the anterior lobe [Gibo et al 1994, Reid et al 1985, Warwick & Williams 1973]. This branch courses through the pars distalis to supply the lower infundibular stalk and anastomose with the vascular ring formed by the inferior hypophyseal artery [Reid et al].

The inferior hypophyseal artery arises from a common trunk – the meningohypophyseal trunk - at the junction of the proximal vertical and horizontal segments of the cavernous internal carotid artery [Pribram et al 1966]. The inferior hypophyseal artery, usually the largest of the 3 branches passes upwards and medially to reach the lateral surface of the neurohypophysis where it divides into superior and inferior divisions, which run in the sulcus between the anterior and posterior lobes of the pituitary. Each division anastomoses with its partner from the opposite side, forming an arterial circle from which many tiny arteries penetrate directly into the substance of the posterior lobe to form a rich capillary network – the inferior hypophyseal arterial circle or inferior capsular arterial rete [Baker 1972, Gibo et al 1994].

There is some difference of opinion in the blood supply to the pars distalis (anterior lobe) of the pituitary. Some investigators believe there is no direct blood supply to pars distalis and all blood flow is via the portal capillaries [McConnell 1953, Rovitt & Fein 1972]. However, it is now believed small arterial branches to the upper half of the anterior pituitary from the trabecular and inferior hypophyseal arteries may also contribute and may account for some sparing of the anterior pituitary in postpartum pituitary necrosis [Reid et al 1986]. The hypophyseal portal system is an extensive capillary network originating from the superior and inferior hypophyseal vessels in the infundibular stem. The arteries in the median eminence and upper and lower infundibulum end in characteristic tufts of capillaries. These tufts drain in descending vessels, which break up into vascular sinusoids between the secretory clumps of the pars anterior and supply virtually the whole blood supply to this area. These portal vessels may be divided into two groups: the long portal vessels and the short portal vessels. The long portal vessels drain the median eminence and upper infundibulum arising from the superior hypophyseal artery branches. These capillaries have scant innervation, are surrounded by poorly developed stroma and their endothelial lining is richly fenestrated and lacks the features of the blood-brain barrier. The short portal vessels drain the lower infundibulum and mainly arise from the inferior hypophyseal artery branches. The inferior artery and its branches are richly innervated, but the capillary bed is irrigated by it (short portal vessels) and also lacks the blood-brain barrier [Cardoso & Peterson 1984, Warwick & Williams 1973]. The venous drainage from the anterior lobe is through a series of veins that penetrate the capsule all over the surface of the gland and enter the neighboring venous sinuses. The portal vessels are of great functional significance, carrying hormone releasing factors elaborated in

the parvocellular groups of hypothalamic neurons and which control the secretory cycles of the cells of the pars anterior (distalis) (Figure 1.1).

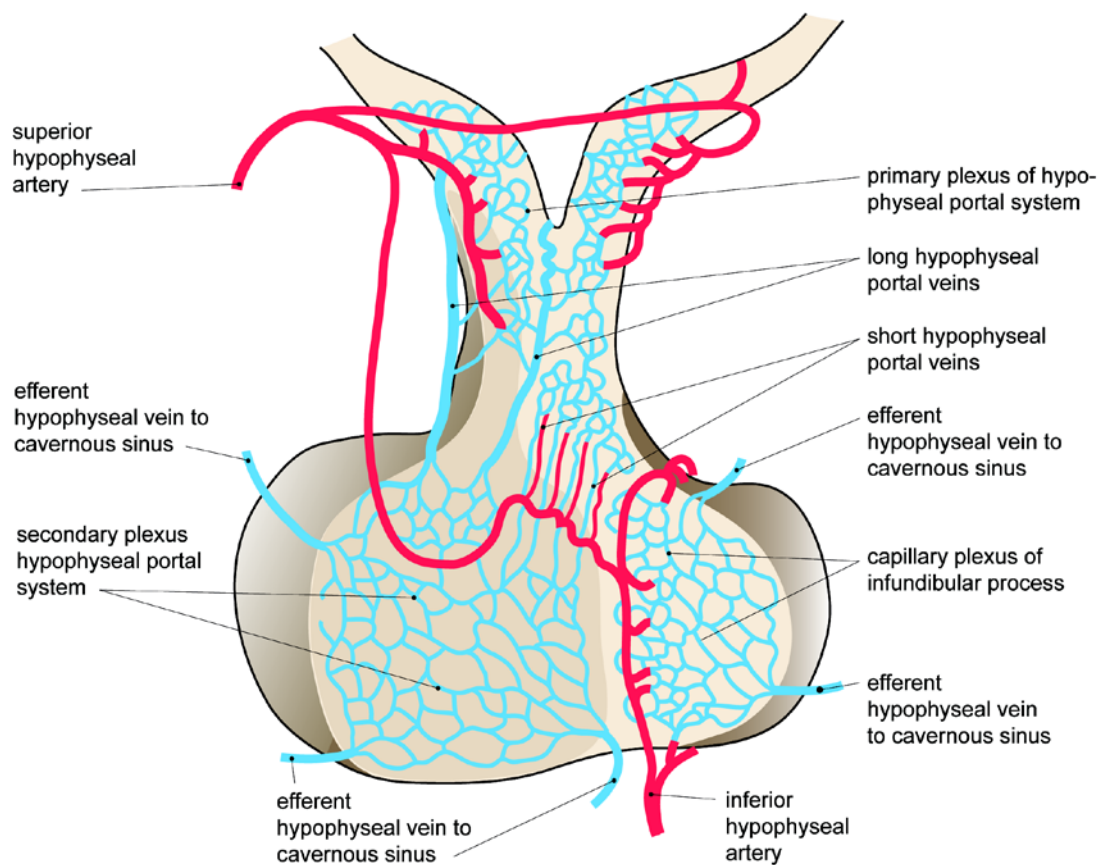


Figure 1.1: The vascular supply of the pituitary stalk and gland

### 1.5 The anatomical relations of the pituitary gland

The pituitary gland is located below the brain in the centre of the skull base. Below the pituitary gland is the body of the sphenoid containing the right and left sphenoid sinuses; behind is the dorsum sellae, basilar artery and brainstem; lateral are the left and right cavernous sinuses and their contents: and above is the diaphragma sellae separating the hypophysis from the optic chiasm and the interpeduncular cistern [Tobias & Arnold 1977] (Figure 1.2)

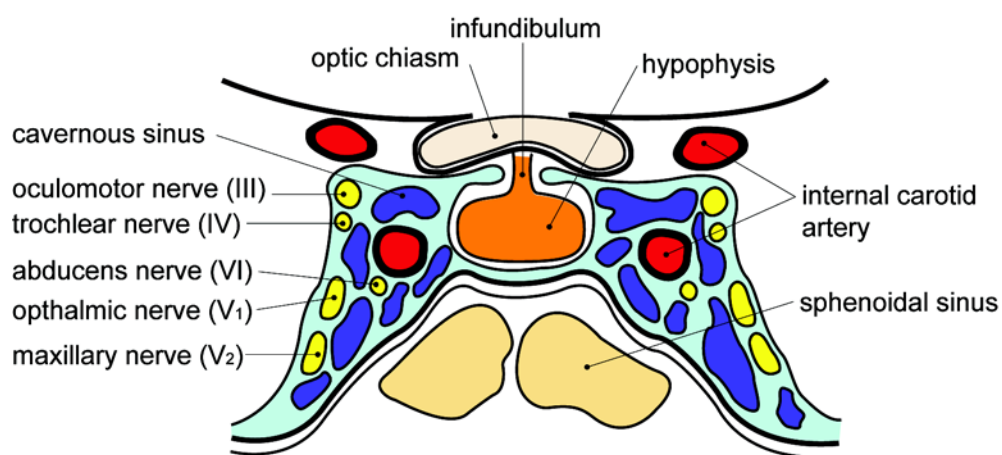


Figure 1.2: The anatomical relations of the pituitary gland

The body of the sphenoid bone is in intimate contact with the nasal cavity below and the pituitary gland above. The body of the sphenoid bone is cuboidal in shape and contains the sphenoid sinus. The pituitary fossa occupies the central part of the body of the sphenoid bone and is bounded anteriorly by the tuberculum sellae and posteriorly by the dorsum sellae. The upper limit of the normal size of the pituitary fossa is 13mm in depth, 17mm in length and 15 mm in width [Bergland et al 1968, Quaknine & Hardy 1987, Rhoton 2002]. The sphenoid sinus separates the pituitary gland from the nasal cavity and is subject to considerable variation in size, shape and degree of pneumatization. There are three different types of sphenoid sinus present in the adult: in the conchal type the area below the sellar is a solid block of bone without any pneumatization; in the presellar type the pneumatization does not extend beyond the vertical plane parallel to the anterior sellar wall; and in the sellar type of sphenoid sinus, the most common, the air cavity extends into the body of the sphenoid sinus below the pituitary fossa as far posteriorly as the clivus [Rhoton 2002]. The septae within the sphenoid sinus are highly variable. The carotid sulcus produces a prominence within the sinus wall below the floor and anterior margin of the sella – this prominence is variable in size.

The diaphragma sellae forms the roof of the sella turcica, covering the pituitary gland except for a small central opening through which the pituitary stalk projects. The diaphragma tends to be thinner around the infundibulum than at the periphery. There is usually a separation between lateral surface of the gland and the carotid artery although in 25% of cases the carotid artery will project through the medial wall of the cavernous sinus to indent the pituitary gland [Rhoton 2002]. Intercavernous sinuses

connecting the two cavernous sinuses can occur anteriorly, inferiorly, and posteriorly to the gland or may be absent.

The cavernous sinuses are located on each side of the sphenoid sinus, sella and pituitary gland. They extend from the superior orbital fissure to the petrous apex. The medial wall of the cavernous sinus forms the lateral margin of the sella [Yasuda et al 2004]. The horizontal portion of the carotid artery is surrounded by the cavernous sinus. The carotid artery enters the cavernous sinus lateral to the posterior clinoid process where it leaves foramen lacerum and exits along the medial side of the cavernous sinus where it penetrates the roof of the cavernous sinus. The oculomotor, trochlear and ophthalmic nerves lie from superior to inferior between the two dural leaves of the lateral sinus wall. The abducens courses within the cavernous sinus medial to the ophthalmic nerve and is adherent to the lateral aspect of the carotid artery.

The suprasellar area corresponds to the anterior incisural space between the free edges of the tentorium and the front of the midbrain. This area is occupied by the optic chiasm, circle of Willis and hypothalamus. The optic chiasm is situated at the junction of the anterior wall and floor of hypothalamus. It is situated above the diaphragma sellae and pituitary gland. The anterior cerebral arteries, anterior communicating artery, lamina terminalis and third ventricle are located above the chiasm. This area contains all the components of the circle of Willis: the basilar artery and posterior part of the circle of Willis are located in the anterior incisural space below the floor of the third ventricle; the anterior part of the circle of Willis including the anterior cerebral

and anterior communicating arteries are intimately related to the anterior wall of the third ventricle [Rhoton 2002].

### **1.6 Aims of present study**

- a. Review a large contemporary series of patients with pituitary apoplexy from University of Virginia, Charlottesville, USA and University of Cape Town, South Africa. The differential diagnosis, clinical presentation, diagnosis, treatment and outcome are assessed (Chapter 2).
- b. Analyze the histopathological studies of patients with pituitary apoplexy that were divided into two groups: 1. hemorrhage or hemorrhagic infarction and 2. infarction alone. The clinical presentation and outcome of the patients in the two different histopathological groups were compared to assess if there was any difference between them (Chapter 3).
- c. Review MRI studies on consecutive patients to assess if the histopathology found at surgery could be predicted reliably on the MRI scan done pre-operatively. In this way it would be possible to predict the severity of the presentation and outcome on the MRI scan done at the time of diagnosis (Chapter 4).
- d. Determine the clinical relevance of the precipitating factors in patients with pituitary apoplexy. Assess whether any particular histological group was found more commonly in patients with known precipitating factors and whether the presence of precipitating factors influenced the outcome (Chapter 5).

## **CHAPTER 2**

# **PITUITARY APOPLEXY: A CO-OPERATIVE STUDY BETWEEN TWO CENTRES**

### **2.1 Introduction**

A large contemporary series of patients with pituitary apoplexy from University of Virginia, Charlottesville, Virginia, USA and University of Cape Town, Cape Town South Africa is reviewed. The differential diagnosis, clinical presentation, diagnosis, treatment and outcome are assessed.

### **2.2 Patients and methods**

The Departments of Neurosurgery at the University of Virginia (UVA), Charlottesville, Virginia, USA and Groote Schuur Hospital (GSH), University of Cape Town, Cape Town, South Africa co-operatively combined their experience in a retrospective series of patients who were treated for pituitary apoplexy. A combined UVA-GSH Health Insurance Portability and Accountability Act-compatible database was developed using a website (UVA-GSH Pituitary Apoplexy Database) designed by UVA and based on a common protocol. An investigator from each institution, using password protection, was able to access the UVA-GSH Pituitary Apoplexy

Database website and enter data for each patient. The captured data on the patients was then retrospectively analyzed.

The definition of pituitary apoplexy used for entry of patients into the study included a history and clinical features consistent with pituitary apoplexy; appropriate findings on imaging; and histological confirmation of hemorrhage, infarction, or both. Three patients, however, were treated conservatively, and in them, the diagnosis was made on the basis of the clinical picture and Magnetic Resonance Imaging (MRI) features of pituitary apoplexy. Thirty-eight consecutive patients from the period 1970 to 2003 treated by two surgeons at GSH were entered into the study. Twenty-four patients treated by a single surgeon at UVA from 1992 to 2003 were entered. During the same period a total of 586 patients at GSH and 1019 patients at UVA were operated on for pituitary tumors at both institutions.

Information entered into the database included presentation, possible precipitating factors, imaging, endocrine investigations, findings at surgery, surgical approach, histopathological reports and both clinical and endocrine outcome.

### **2.3 Results**

Sixty-two patients were entered into the study. The mean age was 51.6 years with a range of 18-82 years. Men were in the majority, with 38 men (61%) compared with 24 women (39%). The mean length of follow-up was 55 months (range 1 month – 22 years)

### **2.3.1 Presentation and clinical findings**

The average length of time from onset of symptoms until presentation in the neurosurgery department was 14.2 days, with a range from just a few hours to 80 days. Fifty (81%) patients had no previous history of a pituitary tumor or known endocrine dysfunction, 8 (13%) had a known pituitary tumor but had not undergone surgery, and only 4 (5%) had previously had surgery for a pituitary adenoma. The most common differential diagnosis entertained was subarachnoid hemorrhage (40 patients), followed by meningitis (19 patients), with syncope and myocardial infarction being uncommon (1 patient each). In 96% of patients, no precipitating factor was identified. Radiotherapy, cardiac surgery, and head trauma were identified as precipitating factors in a single patient each.

Headache, typically of sudden onset, was the presenting complaint in 52 patients (84%) and was accompanied by nausea or vomiting in 15 patients. Eight patients (13%) had a diminished level of consciousness at presentation, and two of these were in a coma (1 of these was in coma after cardiac surgery and later was found to be blind, so it is uncertain whether the coma was the result of cardiac surgery or pituitary apoplexy). Twenty-six patients (42%) complained of decreased visual acuity or visual fields, and 6 (10%) presented with bilateral blindness. Twenty-three patients (37%) had diplopia or other symptoms related to cranial nerve dysfunction at presentation. Six patients complained of fatigue and lethargy, and 2 had amenorrhea. Seventeen of the patients had a history of previous endocrine-related symptoms

The average Glasgow Coma Score was 14, although the majority (n=54) had a GCS of 15. Visual acuity was normal in 22 patients (39%), reduced but functional in 25 (44%), reduced and non-functional in 4 (7%), and blind in 6 (10%). In 5 patients, the visual status was unknown. Bitemporal hemianopia was found in 21 patients (43%), although in 13 patients visual fields could not be tested or were unknown. Cranial nerve abnormalities were present in 26 patients (43%): oculomotor palsies in 12 (20%), abducent nerve palsy in 3 (5%), and multiple cranial nerve palsies in 11 (18%). In 2 patients, the cranial nerve function was unknown. Long-tract signs (hemiplegia) were present in 2 patients. Seventeen of the patients had a history of previous endocrine-related symptoms. The clinical features are tabulated in Figure 1.

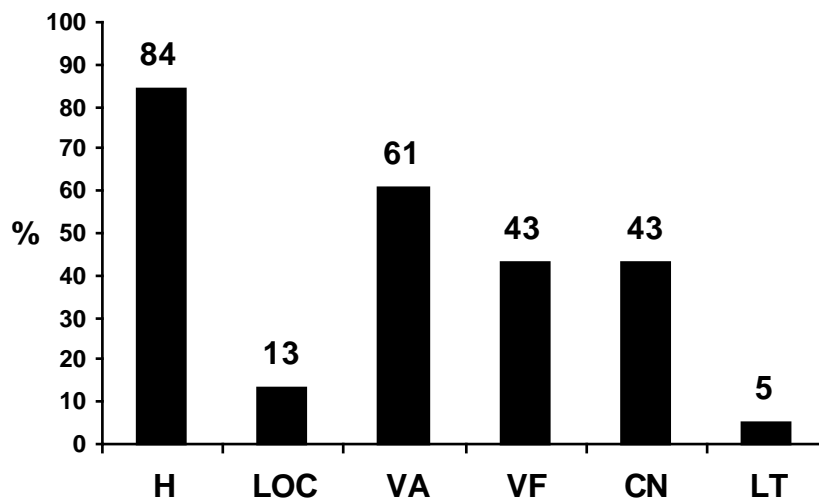
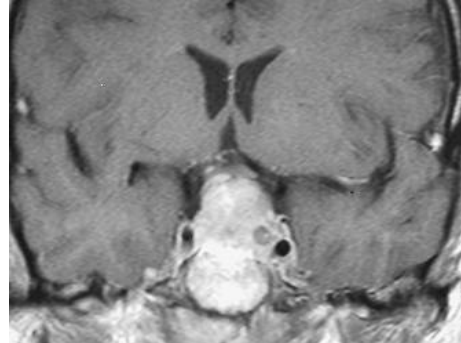
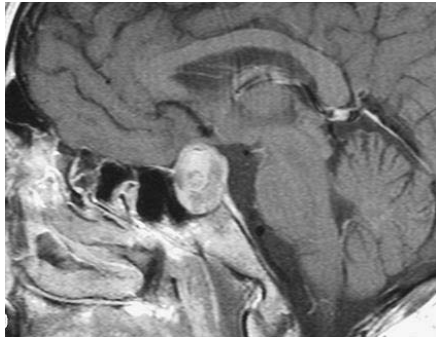


Figure 2.1: Clinical features in 62 patients with pituitary apoplexy. H= headache, LOC = diminished level of consciousness, VA = diminished visual acuity, VF = bitemporal hemianopsia, CN = cranial nerve palsy, LT =long tract signs.

### **2.3.2 Imaging**

MRI has become the imaging modality of choice in pituitary tumors, and consequently, all patients with tumors currently undergo MRI. The most recent 37 patients underwent MRI as the primary investigation; before this, the patients routinely had a CT scan. The tumors were all macroadenomas, with an average size of 258mm<sup>3</sup>. The MRI findings were tumor alone in 12 patients, mixed hemorrhage and infarction in 12, and hemorrhage in 13 (Figure 2). None of the MRI scans were normal.

(a)



(b)

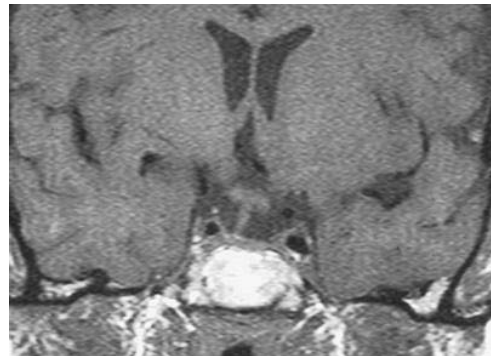
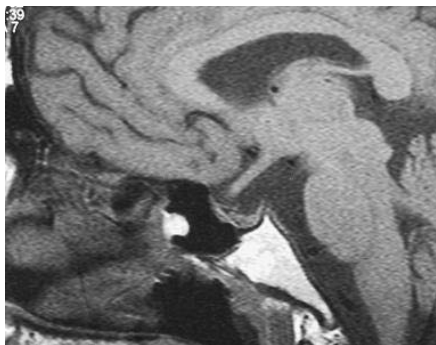


Figure 2.2: (a) MRI scan of a 44 year old man who presented with headache and diplopia showing a large pituitary adenoma that is compressing the optic chiasm and shows evidence of hemorrhage and necrosis. (b) MRI scans 3 months after a hemorrhagic / necrotic pituitary macroadenoma was removed transsphenoidally

### 2.3.3 Endocrine findings

Seventy-three percent of the patients (45 patients) had evidence of hypopituitarism, 24% (15 patients) had normal function, and only 3% (2 patients) had hyperfunction. Thirty-nine of the patients had prolactin levels measured; of these, 63% had a result in the normal range, and only 4 patients had a level above 50ng/ml. The average prolactin level was 39ng/ml. Five patients had diabetes insipidus (DI), and 9 had hyponatremia at presentation. Table 1 shows the more specific details of individual hormone assessment.

**Table 2.1: Endocrine investigations in pituitary apoplexy.**

	<i>Hypofunction</i>	<i>Normal</i>	<i>Hyperfunction</i>	<i>Unknown</i>
<b>T4</b>	34 (55%)	24 (39%)	0	4 (6%)
<b>Cortisol</b>	38 (61%)	21 (34%)	0	3 (5%)
<b>GH</b>	4 (6%)	16 (26%)	1 (2%)	41 (66%)
<b>Prolactin</b>	1 (2%)	39 (63%)	7 (11%)	15 (24%)
<b>IGF1</b>	2 (3%)	4 (6%)	0	56 (90%)
<b>G/T</b>	25 (40%)	15 (24%)	0	22 (36%)

GH = Growth Hormone, G/T = Gonadotrophins (FSH, LH) and/or Testosterone, T4 = Thyroid function.

### 2.3.4 Surgery

Transsphenoidal surgery was undertaken in 77% of the patients (48 patients), craniotomy in 16% (10 patients), and 5% (3 patients) were managed conservatively. One patient died before any treatment. Most of the craniotomies were performed earlier in the series. The most common macroscopic finding at surgery was hemorrhagic necrosis in 47% of patients. Nineteen percent of patients (12 patients) were found to have infarcted tumor or necrotic material. Acute hemorrhage was found in 8% (5 patients) and old hemorrhage in 6% (10 patients). The macroscopic findings were not reported in 10% (6 patients) and 6% (4 patients) did not have surgical treatment (1 patient died prior to any treatment and 3 managed conservatively).

### **2.3.5 Conservative treatment**

Three patients were treated conservatively (Table 2). One of the patients had two previous pituitary operations and was awaiting radiotherapy for acromegaly, and the other two patients had no previous pituitary history. The diagnosis was made on the basis of the history, the typical findings of an apoplexy on imaging studies, and the subsequent course. None of these patients had visual loss, and all of them had partial ophthalmoplegia. Two patients had suprasellar extension of the tumor, and one had predominant cavernous sinus involvement. One patient had prolactin levels of 1200ng/ml, and one patient was a known acromegalic. All three patients were placed on hydrocortisone, and one patient was treated with bromocriptine. All had rapid resolution of symptoms, and the ophthalmoplegias resolved within a few months. One patient remains on endocrine replacement therapy and bromocriptine. The other two have normal pituitary function.

**Table 2.2: Patients conservatively managed.**

	<b>Patient 1</b>	<b>Patient 2</b>	<b>Patient 3</b>
<b>Pituitary history</b>	nil	acromegaly	nil
<b>Visual acuity</b>	normal	normal	normal
<b>Visual fields</b>	normal	normal	unilateral scotoma
<b>Cranial nerves</b>	multiple	multiple	nil
<b>MRI</b>	suprasellar mixed haemorrhage & infarct	cavernous sinus mixed haemorrhage & infarct	suprasellar mixed haemorrhage & infarct
<b>Endocrine</b>	normal	acromegaly	hypopituitary prolactinoma
<b>Management</b>	hydrocortisone	hydrocortisone	hydrocortisone
<b>Visual outcome</b>	normal	normal	normal
<b>Replacement</b>	no	no	yes
<b>Radiotherapy</b>	no	yes	yes

### 2.3.6 Pathological findings

Forty-eight (77%) of the patients had clinically non-functioning pituitary adenomas, 1 had a somatotrophic adenoma (2%), 1 a prolactinoma, 1 an inflammatory lesion (2%), and in 8 patients (13%), the diagnosis was not confirmed histologically (this includes the 3 patients [5%] treated conservatively). The most common histological finding

was hemorrhagic infarction in 29 patients (47%), followed by infarction (or ghost cells) in 25 (40%), haemorrhage only in 5 (8%), and in the 3 patients (5%) treated conservatively the histology was unknown.

### 2.3.7 Outcome

The average length of follow-up in this series was 55.8 months (range, 1month-22 years). The patients most recent clinical state at follow-up was assessed and divided into the following groups: alive, no symptoms, 37 patients (60%); alive with non-disabling symptoms, 12 patients (19%); alive and disabled, 4 patients (6%); dead as a result off pituitary apoplexy, 3 patients (5%); and dead as a result of other causes, 6 patients (10%) (Figure 30).

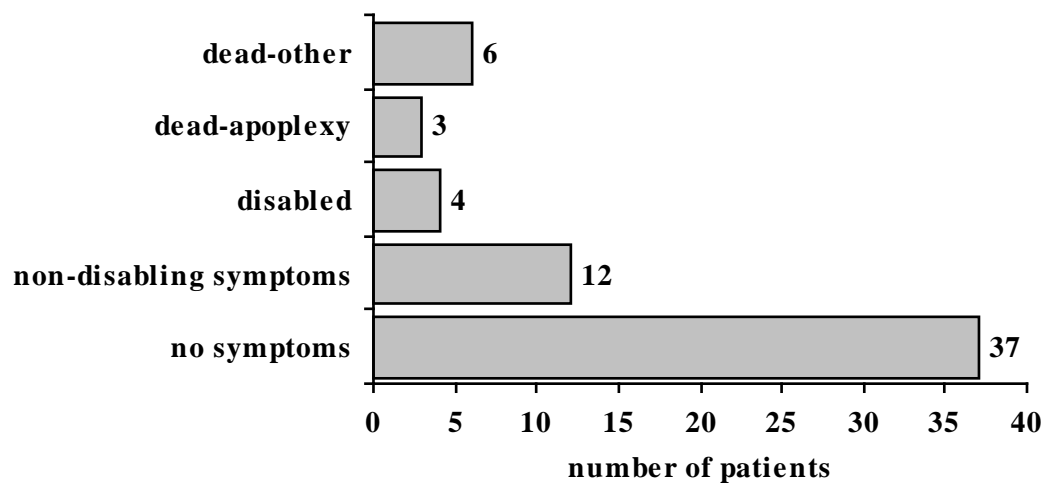


Figure 2.3: Patients' outcome in a series of 62 patients

Visual acuity follow-up was available on 55 patients and was normal in 38 (69%), improved but not normal in 9 (16%), and unchanged in 2 (4%). None were worse, although 6 patients (11%) remained blind. Visual fields at follow-up (52 patients)

were normal in 38 patients (73%), improved but not normal in 11 (21%), unchanged in 2 (4%), and worse in 1 (2%). Cranial nerve function (54 patients followed up) was found to be normal in 43 patients (80%), improved but not normal in 11 (20%), and worse or unchanged in none. The visual outcomes are summarized in Table 3.

**Table 2.3: Outcome of visual and ocular nerve function of patients with pituitary apoplexy. CN = cranial nerve (61 surviving patients)**

	<b>Normal</b>	<b>Improved, not normal</b>	<b>Unchanged</b>	<b>Worse</b>	<b>Blind</b>
<b>Visual acuity</b> (n=55)	38 (69%)	9 (16%)	2 (4%)	0	6 (11%)
<b>Visual fields</b> (n=52)	38 (73%)	11 (21%)	2 (4%)	1 (2%)	NA
<b>CN palsies</b> (n=54)	43 (80%)	11 (20%)	0	0	NA

Data on post-operative endocrine function were available on 58 patients. The majority, 48 patients (83%), required endocrine replacement. Three patients (5%) were hypopituitary but at follow-up were not on replacement, and 7 patients (12%) had normal pituitary function. DI was not present in 50 patients (86%), was transient in 3 (5%), and 5 patients (9%) were left with permanent DI. Post-operative radiotherapy was undertaken in 46 patients (74%), mainly early in the series.

## **2.4 Discussion**

The methodology of setting up a website using a common protocol and having two or more institutions entering patients, although not unique, is a very useful tool for collecting data. This allows for a wider experience not only in terms of numbers but also in the surgeons' approaches to the clinical problems and assessment of complications of treatment and outcome. The website can be expanded and can be applied to answer other questions using the same principles. The data from the different participating centres can be scrutinized and differences between institutions and their results compared and analyzed.

The definition of pituitary apoplexy has not always been uniform, with the most common factors being a characteristic clinical diagnosis associated with appropriate pathological features on histology. The majority of authors agree, however, that pituitary apoplexy is a clinical syndrome resulting from the haemorrhage, infarction or hemorrhagic infarction of a pituitary tumor that results in its sudden and fulminant expansion [Bills et al 1993, Bonicki et al 1993, Cardoso & Petersen 1984, Goel et al 1995]. Apoplexy is of sudden onset and may be characterised by sudden headache, visual disturbance, ophthalmoplegia, pituitary hypofunction, physical collapse, impaired level of consciousness, and death. All the patients in our series conformed to this definition of pituitary apoplexy.

Pituitary apoplexy typically occurs in pituitary macroadenomas, which may be hyperfunctional or clinically non-functional tumors [Bills et al 1993, Randeva et al 1999]. There is no subtype of adenoma that confers a higher risk of apoplexy [Biusse et al 2001]. Pituitary apoplexy has also been described in the normal pituitary gland, craniopharyngiomas, associated with lymphocytic hypophysitis, intrasellar teratoma,

and in Rathke's cleft cysts [Bills et al 1993, Binning et al 2008, Brisman et al 1996, Dan et al 2002, Ebersold et al 1983, Fernandez-Real et al 1995, Findling et al 1981, Lee & Pless 2003, Pawar et al 2002, Podgorski et al 1991, Reid et al 1985, Rolih & Ober 1993].

The majority of patients (81%) presenting with pituitary apoplexy in our study did not have a known pituitary tumor, and consequently making the correct diagnosis can be a challenge. Subarachnoid hemorrhage was the most common differential diagnosis in our series (65% of patients). Although subarachnoid hemorrhage can be a presenting feature of pituitary apoplexy, it is important to differentiate this condition from a subarachnoid hemorrhage from an intracranial aneurysm or vascular malformation [Cardoso & Petersen 1984, Ebersold et al 1983, Maccagnan et al, Sibal et al 2004, Wakai et al 1981]. In addition, aneurysms can be present in patients with pituitary tumors, and subarachnoid hemorrhage can be attributed to the aneurysm as well as pituitary apoplexy in previously described patients [Wakai et al 1981]. Errors in diagnosis are not uncommon, and the differential diagnosis can also include migraine, optic neuritis, stroke, myocardial infarction, encephalitis, sinusitis, cavernous sinus thrombosis and pituitary abscess [Ebersold et al 1983, Xenellis et al 2003].

Although the majority of cases of pituitary apoplexy are spontaneous, numerous precipitating factors have been suggested. Biousse et al [2001] reduced the multiple factors reported as precipitants of apoplexy into four categories: 1) reduced blood flow to the gland, 2) acute increase in blood flow in the pituitary gland, 3) stimulation of the pituitary gland, and 4) the anticoagulated state. Reduced blood flow may be associated with fluctuations in blood pressure, including hypotension often associated

with surgery, changes in intracranial pressure associated with head injuries, repetitive coughing, and procedures such as lumbar puncture, spinal anesthesia, myelography, and angiography, or after radiation, which may damage blood vessel integrity and impair blood supply [Biousse et al 2001, Cardoso & Petersen 1984, Holness et al 1983, Randeva et al 1999, Wakai et al 1981]. Hemorrhagic infarction after partial removal of a large macroadenoma has been described, and it was postulated that the surgical removal of a considerable proportion of the tumors blood supply led to the apoplexy [Goel et al 1995]. One of our patients seems to have had a definite association with head injury, another followed cardiac surgery, and a third followed radiosurgery. Endocrine stimulation tests have been implicated in pituitary apoplexy, including administration of gonadotrophin-releasing hormone, thyrotropin-releasing hormone, and corticotrophin releasing hormone [Biousse et al 2001, Matsuura et al 2001, Randeva et al 1999, Rotman-Pikielny et al 2003, Sugita et al 1995]. The pathophysiological mechanisms are poorly understood, although it had been postulated that stimulation might abruptly increase the metabolic activity in these tumors, resulting in insufficient blood supply and thus precipitating apoplexy [Rotman-Pikielny 2003]. A similar mechanism may apply to stimulation with exogenous estrogens or during pregnancy [Biousse et al 2001, Cardoso & Petersen 1984, Wakai et al 1981]. Bromocriptine therapy, both during and after withdrawal of therapy, has been associated with apoplexy [Biousse et al 2001, Cardoso & Petersen 1984, Goel et al 1995, Maccagnan et al 1995]. An anticoagulated state, whether iatrogenic from the administration of anticoagulant drugs or thrombolytic agents or pathological from thrombocytopenia, may also be associated with pituitary apoplexy [Biousse et al 2001, Cardoso & Petersen 1984, Randeva et al 1999, Rovitt & Fein 1972].

The pathogenesis of the vascular event that results in the apoplexy is often poorly understood. Three main theories have been proposed in the literature; however, none fully explain the pathogenesis, and it may possibly vary in different tumors. A popular theory is that with rapid growth, the tumor outstrips its blood supply, resulting in ischemic necrosis and then hemorrhage [Cardoso & Petersen 1984, Ebersold et al 1983, Goel et al 1995, Mohr & Hardy 1982, Randeva et al 1999, Schechter 1972]. Hemorrhage with and without apoplexy may, however, occur in small tumors [Cardoso & Petersen 1984, Randeva et al 1999]. It has been suggested that with tumor growth, the trabecular arteries arising from the superior hypophyseal artery may be compressed by the diaphragma sellae, resulting in ischemia and secondary necrosis of the tumor [Cardoso & Petersen 1984, Mohr & Hardy 1982, Onesti et al 1990, Rovitt & Fein 1972]. However, the inferior hypophyseal artery often is found angiographically to supply the adenoma; therefore, it is possible that ischemia initially begins in the normal gland rather than in the adenoma [Randeva et al 1999]. Cardoso & Petersen [1984] have postulated that an intrinsic vasculopathy in pituitary adenomas renders them more susceptible to infarction and hemorrhage. This may explain why pituitary adenomas are more susceptible to vascular injury than other tumors [Randeva et al 1999].

The manifestations of pituitary apoplexy can be variable, ranging from mild symptoms to a catastrophic presentation with permanent neurological deficit or even death [Milazzo et al 1996, Rolih & Ober 1993]. The clinical syndrome of pituitary apoplexy is usually of sudden onset, typically initially with headache, followed hours

or days later by other clinical manifestations. The clinical syndrome has usually fully evolved in a few hours to two days [Cardoso & Petersen].

In this study, men (61%) were slightly more commonly affected than women, and the average age was 51 years, which is in agreement with other series [Cardoso & Petersen 1984]. Pituitary apoplexy in childhood is extremely rare [Sugita et al 1995].

The clinical manifestations from a clinicopathological point of view have been divided into three groups: 1) destruction or compression of the pituitary resulting in hypopituitarism; 2) sudden enlargement upward or laterally, resulting in compression of neural structures; and 3) leakage of blood and necrotic tissue, resulting in meningism and symptoms similar to subarachnoid hemorrhage [Reid et al 1985].

In the current series, 84% of the patients presented with a sudden onset of headache. The cause of the headaches is not completely clear, although it is thought to be a result of pressure on the diaphragma sellae or meningeal irritation [Cardoso & Petersen 1984]. Eight patients had a diminished level of consciousness, and 3 were in coma. Sixty-one percent had impaired visual acuity, bitemporal hemianopia was present in 43%, and ophthalmoplegia was found in 43%. These clinical features are similar to those previously reported [Bills et al 1993, Cardoso & Petersen 1984, De Villiers & Marus 1988, Ebersold et al 1983, Maccagnan et al 1995, MacFadzean et al 1991, Milazzo et al 1996, Randeva et al 1999, Reid et al 1985, Rolih & Ober 1993]. Signs and symptoms from hypopituitarism are less frequent than headache and visual disorders and are usually detected by laboratory investigations, although 17 of the patients in the present series on history had some endocrine symptoms before the

apoplexy. The cure of syndromes associated with pituitary hypersecretion (e.g., acromegaly, hyperprolactinemia, and Cushing's disease) after a pituitary apoplexy have been described [Findling et al 1981, Jones &Finer 1984, Kulah et al 1995].

MRI is undoubtedly the imaging tool of choice, because it clearly demonstrates the features of hemorrhage and infarction, the suprasellar extension, compression of the chiasm, and extension into the cavernous sinuses [Bills et al1993, Dubuisson et al 2006, Milazzo et al 1996, Onesti et al 1990, Ostrov et al 1989, Piotin et al 1999]. A CT scan is also helpful if MRI is unavailable or is contra-indicated [Chanson et al 2004, Laws & Ebersold 1982, Onesti et al 1990, Ostrov et al1995, Post et al 1980, Wakai et al 1981, Weisberg 1977]. As an initial emergency room investigation, a lateral cranial x-ray may show an enlarged sella in a patient with suspected apoplexy [Cardoso & Petersen 1984, Fitz-Patrick et al 1980]. Cerebral angiography is sometimes used to exclude a cerebral aneurysm, but MRI and Magnetic Resonance Angiography are as effective and safer.

The two pillars of management of pituitary apoplexy have been transsphenoidal decompression and immediate institution of high dose corticosteroid replacement therapy [Bills et al 1993, Brisman et al 1996, Cardoso & Petersen 1984, Laws & Ebersold 1982, Sibal et al 2004]. There is consensus that high-dose corticosteroid replacement therapy and careful management of fluid and electrolyte balance is mandatory; however, there is some disagreement with regard to surgical treatment [Ayuk et al 2004, Brisman et al 1993, Cardoso & Petersen 1984, Chanson et al 2004, Gruber at al 2006, Reid et al 1985, Zhang et al 2007]. Randeve et al [1999] strongly advocate early transsphenoidal surgery for pituitary apoplexy, with particular urgency

in patients with deteriorating vision. They argue that the procedure has a low morbidity and mortality and that they reliably reversed or improved the neuro-ophthalmological deficits and furthermore noted that the improvement was more likely on those patients operated on within 8 days (73%) compared with those operated on later (42%). De Motta et al [1999] reported a higher mortality rate when the patients were not treated surgically. Bills et al [1993] analyzed retrospectively a series of 38 patients and concluded that there was significantly improved outcome of visual acuity and a similar trend in visual field improvement in patients operated on in the first week. They therefore thought that early but not necessarily emergency surgery resulted in better visual outcome. The exception was in patients in whom sudden severe loss of vision occurred, and it was thought that emergency surgery was required in these patients. In patients who present with blindness, some authors have described improvement, whereas others reported no effect from surgery [Agrawal & Mahapatra 2005, Bills et al 1993, Onesti et al 1990]. Even late surgery for pituitary apoplexy is described as having satisfactory results in improved visual function [Bills et al 1993, Epstein et al 1971, Peter & Tribolet 1995, Randeva et al 1999]. Some authors have also described a lower incidence of hypopituitarism in patients treated surgically [Chuang et al 2007, Onesti et al 1990, Randeva et al 1999]. The lack of predictability of the clinical course of pituitary apoplexy after the initial ictus has been cited as an indication for early surgery [Brisman et al 1996]. Craniotomy is used very rarely and only when there is a contraindication to transsphenoidal surgery. Stereotactic surgery may have a role in patients who are medically unfit for a more invasive procedure [Onesti et al 1990]. The successful use of endoscopic techniques for pituitary surgery will certainly extend to the treatment of pituitary apoplexy [Cappabianca et al 2002].

Maccagnan et al [1995], in a prospective study in which all patients were initially treated with high-dose dexamethasone and in whom surgery was performed only if there was no improvement in the first week, concluded that patients with visual impairment or a diminished level of consciousness would benefit from surgery, but in those presenting with ophthalmoplegia, conservative treatment was just as effective. Improvement of ocular paresis has been well described with surgery, but conservative treatment has also been successful [Bills et al 1993, Brisman et al 1996, Maccagnan et al 1995, Onesti et al 1990, Randeva et al 1990, Seyer et al 1992]. Sibal et al [2005] in their retrospective review of forty-five patients with pituitary apoplexy concluded that those patients without neuro-ophthalmic signs or who exhibited mild and non-progressive signs could be managed conservatively in the acute stage. Ayuk and co-workers, in their retrospective analysis of 33 patients with pituitary apoplexy, found that 54% of them were treated conservatively. They concluded that patients presenting acutely with pituitary apoplexy in whom there was no evidence of visual deficit or where there was evidence of spontaneously resolving deficit, could be treated conservatively without any deleterious effect on vision or endocrine outcome [Ayuk et al 2004]. Gruber et al [2006] found no apparent difference in visual outcome between those patients managed surgically and those managed conservatively; they found that apart from blindness, nearly all visual defects improved significantly or resolved completely in both conservatively and surgically managed patients over long-term follow-up. In our series three patients were successfully treated conservatively. Two of the patients were already showing signs of improvement of the headaches and ophthalmoplegia at the time of presentation. The third patient was found to have a markedly elevated prolactin level and hyponatremia and responded

very well to bromocriptine, hydrocortisone and electrolyte correction. Two of the patients had entirely normal vision, and the third had a minimal visual field defect and normal acuity. Bromocriptine use in prolactinoma patients who have had apoplexy is well described [Brisman et al 1996].

Although there is varying opinion among different authors, a reasonable guideline for surgical treatment of pituitary apoplexy is outlined below. Surgery is indicated if there is a diminished level of consciousness, hypothalamic disturbance, or visual impairment. Emergency surgery is required when there is deteriorating vision, sudden onset of blindness, or diminished level of consciousness. Early surgery within the first week is recommended with visual impairment. If the patient is examined sometime after the ictus (days or weeks) and shows a stable or improving ophthalmoplegia, then conservative treatment is justified. The most difficult decision involves ophthalmoplegia, and although we would advocate surgery in the early presentation, conservative management can be justified, particularly if there is an isolated ocular palsy.

There has been a marked improvement in outcome in pituitary apoplexy over the past 30 years that reflects the progress of surgical and endocrine management. The visual outcome is related to length of history, severity of the initial visual defect, the appearance of the optic disc, and early decompression [Bills et al 1993, Esasser et al 2005, McFadzean et al 1991, Parent 1990, Peter & de Tribolet 1995, Randeva et al 1999]. In our series there was an improvement in visual acuity of 76% and of visual fields of 79%, which is similar to other series [McFadzean et al 1996, Peter & de Tribolet 1995, Randeva et al 1999]. Ocular paresis whether treated conservatively or

with transsphenoidal decompression, has a good prognosis, with normalization or improvement in up to 91% [Bills et al 1993, Kim et al 2007, McFadzean et al 1996, Seyer et al 1992, Tanriverdi et al 2007]. Seventy-seven percent of patients in the present series required endocrine replacement therapy, usually thyroid or cortisol replacement, which is similar to other published series [Bills et al 1993, Dubuisson et al 2006, Ebersold et al 1983, Fernandez-Real 1991, Laws & Ebersold 1982, Lubina et al 2005, Vidal et al 1992]. DI is much less common, probably because the blood supply of the posterior pituitary is different from that of the anterior [Bills et al 1993]. We found transient DI in 5% of patients and permanent DI in 8%. The overall outcome was good, with 60% of patients alive with no symptoms and 19% alive with minor non-disabling symptoms. Only 6% of patients were severely disabled and 5% died as a consequence of the apoplexy.

## **2.5 Conclusion**

Pituitary apoplexy is a rare but potentially life-threatening condition. The diagnosis is easily missed, because in the majority of patients, the pituitary adenoma is undiagnosed, and clinically, the picture can be mistaken for subarachnoid hemorrhage or meningitis. The majority are spontaneous, although a number of precipitating factors have been implicated. The diagnosis therefore rests on a high suspicion in patients presenting with headache, visual acuity and field abnormalities, ocular muscle palsies, diminished level of consciousness, or hypothalamic disturbance. An MRI scan is the imaging procedure of choice. High-dose corticosteroid replacement should be given to all patients. Emergency transsphenoidal decompression should be performed in patients with a diminished level of consciousness, hypothalamic

disturbance, and sudden severe visual disturbance or blindness. In patients with mild or moderate visual impairment, the surgery should be performed as soon as possible within the first week. There is evidence that isolated cranial nerve palsies may be successfully managed conservatively, as may patients who present long after the ictus and are improving.

## **CHAPTER 3**

# **PITUITARY APOPLEXY: DO HISTOLOGICAL FEATURES INFLUENCE THE CLINICAL PRESENTATION AND OUTCOME**

### **Introduction**

In the majority of published series, no differentiation is made between pure infarction and hemorrhage with or without infarction, and very few cases of pituitary apoplexy due to pure infarction have therefore been described. As most cases of pituitary apoplexy are associated with hemorrhage, cases due to infarction have been included in series with hemorrhagic cases, with no distinction being made between the two. However, a small number of cases of pure infarction have been previously described by Brougham et al [1950], Ebersold et al [1983], Gurling [1955], Mohr & Hardy [1982], and Rovit & Fein [1972]. De Villiers and Marus [1988], after histopathological examination of resected tumors, described five cases of infarction with no hemorrhage, in their series of 15 patients with pituitary apoplexy. Chako et al [2002] found that 15 of the 41 patients with pituitary apoplexy included in their series had infarction alone on histopathological examination.

In this study, which combines the experience of two neurosurgical centers, we compare the patients with pituitary apoplexy who were found on histological examination to have pure infarction with those who had hemorrhage or hemorrhagic infarction of a pituitary tumor. Particular attention was paid to clinical presentation and outcome.

### **3.2 Clinical material and methods**

A retrospective series of 62 patients with pituitary apoplexy treated at Groote Schuur Hospital (GSH), University of Cape Town, South Africa, and University of Virginia Health System (UVA), Charlottesville, Virginia, USA, was collated. Thirty-eight consecutive patients were treated by two surgeons at GSH between 1972 and 2003, and 24 were treated by a single surgeon at UVA between 1992 and 2003. Fifty-eight patients were surgically treated, one patient died pre-operatively but underwent a post-mortem examination, and three patients were treated conservatively.

For the purposes of this study, the histopathological reports from the pathology departments of both institutions were used to divide the patients into two groups: those in whom the histological finding was infarction (or ghost cells), and those in whom only hemorrhage or hemorrhagic infarction was encountered. The three patients who were treated conservatively had no histological confirmation of the pathological entity and were therefore excluded from the study. In the patient who died pre-operatively, however, a histological examination of the pituitary tumor found at post-mortem was performed and this individual could therefore be included.

Fifty-nine patients (mean age 51.1 years) were entered in the study. The mean duration of follow-up was 55 months (range 1 month – 22 years). Forty-eight patients had clinically non-functional pituitary adenomas, one each had a somatotroph adenoma, a prolactinoma, and an inflammatory lesion, and in eight a pituitary adenoma or other underlying disease was assumed, but could not be confirmed because the tissue studied was necrotic and / or hemorrhagic. Histopathological examination of the pituitary lesion underlying the pituitary apoplexy was performed in 59 patients, who could therefore be included in the retrospective analysis. Our standard procedure was to collect the entire pathological specimen for histological examination to improve the accuracy of the diagnosis. Twenty-two patients (37%) had infarction alone on histopathological examination (Figure 3.1) and 37 (63%) had hemorrhagic infarction or hemorrhage (Figure 3.2). In Figure 3.3, photomicrographs of specimens obtained in the two major histopathological types are contrasted. Twenty-two patients were found to have infarction alone, hemorrhage alone was present in five, and hemorrhagic infarction in 32 patients on histological examination. The two groups were then compared with regard to clinical presentation and outcome. Data were analyzed using Stata Version 10.0 (Stata Corporation, College Station, Texas, USA). Proportions were compared using Fisher's exact tests and odds ratios with 95% confidence intervals (CI). Continuous variables were described as means and medians, and compared with Wilcoxon rank-sum tests. All statistical tests are two-sided at  $\alpha = 0.05$ .

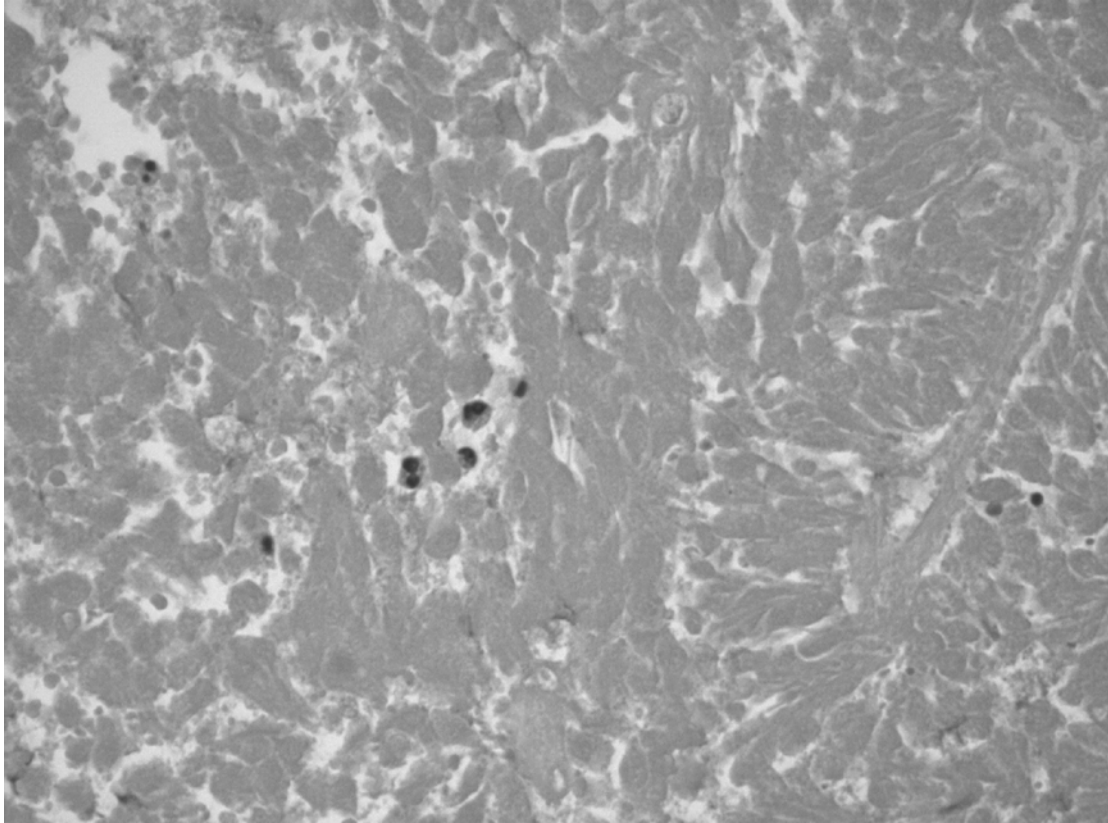


Figure 3.1: Pituitary Infarction. Haematoxylin & Eosin staining at x200 magnification. Shows outlines of homogeneous (and now non-nucleated/necrotic) neoplastic pituicytes consistent with an infarcted pituitary adenoma (the only surviving nuclei present being those in a few neutrophils (which probably represent an early “vital-reaction” to the infarct)).

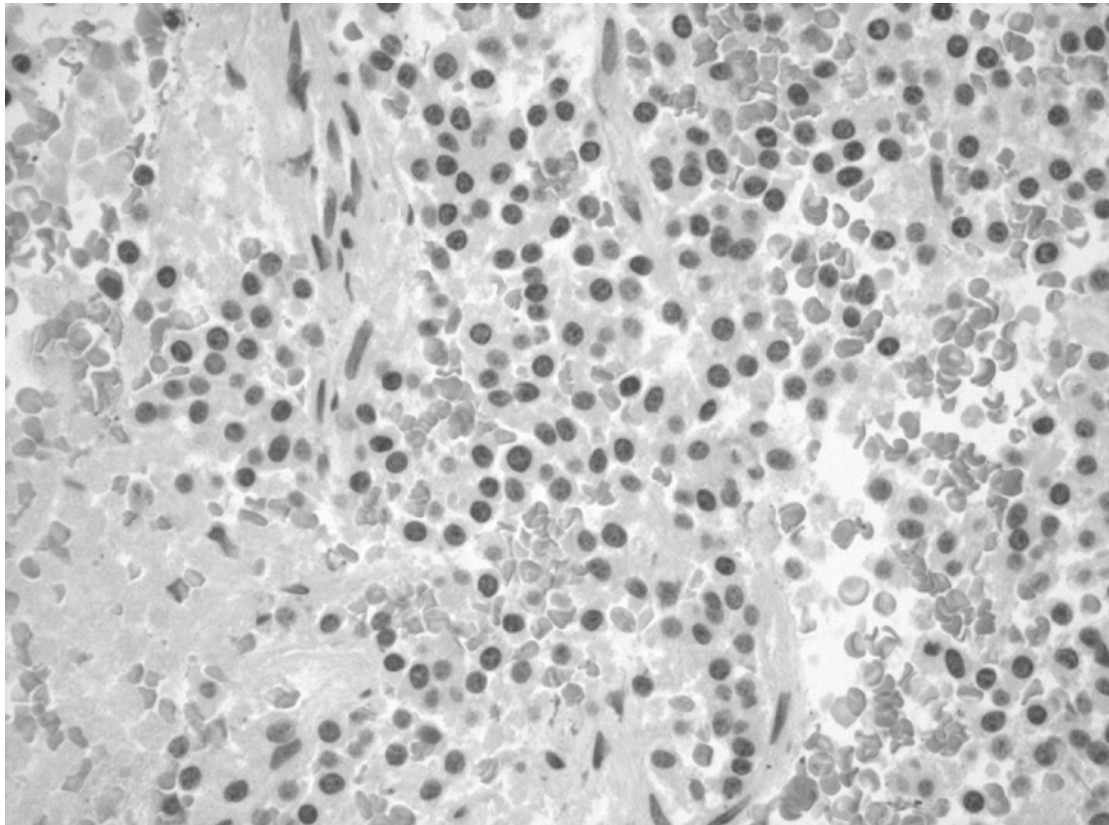


Figure 3.2: Pituitary Haemorrhage. Haematoxylin & Eosin staining at x200 magnification. Shows (non-nucleated) red cells interspersed amongst homogeneous (nucleated) neoplastic pituicytes – consistent with haemorrhage into a pituitary adenoma).

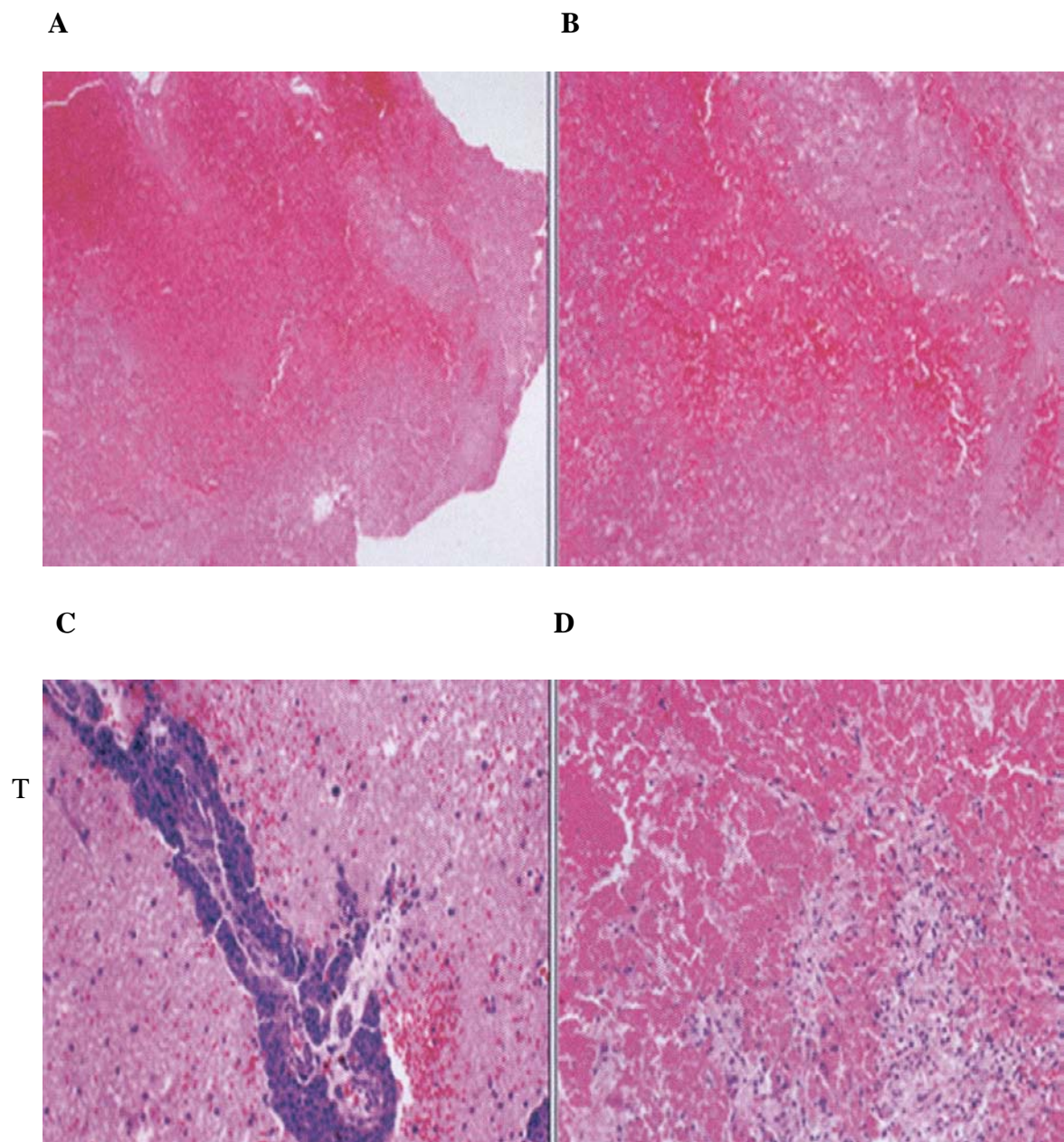


Figure 3.3: Photomicrographs showing histopathological features of pituitary apoplexy. A and B: Extensive hemorrhagic infarction of a pituitary adenoma with complete replacement of the tumor mass by hemorrhage and necrosis. C and D: A large, infarcted corticotroph adenoma showing a focus of residual tumor cells in the centre of the section, surrounded by extensive necrotic tumor, which is more easily seen in panel D. H & E, original magnifications X100 (A and C) and X 200 (B and D).

### 3.3 Results

Details of patient distribution according to sex, age, and type of apoplexy are presented in Table 3.1.

**Table 3.1: Categorization of 59 patients with pituitary apoplexy**

Patient Data	Type of Apoplexy	
	INF	HNF
men	12	22
women	10	15
total	22	32 / 5 *
mean age (years)	52.8	50.4

HINF = hemorrhagic infarction / frank hemorrhage; INF = infarction alone.

\* In this group, 32 had hemorrhagic infarction and five had frank hemorrhage.

### 3.3.1 Presenting symptoms

Although their presenting symptoms were similar, there was a marked difference between the two groups in the duration of symptoms before presentation at the neurosurgical departments. In patients with hemorrhage and / or infarction this was 10.9 days, which is half the time of patients in the group with infarction alone (20.1 days). The median duration of presenting symptoms was 4 days for patients with hemorrhage or hemorrhagic infarction and 9 days for infarction alone. Comparison of the medians was  $p = 0.099$  which approaches statistical significance.

Headache was the most common presenting symptom in both groups; it was found in 18 patients (82%) in the infarction and 31 (84%) in the hemorrhage or haemorrhagic infarction group. Five patients with infarction alone (23%) reported mild visual impairment (acuity and / or field defects) and none presented with non-functional vision or blindness. In the group with hemorrhage or hemorrhagic infarction, however, 19 patients (51%) presented with visual impairment, and 5 more (13.5%) presented with blindness. Individuals with visual impairment were more likely to have hemorrhage or hemorrhagic infarction although this did not reach statistical significance ( $p = 0.054$ ). Six patients (27%) from the infarction-only group experienced ptosis or diplopia, and eight (21.6%) in the hemorrhage or hemorrhagic infarction group presented with these symptoms. Two patients (5.4%) with hemorrhage or hemorrhagic infarction presented in a comatose state, while no patient with infarction alone presented in this manner ( $p = 0.052$ ) (Figure 3.4).

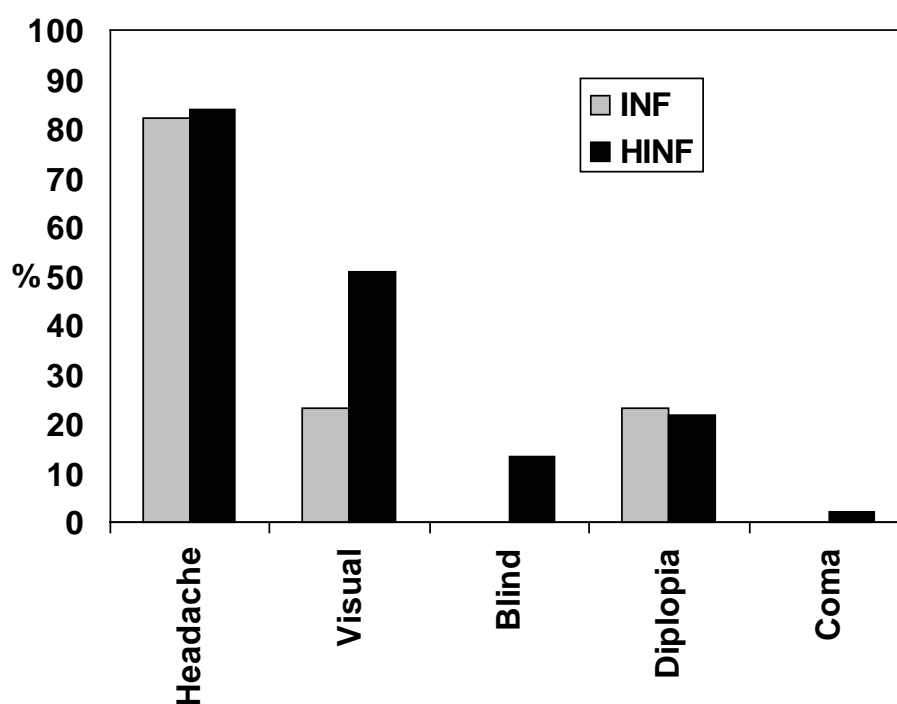


Figure 3.4: Clinical presentation of patients in the infarction-only (INF) and hemorrhage or hemorrhagic and infarction (HINF) groups.

### 3.3.2 Clinical findings and endocrine status

The level of consciousness (assessed according to the Glasgow Coma Scale) was diminished in one patient (5%) with infarction alone, but in the group with hemorrhage or hemorrhagic infarction this was the clinical finding in eight (21.6%) ( $p = 0.133$ ). Visual function (visual acuity and fields) was normal in 11 patients with infarction alone (50%), and the other 11 had

only mild visual impairment. There were no patients with non-functional vision or blindness in this group. In the patients with hemorrhage or hemorrhagic infarction, six (16.2%) had normal vision, 19 (51.4%) had impaired but functional vision, three (8%) had non-functional vision, and six (16.2%) were blind. Three could not be assessed because of coma. On statistical comparison significantly more patients with infarction alone were found to have normal vision ( $p = 0.008$ ), and significantly more patients with hemorrhage or hemorrhagic infarction had non – functional vision or were blind ( $p = <0.001$ ). Six patients (27%) with infarction alone were found to have an ophthalmoplegia involving one or more cranial nerves, compared with eighteen patients (48.6%) with hemorrhage or hemorrhagic infarction. On endocrinological assessment, 17 patients (77%) with infarction alone showed evidence of hypopituitarism, four had normal pituitary function, and one had acromegaly. Thirty-one (83.8%) of the patients with hemorrhage or hemorrhagic infarction had hypopituitarism on investigation (Figure 3.5).

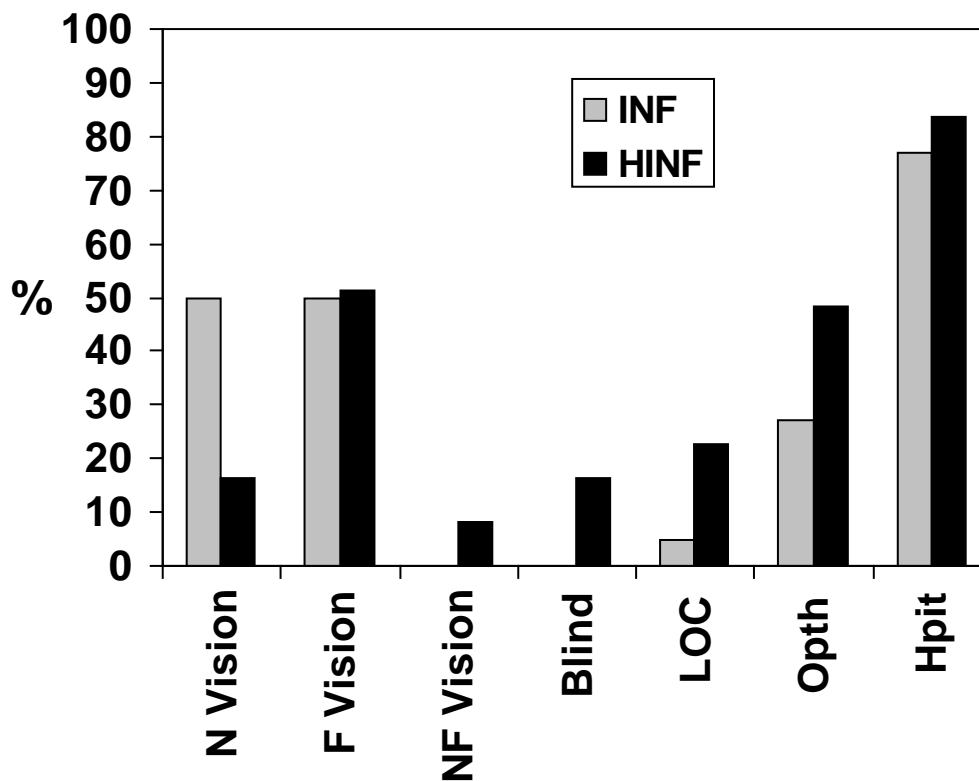


Figure 3.5: Clinical examination and endocrinological assessment in patients with infarction alone and in those who had hemorrhage or hemorrhagic infarction. N Vision = normal vision, F Vision = functional vision, NF Vision = non-functional vision, LOC = diminished level of consciousness, Opth = ophthalmoplegia, Hpit = hypopituitarism (based on results of endocrine testing).

### 3.3.3. Clinical outcome

The mean duration of the follow-up in this series was 55.8 months (range 1 month – 22 years). The outcome of the patients at follow-up examination was divided into the following categories: alive with no symptoms; alive with non-disabling symptoms (minor deficit); alive and disabled (major deficit); and dead due to the pituitary apoplexy or other causes (Figure 3.6). Of the patients in the infarction only group, 17 (77%) were alive and well, four (18%) had minor disabilities, and none had major disabilities or had died (one patient was lost to follow-up). Of the patients who were assigned to the hemorrhage or hemorrhagic infarction group, 15 (37.8%) were well, 13 (35.1%) had minor disabilities, six (16.2%) had major disabilities, three (8.1%) died as a result of the pituitary apoplexy. Overall, poor outcomes were observed significantly more often in patients with hemorrhage or hemorrhagic infarction ( $p = 0.013$ )

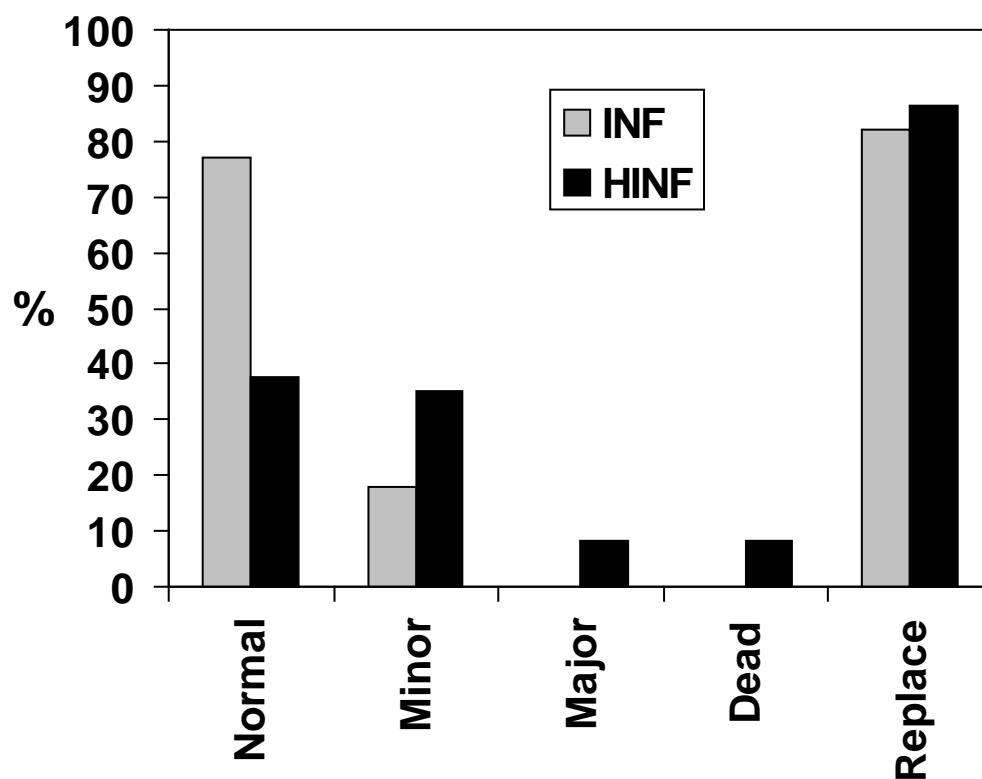


Figure 3.6: Clinical outcome of patients in the two groups. Replace = hormone replacement therapy.

Visual function was evaluated at follow-up review (Figure 3.7) and was regarded as normal if visual acuity was normal and the visual fields were full. Visual function was divided into normal, improved but not normal, not improved, worse or blind. In patients with infarction only, vision was normal at follow-up review in 21 (95%), and one patient (5%) was lost to follow-up. In the group with hemorrhage or hemorrhagic infarction, vision was normal in 17 patients (45.9%), improved but not normal in nine (24.3%), and seven (18.9%) remained blind. There was no patient in whom there was either no visual improvement, or worsening of vision, and in three patients assessment was not possible because they had died. Patients with hemorrhage or hemorrhagic

infarction were likely to experience poor visual outcomes compared to patients with infarction alone ( $p = <0.001$ ).

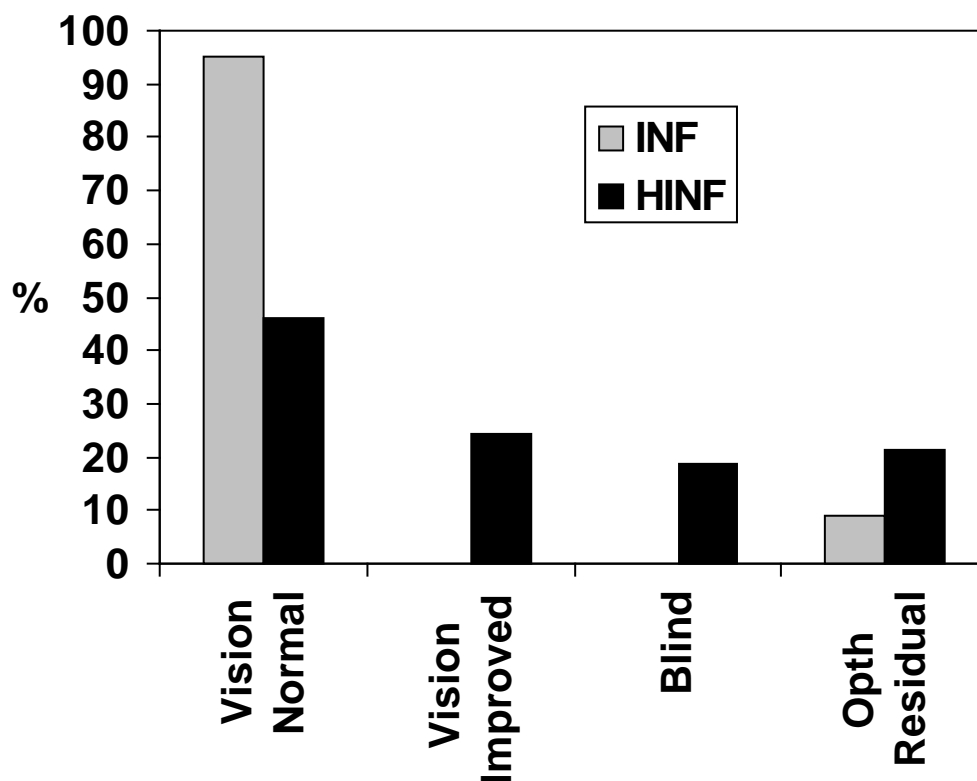


Figure 3.7: Outcome of patients in the two groups in terms of visual function. Opth Residual = residual opthaolmoplegia.

For assessment of ophthalmoplegia at follow up, the patients were divided into those with no symptoms, those whose ophthalmoplegia had improved but who had a residual deficit, and those with no improvement. In the infarction-only group, six patients were found to have ophthalmoplegia at presentation. Of these, four were found to have no ophthalmoplegia at follow-up review and two were improved but still had a mild

residual deficit. In reviewing the entire infarction-only group, 19 patients (86%) had no ophthalmoplegia at follow-up, two (9%) had a residual deficit, and one (5%) was lost to follow-up. In the group with hemorrhage or hemorrhagic infarction, 18 patients had ophthalmoplegia at presentation. In 11 of these patients, the ophthalmoplegia had completely resolved at follow-up evaluation, and in seven, it had improved. In reviewing the hemorrhage or hemorrhagic infarction group as a whole, 22 patients (59.5%) had no evidence of ophthalmoplegia at follow-up, seven (18.9%) had improved, and one (2.7%) had shown no improvement. Three patients died before they could be assessed. Resolution of ophthalmoplegia was more common in infarction alone compared to hemorrhage or hemorrhagic infarction, and this difference approached statistical significance ( $p = 0.054$ ). Eighteen (82%) of the 22 patients in the infarction group required long-term hormone replacement therapy for hypopituitarism, three (13%) had normal pituitary function, and in one case (5%) the pituitary status was unknown because the patients were lost to follow-up. Thirty-two (86.5%) of the thirty-seven patients in the group with hemorrhage or hemorrhagic infarction required endocrine replacement therapy. Of the five remaining patients, three did not survive (they died in the acute phase of the apoplectic episode) and the endocrine replacement status of the other two was unknown.

### 3.4. Discussion

We assessed 59 patients with pituitary apoplexy to see if there were differences in clinical presentation and outcome when patients were divided based on the histopathological findings of infarction alone or hemorrhage and hemorrhagic infarction. Histopathological differentiation was chosen because this is the most reliable method of distinguishing between the two groups. Although MRI is currently the most effective neuroimaging method for diagnosing pituitary apoplexy, Kurihara et al [1998] found that 12 of the 14 cysts judged pre-operatively as nonhemorrhagic in fact contained hemorrhagic components. Piotin et al [1999], in their series in which MRI studies were obtained in 11 patients with pituitary apoplexy, concluded that this disease may present with varying MRI features, including nonhemorrhagic and hemorrhagic changes on T<sub>1</sub>-weighted images. It is well described that the MRI features of the blood components in a hemorrhage change over time. Acute hemorrhage may therefore may not be demonstrated unless the correct sequences are used, and furthermore, the imaging characteristics of the blood in a hemorrhage change between the acute and the subacute stages [Lacallee et al 1995, Piotin et al 1999]. Consequently it is possible to miss a hemorrhage in the acute stage, and unless follow-up MRI studies are performed to allow the changed characteristics of the hemoglobin degradation products to be recognised, the differentiation between hemorrhage and infarction may not always be clear.

On CT scans the density of the blood changes as it degenerates, thus making it difficult to distinguish between hemorrhage and infarction, and acute hemorrhage found at operation is not always visible on the pre-operative scan [Post et al 1980]. It

must be noted, however, that an error could result if only a small surgical specimen is sent for histopathological examination; that particular fragment may not necessarily represent the findings throughout the tumor. Therefore, it is important to collect the entire specimen, if possible, for histological examination. Although sometimes it may be difficult to distinguish between pure infarction and hemorrhage or hemorrhagic infarction on histological examination, it is not impossible, because in the majority of cases the histological appearance is easily distinguishable.

The clinical presentation of pituitary apoplexy varies from a clinically relatively benign event to a catastrophic episode with severe neurological deficit, endocrine failure, or even death [Rohli & Ober 1993]. When we compared the clinical presentations and findings in patients in our series, we found a difference between individuals who had histological evidence of infarction only, compared with those who had hemorrhage or hemorrhagic infarction only. The interval between onset of symptoms and presentation at the neurosurgical department was twice as long in those who had infarction alone (20.1 days), compared with those who had hemorrhage or hemorrhagic infarction (10.9 days), while the median duration was 9 and 4 days respectively. In both groups of patients, the most common presenting symptom was headache, but the visual symptoms were more common and of greater severity in the hemorrhage or hemorrhagic infarction group than in the infarction-only group. Twenty-two percent of the patients with infarction had relatively mild visual symptoms, retaining functional vision. In contrast, in the group of patients with hemorrhage or hemorrhagic infarction, visual symptoms occurred in 64.5% and were more severe; 13.5% presented with blindness. Patients with visual impairment were more likely to have hemorrhage or hemorrhagic infarction ( $p = 0.054$ ). Diplopia was

equally common in both groups. Two patients in the group with hemorrhage or hemorrhagic infarction presented in a comatose state.

Clinical findings were similar, with an increase in the number and severity of neurological deficits in patients with hemorrhage or hemorrhagic infarction. The visual findings in the patients with infarction were normal in 50%, and mild deficits of functional vision were present in the remaining 50%. In contrast, in the group of patients with hemorrhage or hemorrhagic infarction, normal vision was present in only 16.2%, whereas 52.3% had diminished but still functional vision, 8.1% had nonfunctional vision, and 16.2% were blind (vision could not be assessed in 8%). Significantly more patients with infarction alone had normal vision ( $p = 0,008$ ), while patients with hemorrhage or hemorrhagic infarction were more likely to have non-functional vision or blindness ( $p = <0.001$ ). Ophthalmoplegia was also a more common finding in the patients with hemorrhage or hemorrhagic infarction. Only 5% of patients with infarction alone had a diminished level of consciousness (GCS less than 15), compared to 22.2% in the group with hemorrhage or hemorrhagic infarction. This is in agreement with the findings of De Villiers and Marus [1988]. From the difference in time to presentation we may infer that the symptoms in the group of patients with infarction alone were less severe and not as catastrophic, resulting in a longer interval elapsing before they sought medical help. Chacko and coworkers [2002] described a longer symptomatic interval in patients who were found to have pale necrotic tissue with no evidence of hemorrhage at surgery. They ascribe this to the resorption of blood products, however, in my view these patients had pure infarction with no hemorrhage, because blood breakdown products would have been present if hemorrhage had also occurred.

The pathogenesis of events that lead to infarction, hemorrhage, or a combination of the two are poorly understood, and a number of theories have been proposed (see Chapter 2). In the case of hemorrhage, it is not always possible to determine if the primary event was infarction followed by hemorrhage or if the primary event was the hemorrhage itself.

The fact that the patients with infarction alone appear to have a more benign presentation than those with hemorrhage or hemorrhagic infarction supports the suggestion that the expansion of the tumor and compression of the surrounding structures is not as severe in pure infarction as in the latter condition. The infarction may raise the pressure in the tumor, but possibly not as rapidly or severely as in a hemorrhage or hemorrhagic infarction, so that tumor expansion is less marked and compression of the surrounding structures is consequently less severe.

Patients in our series who had infarction alone had a better outcome than those with hemorrhage or hemorrhagic infarction. The patients in the group with infarction were normal neurologically in 77% of cases, compared with 37.8% of patients in the group with hemorrhage or hemorrhagic infarction. The remainder of the group with infarction alone only had minor neurological deficits (5% were lost to follow-up). This was in contrast to the patients with hemorrhage or hemorrhagic infarction, in whom 35.1% had a minor neurological deficit, 16.2% a major one, and in whom 8% died as a direct result of the apoplexy (five died of other unrelated causes). Overall, poor outcomes were significantly more common in patients with hemorrhage or hemorrhagic infarction ( $p = 0.013$ ). Visual function, when assessed as an independent

factor, also proved to have a much better outcome in the patients with infarction alone. In this group, vision at follow-up was normal in 95%. In the patients with hemorrhage or hemorrhagic infarction, however, vision was normal in only 45.9%, it had shown improvement but was not normal in 24.3%, and 18.9% of the patients in this group had remained blind (the three deaths were excluded). Patients with hemorrhage or hemorrhagic infarction were more likely to have a poor visual outcome ( $p = <0.001$ ) There was also a greater improvement in the ophthalmoplegia of the patients with infarction alone.

Similar numbers of patients from both groups required hormone replacement therapy for hypopituitarism, indicating that the degree of destruction of normal pituitary tissue was comparable. The origin of the hypopituitarism may be due to compression or destruction of the pituitary gland, interruption of the blood supply to the gland, or pituitary stalk damage. This may present in varying degrees in both groups, resulting in hypopituitarism. Nevertheless, the worst outcome may again be related to the severity of the initial ictus, in which there may be greater pressure from hemorrhage or hemorrhagic infarction than from infarction alone within the adenoma, resulting in more severe and rapid expansion of the tumor, leading to more severe injury to surrounding structures. The blood may also escape from the confines of the tumor capsule, resulting in clinical features similar to subarachnoid hemorrhage.

The fact that pure infarction-related apoplexy seems to have a less catastrophic course than apoplexy due to hemorrhage or hemorrhagic infarction may have some implications for the management of pituitary apoplexy. The endocrine replacement therapy requirement does not appear to be influenced by the histological findings.

### **3.5 Conclusion**

Pituitary apoplexy remains a potentially life-threatening disease. Its presentation, however, may vary from that of a relatively benign illness to major neurological deficits and even death. Consequently, its early recognition and treatment are vital. Histopathologically the findings may be infarction, hemorrhagic infarction, or hemorrhage alone. Patients who present with pituitary apoplexy due to infarction alone in a pituitary adenoma have a more benign illness with a less severe presentation and better outcome than those in whom histological studies show hemorrhagic infarction or hemorrhage alone.

## **CHAPTER 4**

# **PITUITARY APOPLEXY: CORRELATION OF MRI AND HISTOPATHOLOGY**

### **4.1. Introduction**

The aim of this study was to review the operative findings, histopathological reports and MRI scans on consecutive patients to assess if the histopathology found at surgery could be reliably predicted on the MRI scan pre-operatively. If one were able to correlate the histological findings with those found on MRI then we may get an improved understanding of the presentation and may be able to better predict the outcome of these patients pre-operatively.

### **4.2. Clinical material and methods**

Thirty-eight patients were treated for pituitary apoplexy in the Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA from January 1996 to March 2006. Two surgeons carried out transsphenoidal surgery, either microscopic or endoscopic on these patients. The operative specimens were characterized by the Department of Neuropathology, University of Virginia into two

separate groups: those in whom the histological findings were of infarction with no evidence of hemorrhage and; the second group which was characterized hemorrhagic infarction or hemorrhage alone. The entire mass of removed pituitary tumor was sent as the specimen for histological study.

Thirty-six of the patients had pre-operative MRI scans and in 2 patients CT scans were the only pre-operative imaging. One patient was unable to have an MRI scan as he had a cardiac pacemaker. The other had a CT scan done in a foreign country and was transferred to Charlottesville as an emergency, therefore the CT scan was assessed as being diagnostic and no further imaging was thought necessary prior to emergency surgery. The two patients who only had CT scans and no MRI study were excluded from the study. The MRI scans were collected and reviewed. When the scans were no longer available the radiologists report alone was reviewed. The MRI images as well as the radiologists' report were studied in 19 patients and in 17 patients the radiologists' report alone was documented. The features that were noted in particular were: the presence of blood products indicating hemorrhage or hemorrhagic infarction, appearance of infarction alone with no blood products, the presence of pituitary tumor alone with no obvious evidence of pituitary apoplexy and the presence of mucosal thickening in the sphenoid sinus.

The MRI scan findings on 36 patients were divided into 3 groups. The first group was those in whom imaging features were in keeping with infarction alone. Typically this group showed no hemorrhage on T1 or T2 sequences, and no enhancement with gadolinium except for characteristic rim or capsule enhancement (Figure 4.1). The timing of the MRI scan was also taken into consideration when looking for blood

breakdown products. The second group showed evidence of hemorrhage with or without infarction on T1 and T2 sequences (Figure 4.2). The third group clearly showed a pituitary tumor, but there was no evidence of hemorrhage or infarction and the radiological report at the time was only that of a pituitary tumor.

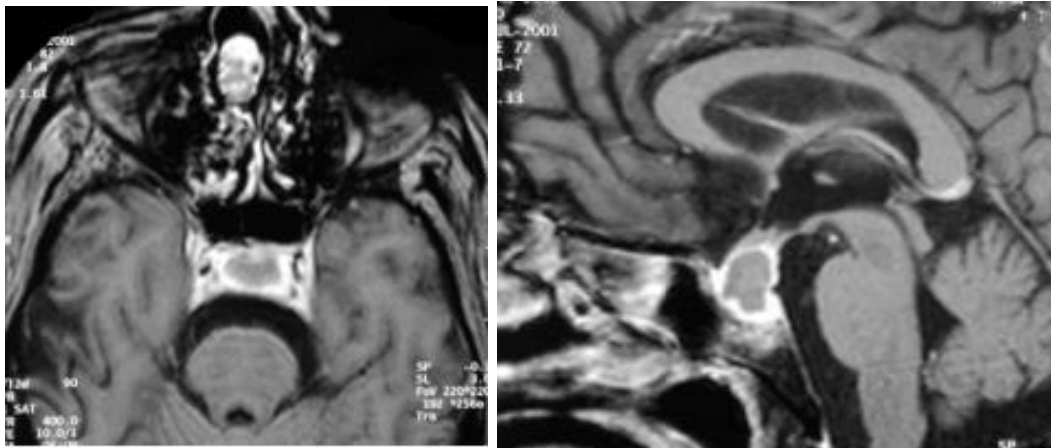


Figure 4.1: T1 sequence of MRI in axial and sagittal plane with contrast. There is enhancement of the capsule with low intensity signal within the tumor. This picture may suggest infarction of the tumor, but hemorrhage, depending on the timing of the scan may also be low intensity. This particular patient had infarction alone on histopathological studies.

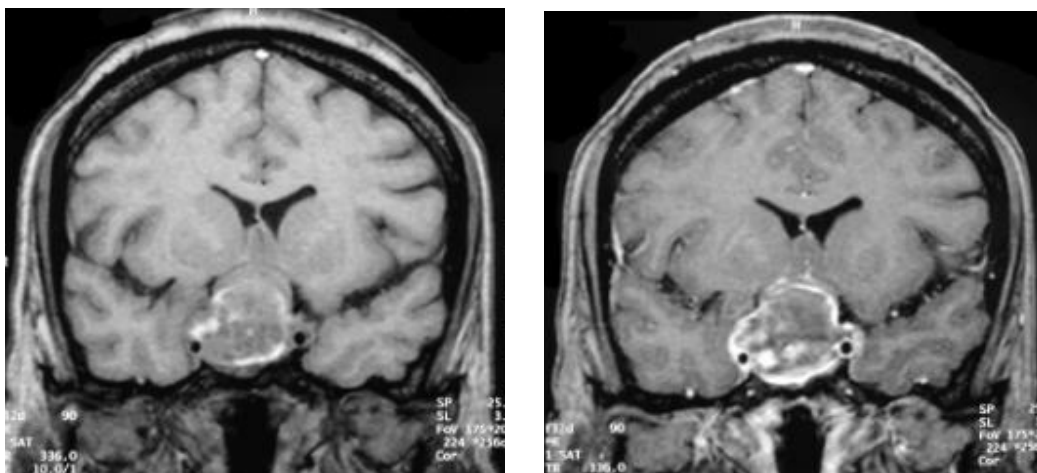


Figure 4.2: Coronal MRI T1 sequence without contrast (Left scan) and with contrast (Right scan). The high intensity signal on the uncontrasted scan suggests the presence of blood products. On the contrasted scan the low intensity signal may represent infarcted areas that are mixed with the blood products suggesting the picture of hemorrhagic infarction, which was confirmed on histopathological studies.

The MRI scans were reviewed separately from the histopathological reports in a blinded fashion. The results from the histological groups were then retrospectively compared with the MRI findings to see if accurate prediction of infarction alone or hemorrhage or hemorrhage infarction on the MRI scan was possible. In addition the histological groups were compared with regard to severity of presenting symptoms and outcome in this series of patients. Data were analyzed using Stata Version 10.0 (Stata Corporation, College Station, Texas, USA). Proportions were compared using Fisher's exact tests and odds ratios with 95% confidence intervals (CI). Continuous variables were described as means and medians, and compared with Wilcoxon rank-sum tests. All statistical tests are two-sided at  $\alpha = 0.05$ .

### **4.3 Results**

The mean age of the patients was 52.8 years with a range from 19 to 82 years, and there were 20 men and 16 women. The average length of time from onset of symptoms until presentation at the department of Neurosurgery, University of Virginia, or the referring physician was 14.8 days with a range of 1 day to more than 90 days. Four patients had a previous history of pituitary adenoma: two patients had been treated conservatively, one had Nelson's syndrome, and one had previous surgery for a pituitary adenoma.

The histopathological findings were in keeping with a pituitary adenoma, which had undergone apoplexy in 35 patients, and in 1 patient there had been a hemorrhage into a Rathke's cleft cyst. For the purposes of this study the histopathological findings were divided into two groups. The first group included patients in whom only infarction could be identified on histopathological examination (ghost cells) with no evidence of hemorrhage. The second group consisted of patients in whom the histopathological sections showed hemorrhagic infarction or hemorrhage alone. The routine practice is to send the entire removed apoplectic tumor for histology examination, and in this way we try to prevent small specimens only representing part of the tumor from being incorrectly classified.

#### **4.3.1 MRI vs. histopathology and intra-operative findings**

Thirty-six patients had MRI scans that could be compared to the histopathology. Fifteen patients had MRI features consistent with hemorrhagic infarction or

hemorrhage alone; in 17 patients only infarction of the pituitary tumor was evident and in 4 patients only a pituitary tumor was demonstrated with no imaging evidence of hemorrhage or infarction.

The MRI diagnosis of hemorrhagic infarction or hemorrhage alone was then compared to the surgeon's observations intra-operatively. In 14 of the patients the intra-operative observations of the surgeon were hemorrhagic infarction or hemorrhage; in only one case did the surgeon think that infarction alone was present. Therefore the MRI findings of hemorrhagic infarction or hemorrhage correlated in 14 out of 15 patients (93%) with surgical observations (95% CI: 68-99%). When the MRI diagnosis of hemorrhagic infarction or hemorrhage was compared with the histopathological slides, 13 patients had the typical findings of hemorrhagic infarction or hemorrhage and only 2 of those had infarction alone: the MRI scan findings correlated in 13 of 15 patients (86%) with the histopathology (95% CI: 60-98%) (Figure 4.3).

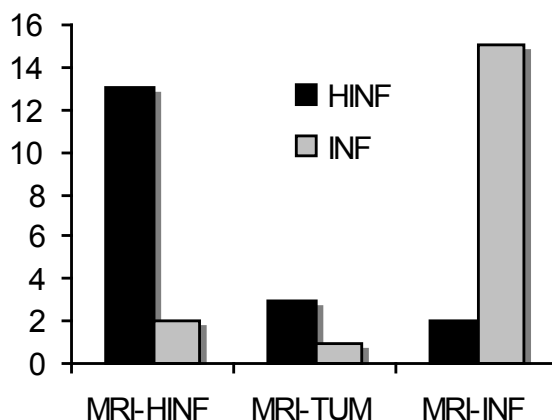


Figure 4.3: MRI scan vs. histopathology. HINF = hemorrhagic infarction or hemorrhage on histopathology, INF = infarction alone on histopathology. MRI-HNF = hemorrhagic infarction or hemorrhage on MRI scan, MRI-TUM = tumor alone on MRI scan, MRI-INF = infarction alone on MRI scan

The MRI scan diagnosis of infarction, when compared to the surgeon's intra-operative observations was accurate in 16 patients (94%) (95% CI: 71-100%), matched the histopathology in 15 of 17 patients (88%) (95% CI: 64-99%), and were found to be hemorrhagic infarction or hemorrhage in only 2 (11%). There were 4 patients with the diagnosis of a pituitary tumor alone on MRI scan. In two patients the surgeon thought the findings were consistent with infarction and in 2 hemorrhagic infarction or hemorrhage, while the histopathology in 3 patients demonstrated hemorrhagic infarction or hemorrhage, and in 1 infarction alone.

In the 19 patients where the actual MRI scans and reports were reviewed, it was felt that sphenoid sinus mucosal thickening was definitely present in 13 patients (68%).

There was possible subtle mucosal thickening in 4 patients and no mucosal thickening in two.

### 4.3.2. Histopathology vs. MRI

The histopathological studies on the 36 patients demonstrated infarction-alone with no evidence of hemorrhage in 17 patients and hemorrhagic infarction or hemorrhage alone in 19 (hemorrhagic infarction was present in 17 patients and hemorrhage alone in 2). The histopathological diagnosis was then compared to the MRI scan findings (Figure 4.4).

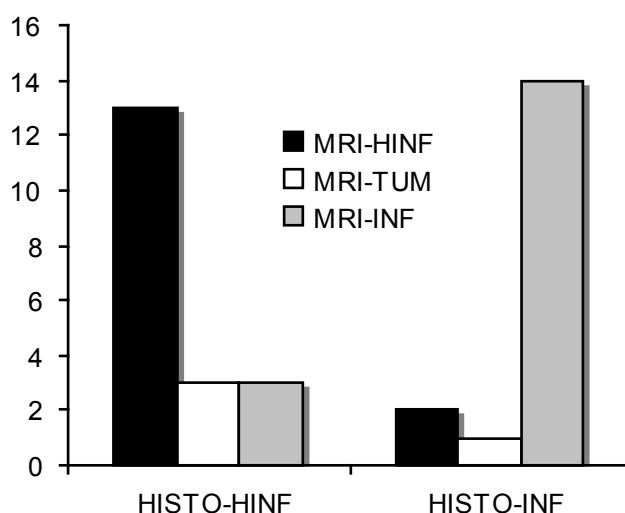


Figure 4.4: Histopathology vs. MRI scan. HISTO-INF = infarction alone on histopathology, HISTO-HINF = hemorrhagic infarction or hemorrhage on histopathology, MRI-HINF = hemorrhagic infarction on MRI scan, MRI-TUM = tumor alone on MRI scan, MRI-INF = infarction alone on MRI scan.

The nineteen patients who were in the histopathological grouping of hemorrhagic infarction or hemorrhage were diagnosed on MRI scan to have demonstrated

hemorrhagic infarction or hemorrhage in 13 patients (68%), pituitary tumor in 3 (16%), and infarction alone in 3 (16%). Therefore in 68% of cases the histopathology correlated with what had been demonstrated on MRI scan (95% CI: 43-87%).

Of the 17 patients with a histopathological diagnosis of infarction alone, 14 (82%) were thought to only have evidence of infarction on MRI scan, two (12%) hemorrhagic infarction or hemorrhage and one (6%) a pituitary tumor only. Therefore the histopathological correlated with the MRI scan findings when viewed retrospectively in 82% of patients (95% CI: 57-96%).

#### **4.3.3. Histopathology vs. clinical presentation**

The seventeen patients in whom the histopathology was infarction alone presented with headache in 14 cases, visual impairment in 8 - although none were blind and all had functional vision – and diplopia in 2 patients. One patient presented with a history of a diminished level of consciousness, and 1 had Cushing's disease. The nineteen patients with hemorrhagic infarction or hemorrhage alone presented with headaches in 17, diminished vision in 7 (including 2 with blindness), two with diplopia, and 2 with a diminished level of consciousness.

The mean duration of symptoms was 12.4 days for the infarction group, and 15.4 days for the patients who had hemorrhage or hemorrhagic infarction. However, these mean values may be misleading, as in the case of the patient with Cushing's disease who was found to have infarction of a pituitary macroadenoma, had mild symptoms of visual impairment for a year with no abrupt headache or visual change suggestive of

an ictus, and therefore was not included in determining the mean value. In addition, a patient who was found to have hemorrhagic infarction on histology of a pituitary macroadenoma, had headaches for three months with no other symptoms.

The time from the ictus to presentation was also divided into the first week following the ictus, the second week after the ictus, and more than 2 weeks following the ictus. In the first week following the ictus, nine patients in the infarction group, and 15 patients in the hemorrhage or hemorrhagic infarction group presented to hospital. From day 8 to day 14 post-ictus, four patients in the infarction group and only 1 in the hemorrhage or hemorrhagic infarction group presented. Four patients in the infarction group, and 3 in the hemorrhage or hemorrhagic infarction group presented later than 2 weeks following the ictus (Figure 4.5.). Therefore, 53% of patients in the infarction group presented within a week, compared to 79% of patients with hemorrhage or hemorrhagic infarction. Patients with infarction were 30% as likely to present in less than 1 week compared to those with hemorrhage or hemorrhagic infarction, but the difference is not statistically significant ( $p = 0.150$ )

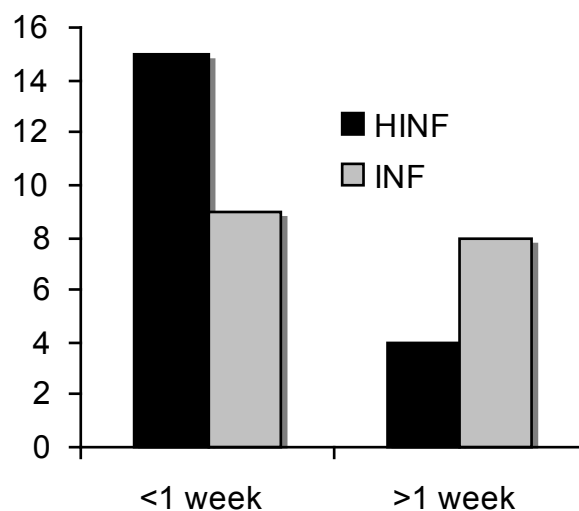


Figure 4.5: Histopathology vs. time to presentation following ictus. HINF = hemorrhage or hemorrhagic infarction on histopathology, INF = infarction on histopathology.

The clinical findings of both the patients with infarction only on histopathology and those with hemorrhage or hemorrhagic infarction are shown on Table 4.1. Only one of 17 patients (6%) in the infarction group had a diminished level of consciousness at presentation, but 6 (32%) in the hemorrhage or hemorrhagic infarction group did ( $p = 0.092$ ). The visual findings are similar in both groups, except that 3 patients in the hemorrhage or hemorrhagic infarction group were blind, compared to none in the patients with infarction only. There was not a significant difference in visual findings between the two groups. Individuals with hemorrhage or hemorrhagic infarction were significantly more likely to have ophthalmoplegia than those with infarction alone ( $p = 0.010$ ). Therefore although the clinical findings were not markedly different between the two groups, there appeared to be a slight increase in severe neurological deficits,

namely diminished level of consciousness and blindness in those patients with hemorrhagic infarction or hemorrhage on histopathology.

**Table 4.1: The histopathology related to the clinical presentation.**

Histology	GCS		Vision				Ophthalmoplegia	
	15	<15	N	F	NF	B	Absent	Present
<b>Infarction (Total 17)</b>	16	1	9	6	2	0	13	4
<b>Hemorrhagic Infarction (Total 19)</b>	13	6	9	6	1	3	6	13

GCS = Glasgow Coma Scale, N = normal, F = functional, NF = non functional, B = blind.

#### **4.3.4. Histopathology vs. outcome**

The mean length of follow-up was 29.4 months with a range from 1 week to 7 years. The outcome of these patients was divided into normal with no neurological deficits; minor deficit with very mild neurological impairment but easily able to function independently; major neurological deficit where the patient was not able to function independently; and dead. Eleven of the patients in the infarction group had a normal neurological outcome, five had minor deficits, and one a major deficit. Therefore 16 of the patients (94%) in this group had a good outcome. In the hemorrhage or hemorrhagic infarction group, 13 patients had a normal outcome, 3 had minor deficits, and 3 had major deficit. Eighty-four percent of the patients in the hemorrhage or

hemorrhagic infarction group therefore had a good outcome. There were no deaths in either group (Table 4.2). However, there was not a statistically significant difference between those patients with hemorrhage or hemorrhagic infarction and those with infarction alone ( $p=0.608$ ).

The visual outcome at follow-up in the infarction group was normal in 14 patients (82%), and there were improved minor visual deficits with functional vision in 3 (18%). No patients were blind. In the hemorrhage or hemorrhagic infarction group of patients vision at follow-up was normal in 12 (63%), improved with functional vision in four (21%), and blind in 2 (11%). One patient was lost to follow-up early and was not re-assessed. The difference in visual outcome did not reach statistical significance. Fourteen of the patients in the infarction group had no ophthalmoplegia at follow-up, and 3 still had residual deficits although they were improved. In the hemorrhage or hemorrhagic infarction group of patients 13 had no ophthalmoplegia at follow-up, five were improved, and 1 patient was lost to follow-up and could not be assessed. Fourteen patients required replacement therapy in the infarction group, 16 in the hemorrhage or hemorrhagic infarction group of patients.

**Table 4.2: Histopathology compared to the outcome.**

		<b>INF</b>	<b>HINF</b>
<b>OUTCOME</b>	<b>Normal</b>	<b>11</b>	<b>13</b>
	<b>Minor deficit</b>	<b>5</b>	<b>3</b>
	<b>Major deficit</b>	<b>1</b>	<b>3</b>
	<b>Dead</b>	<b>0</b>	<b>0</b>
<b>VISION</b>	<b>Normal</b>	<b>14</b>	<b>12</b>
	<b>Improved</b>	<b>3</b>	<b>4</b>
	<b>Unchanged</b>	<b>0</b>	<b>0</b>
	<b>Blind</b>	<b>0</b>	<b>2</b>
	<b>NA</b>	<b>0</b>	<b>1</b>
<b>OPHTHALM- OPLEGIA</b>	<b>Normal</b>	<b>14</b>	<b>13</b>
	<b>Improved</b>	<b>3</b>	<b>5</b>
	<b>Unchanged</b>	<b>0</b>	<b>0</b>
	<b>NA</b>	<b>0</b>	<b>1</b>

HINF = hemorrhagic infarction / hemorrhage, INF = infarction alone.

#### **4.4 Discussion**

In Chapter 3 a series of 59 patients with pituitary apoplexy was divided on histopathological examination into two groups, namely infarction alone, or hemorrhage or hemorrhagic infarction, and the clinical presentation and outcome of these two groups of patients was described. The patients who presented with histological features of tumor infarction alone were found to have less severe clinical features on presentation, a longer history prior to presentation, and a better outcome

than those patients found to have hemorrhage or hemorrhagic infarction of the pituitary tumor.

In the current series the histopathology studies were divided in a similar manner, and were compared to the MRI scans to ascertain if it is possible to correlate the imaging findings with the histopathological studies.

MRI is more effective than CT scan in identifying the imaging features of pituitary apoplexy and is the investigation of choice [Bills et al 1993, Chanson et al 2004, Dubuisson et al 2006, Kyle et al 1990, Ostrov et al 1989, Randeva et al 1999]. Bills et al [1993] described the positive identification of a pituitary tumor in 94% of patients with pituitary apoplexy, but radiological features of hemorrhage or infarction were only noted in 46% on CT scan. CT scan cannot differentiate cystic or degenerative changes from old hemorrhage whereas MRI can [Ostrov et al 1984]. This is due to the increasing density of blood on CT scan as the blood degenerates making it impossible to differentiate radiologically subacute or chronic hemorrhage from other causes of low intensity signal such as degenerative changes or abscess. Similarly the low signal intensity with possible rim enhancement in a patient who has undergone infarctive pituitary apoplexy cannot be differentiated from degenerative changes, cysts, or even pituitary adenomas that have not undergone apoplexy that occasionally have rim enhancement [Post et al 1980]. In their series on pituitary apoplexy, Randeva et al [1999], found that CT scan revealed a pituitary tumor in 93%, and pituitary hemorrhage in 21%, whereas MRI identified pituitary tumor in 100% and hemorrhage in 88%. CT scan definitely is of benefit when there is no MRI scan available, but MRI

is far superior and should be the investigation of choice when possible. For this reason the two patients who only had CT scan in this series were excluded from the study.

Pituitary apoplexy may present with different MRI features including hemorrhagic and non-hemorrhagic changes [Piotin et al 1999]. In hemorrhagic pituitary apoplexy in the acute phase (day 1-2) the appearance of hemorrhage is typically hyperintense on T1 images and hypointense on T2 images [Bonneville et al 2006, Lavalley et al 1995, Riedl et al 2000, Tosaka et al 2007). The gadolinium enhanced images ordinarily do not provide additional information with regard to hemorrhage in the presence of blood, although when there is mixed hemorrhage and infarction there can be areas that are of low intensity that do not enhance [Piotin et al 1999, Riedl et al 2000]. Signal intensity changes occur in sub-acute hemorrhage (day 3-15) due to the degradation of hemoglobin into methemoglobin, and the signal should appear bright on both T1 and T2 sequences [Glick & Tiesi 1990, Kyle et al 1990, Lavalley et al 1995, Piotin et al 1999]. In the chronic phase (more than 15 days) the sedimentation of blood products may create a fluid level within the mass, a feature that is highly suggestive of hemorrhagic pituitary apoplexy [Bonneville et al 2006, Piotin et al 1999]. In the case of apoplexy the evaluation of enhanced T1 images alone may be misleading because T1 weighted hyperintense blood products may be mistaken for contrast enhanced tumor [Riedl et al 2006]. Kurihara et al [1998] in a series of 15 patients with hemorrhagic pituitary adenomas, found that the pre-operative finding of hemorrhage on the MRI sequences correlated well with their operative findings. Lazaro et al [1994] described 5 patients in whom pre-operative MRI showed evidence of intratumoral pituitary tumor hemorrhage, and in whom all 5 had operative verification of that hemorrhage.

Infarctive pituitary apoplexy alone has been described as low intensity on T1 and T2 sequences with no contrast enhancement of the tumor, but with associated rim enhancement [Rogg et al 2002]. This appearance in the acute phase does not change in the subacute or chronic phase. Peripheral enhancement is not specific for infarctive pituitary apoplexy, and can also be seen in cystic pituitary adenomas and craniopharyngiomas. Diffusion weighted imaging may be useful in the diagnosis of infarctive pituitary apoplexy because it shows high signal intensity from restricted diffusion from infarction and can help to differentiate it from cystic macroadenomas and craniopharyngiomas [Bonneville et al 2006].

In our series the imaging findings on the pre-operative MRI were correlated with the findings at surgery. In the 15 patients who exhibited features of hemorrhagic infarction on MRI, fourteen were found to have evidence of hemorrhage at surgery (93%). The seventeen patients who were thought to have infarction alone on MRI matched the findings at surgery in 94%. The four patients in whom the MRI showed only tumor were found to have infarction alone in 2 cases and hemorrhagic infarction in two. Therefore, the correlation between our diagnosis on MRI and surgical findings were accurate in the majority of cases. The pre-operative MRI when compared to the histopathological examination was accurate in 87% of patients with hemorrhage or hemorrhagic infarction, and in 88% of patients where infarction alone was diagnosed on the pre-operative MRI. The pre-operative MRI therefore, is able to discriminate the infarction only and hemorrhage or hemorrhagic infarction groups of patients as determined at surgery and on histopathological examination in the majority of

patients. Although this sample size was relatively small, the precision around the estimates (as reflected by 95% CI) are reasonably precise.

When we compared the histopathological diagnosis with pre-operative MRI findings the histopathology correlated with the MRI in 68% of patients with histopathological diagnosis of hemorrhage or hemorrhagic infarction, and in 82% of patients with infarction alone. The histopathological diagnosis could, therefore, be equated with the MRI findings in the majority of cases, although the findings were less accurate in hemorrhage or hemorrhagic infarction group. This is probably because the hemorrhage or hemorrhagic infarction group of patients had a more variable picture in that the appearance changed with time; therefore the likelihood of MRI findings being inaccurate was higher.

Sphenoid sinus mucosal thickening described as a feature of pituitary apoplexy on MRI is thought to be a result of venous engorgement [Bonneville et al 2006]. Arita et al [2001] evaluated the MRI scans of 11 patients with a diagnosis of pituitary apoplexy in whom the MRI was done within 7 days of the ictus. In nine of these patients the sphenoid sinus mucosa was markedly thickened. In the four patients in this group who did not undergo surgery the mucosal thickening regressed spontaneously. In addition three patients who were imaged more than three months following their ictus had no mucosal thickening. Therefore it would appear that sphenoid sinus mucosal thickening is an acute manifestation of pituitary apoplexy that spontaneously resolves. In our series in 13 of the 19 patients (68%) in whom the MRI films could be studied for mucosal thickening, it was found to be present. Liu and Couldwell [2006] recently published their series on mucosal sinus thickening in

patients with pituitary apoplexy and found that it correlated with higher grades of pituitary apoplexy and poorer and neurological and endocrine outcomes.

De Villiers and Marus [1988], and Chacko et al [2002] both described a group of patients in whom necrotic material only was found at surgery. De Villiers ascribed this to infarction of the pituitary tumor whereas Chacko thought it was essentially part of the resorption process of pituitary apoplexy.

In the previous chapter (Chapter 3) the series of patients with pituitary apoplexy were divided on a histopathological basis into those that demonstrated infarction only and those with hemorrhage or hemorrhagic infarction (earlier series: 1970-2003). The patients with infarction only on histopathological examination tended to have a longer presentation history, less severe clinical signs, and a better outcome than those in whom hemorrhage or hemorrhagic infarction was demonstrated. The results from the earlier series of patients in Chapter 3 have now been compared to the current series of patients (current series: 1996-2006).

The time from the ictus to presentation in the earlier series of patients was almost double for the infarctive group of patients compared to those with hemorrhage or hemorrhagic infarction; however, in the current series there was no major difference in the mean calculated time. If, however, the patients were grouped into early (in the first week), and late (later than the first week), fifteen (79%) of the patients with hemorrhage or hemorrhagic infarction presented early and nine (53%) of the patients with infarction only presented early. Therefore, there is still a tendency for patients with hemorrhage or hemorrhagic infarction to present earlier than those with

infarction alone. In the current series of patients the differences in the severity of the clinical features in the two different histopathological groupings of patients was not as marked as in the earlier series, and do not reach statistical significance. However as the sample size is small in statistical terms there is a limitation in interpreting statistical significance (i.e. p values may not be definitive due to small sample size). However, the more severe clinical deficits, namely diminished level of consciousness, and blindness were more prevalent in the hemorrhage or hemorrhagic infarction group of patients. One out of 17 (6%) of the patients in the infarction group had a diminished level of consciousness compared to six out of 19 (32%) in the hemorrhage or hemorrhagic infarction group. In the earlier series 6% of the infarction group, and 22% of the hemorrhage or hemorrhagic infarction group had a diminished level of consciousness. In the current series no patients were blind in the infarction group, but three (16%) were blind in the hemorrhage or hemorrhagic infarction group. This is essentially identical to the earlier series, and, there was little difference when comparing the milder visual deficits (Table 4.3)

**Table 4.3: Clinical comparison**

	<b>Histo</b>	<b>1970-2003</b>	<b>1996-2006</b>
<b>Presentation time &lt; 1 week</b>	INF	48%	54%
	HINF	74%	79%
<b>GCS &lt;15</b>	INF	5%	6%
	HINF	23%	32%
<b>Vision normal or minimal deficit</b>	INF	100%	88%
	HINF	67%	78%
<b>Blind</b>	INF	0%	0%
	HINF	16%	15%
<b>Ophthalmoplegia</b>	INF	27%	23%
	HINF	48%	31%

Histo = histopathology, INF = infarction alone on histopathology examination, HINF = hemorrhage or hemorrhagic infarction on histopathological examination, GCS = Glasgow Coma Score

When comparing outcomes the infarction group of patients had good outcomes in 94% in the current series and 95% in the earlier series. However a much greater number of patients in the hemorrhage or hemorrhagic infarction group had a good outcome in the current series (84%) than in the earlier series (63%). Although the outcome is still not as good in the patients with infarction only, the difference is less marked. There were also no deaths in the current series, whereas there was 8% mortality in the hemorrhage or hemorrhagic infarction group in the earlier series. When visual function was compared, the outcome in the infarctive group in the current series was similar to the earlier series in that all the patients had a good outcome with normal vision or minor deficits. When comparing the group of patients

with hemorrhage or hemorrhagic infarction, there was an improvement from 73% to 84% in functional vision between the earlier series and the current series. Nevertheless, 11% of patients in the current series in the hemorrhage or hemorrhagic infarction group remained blind. The endocrine replacement requirements remains unchanged between the different histopathological groups and series (Table 4.4.).

**Table 4.4: Comparison in outcome**

	<b>Histo</b>	<b>1970-2003</b>	<b>1996-2006</b>
<b>Good outcome</b>	INF	95%	94%
	HINF	76%	84%
<b>Vision normal / minimal deficit</b>	INF	95%	100%
	HINF	69%	84%
<b>Blind</b>	INF	0%	0%
	HINF	19%	11%
<b>Ophthalmoplegia residual</b>	INF	14%	18%
	HINF	40%	28%
<b>Replacement therapy</b>	INF	82%	82%
	HINF	87%	84%

Histo = histopathology, INF = infarction on histopathology, HINF = hemorrhage or hemorrhagic infarction on histopathology

When the presentation, clinical features, and outcome of the current series are compared to the earlier series the infarction group of patients are very similar. The hemorrhage or hemorrhagic infarction group of patients, although still having a higher proportion of severe deficits and poor outcome than the infarction group have shown an improvement between the earlier and current series. Hemorrhage or hemorrhagic

infarction pituitary apoplexy is a more severe illness than pure infarctive apoplexy, and has a higher proportion of severe neurological deficits with a poorer outcome. The earlier series covers a thirty-year period, and during that time the clinical diagnosis, awareness of the disease, diagnostic modalities, surgical techniques and medical therapies have steadily improved. This is reflected in the improved outcome of those patients with hemorrhagic infarction or hemorrhage in the more recent current series.

#### **4.5 Conclusion**

The features of infarction alone, or hemorrhage or hemorrhagic infarction on the histopathological examination correlate well with the operative findings, and the histopathological features can be accurately predicted from the MRI scan. There is a correlation between the histopathological groups regarding clinical presentation and outcome, with patients in the infarction group having a less severe presentation, normally a longer interval between ictus and presentation, and better outcome. The outcome of the hemorrhage or hemorrhagic infarction group has also improved as a result of modern imaging and improved surgical management. MRI is able to predict the histopathological diagnosis and consequently may help in improving the outcome in these patients.

## **CHAPTER 5**

### **CLINICAL RELEVANCE OF PRECIPITATING FACTORS IN PITUITARY APOPLEXY**

#### **5.1. Introduction**

An increasing number of precipitating factors in pituitary apoplexy have been published, usually in the form of case reports or small series. These associated conditions have been linked to the apoplectic event and a variety of theories have been postulated [Biousse et al 2001]. In the majority of patients, there is no known pituitary adenoma, consequently the diagnosis is frequently difficult and may be delayed, which can result in a poor outcome for these patients. A contemporary series of patients with pituitary apoplexy treated by the Department of Neurosurgery at the university of Virginia, in whom precipitating factors were identified, is reviewed in Chapter Five.

#### **5.2. Clinical material and methods**

The records of 38 patients who underwent surgery for pituitary apoplexy between January 1996 and March 2006 were retrospectively reviewed. The patients' clinical features and radiological imaging were all consistent with pituitary apoplexy. All of the patients in this series had histological confirmation of pituitary apoplexy from

tissue obtained at surgery. Patients were assessed as having no precipitating factor if they were in their usual state of health when the apoplectic event occurred and no inciting agent or prodrome was identified. The presenting history, clinical findings, including visual function and ophthalmoplegia, endocrine status, and outcome of the patients with precipitating factors was analyzed and compared with the patients in whom no precipitating factor could be identified. Data were analyzed using Stata Version 10.0 (Stata Corporation, College Station, Texas, USA). Proportions were compared using Fisher's exact tests and odds ratios with 95% confidence intervals (CI). Continuous variables were described as means and medians, and compared with Wilcoxon rank-sum tests. All statistical tests are two-sided at  $\alpha = 0.05$ . The published cases of presumed precipitating factors in pituitary apoplexy are also reviewed.

### **5.3. Results**

Nine patients were identified as having precipitating factors for pituitary apoplexy. Twenty-nine patients had no precipitating factor identified. The predisposing factors that were identified in this series of patients were coronary artery surgery in two patients; hip replacement surgery, surgery for a benign testicular tumor, post-partum status in two patients, liver failure with associated disseminated intravascular coagulopathy, anticoagulant therapy, and subsequent to gamma knife surgery in a patient with Nelson's syndrome (Table 5.1). A pituitary adenoma was identified in eight patients and a hemorrhagic Rathke's cleft cyst in one patient who had a post-partum apoplexy.

**Table 5.1. The 9 patients in a contemporary series of 38 patients with pituitary apoplexy in whom a predisposing factor was identified.**

<b>Patient no.</b>	<b>Predisposing factor</b>	<b>Age</b>	<b>Sex</b>	<b>Past pituitary history</b>	<b>Duration (days)</b>
1	Coronary artery surgery	69	F	-	1
2	Hip surgery	72	M	Untreated pituitary tumor	62
3	Liver failure / DIC	47	F	-	1
4	Coronary artery surgery	65	M	-	65
5	Pregnancy (post-partum)	19	F	-	2
6	Anticoagulation	60	M	-	1
7	Gamma-knife	28	F	Nelson's syndrome	1
8	Surgery (orchidectomy)	52	M	Untreated pituitary tumor	1
9	Pregnancy (post-partum)	30	F	-	30

DIC = Disseminated Intravascular Coagulopathy.

The mean age in patients with a predisposing factor was 48 years; in those without a predisposing factor, the mean age was 52.3 years. The ratio of women to men in the group with a predisposing factor was 5:4; in the group with no predisposing factor, the ratio was 11:18. Three patients (35%) with a predisposing factor had a known pituitary tumor (two pituitary macroadenomas that had been treated conservatively and a Nelson's syndrome tumor), but only one (3.4%) patient had a known tumor in the group with no predisposing factor. Six of the nine (67%) patients with a predisposing factor presented with a very short apoplectic history of less than 1 day. All of the patients who had apoplexy after surgery presented immediately post-operatively, and the patient who underwent gamma knife surgery presented within 12 hours of undergoing treatment. The duration of symptoms before presentation to the neurosurgical department was more variable in those patients without any predisposing factor; eight patients (28%) presented within 1 day of their ictus, nine

(31%) others presented within 1 week, and 12 (41%) presented after more than 1 week.

The clinical presentation of the two groups was compared. There was no difference between the clinical presenting features of patients who did and did not have a precipitating factor. In the group of patients who had a precipitating factor, a larger proportion had an impaired level of consciousness at presentation than in the group without any precipitating factor. Three (33%) patients in the group with a precipitating factor had an impaired level of consciousness at the time of presentation compared with four (14%) in the group with no precipitating factor ( $p = 0.323$ ). Visual function was normal in four patients (45%) in the group with a precipitating factor and in 15 (52%) in the group with no precipitating factor ( $p = 0.999$ ). However, two of the nine patients (22%) in the group with a precipitating factor were blind at presentation compared with only one (3%) in patients in whom no precipitating factor was identified ( $p = 0.134$ ). Ophthalmoplegia was present in three (33%) patients in the precipitating factor group and seven (24%) in the no precipitating factor group ( $p = 0.673$ ). All the patients in whom a precipitating factor was present were found to have hypopituitarism, whereas hypopituitarism was present in 24 (83%) of those patients who had no precipitating factor (Table 5.2.)

**Table 5.2. Comparison of clinical presentation and histopathological studies between patients with a predisposing factor and those without in a series of 38 patients.**

	<b>PRECIPITATING FACTOR (%) (9 Patients)</b>	<b>NO PRECIPITATING FACTOR (%) (29 Patients)</b>
<b>GCS&lt;14</b>	33	14
<b>VISION</b>		
<b>-Normal</b>	45	52
<b>-Functional</b>	33	34
<b>-Non-functional</b>	0	10
<b>-Blind</b>	22	3
<b>OPHTHALMOPLEGIA</b>	33	24
<b>HYPOPITUITARY</b>	100	83
<b>HISTOLOGY</b>		
<b>-Infarction</b>	11	62
<b>-Hemorrhagic infarction &amp; Hemorrhage</b>	89	38

The histopathological reports of the two groups of patients were compared. The group of patients with a precipitating factor were found to have hemorrhagic infarction in six cases (67%), hemorrhage alone in two (22%), and infarction alone in only one patient (11%). The single patient in whom infarction alone was seen had undergone gamma knife radiosurgery for Nelson's syndrome. In the patients in whom there was no precipitating factor identified, the histopathological study showed infarction in the majority of patients, 18 (62%). Hemorrhagic infarction was present in the remaining

11 patients (38%) (Table 5.2.). Patients who had hemorrhage or hemorrhagic infarction were 13.1 times more likely to have precipitating factors compared to those with infarction alone (Odds Ratio = 13.1,  $p = 0.019$ , 95% CI: 1.35-612.2).

Eight of the nine patients with a precipitating factor were followed-up. One patient discharged herself after surgery; thus, no follow-up data was available for that patient. The mean length of follow-up period was 25 months. Four (50%) of the patients were normal at the time of follow-up evaluation, three had a minor visual deficit, and one (12.5%) had a major neurological deficit (blindness). The visual function of these patients at the time of follow-up evaluation was normal in six (75%), not normal but functional in one (12.5%), and one patient remained blind (12.5%). Three patients (37.5%) had residual ophthalmoplegia / paresis at the time of follow-up evaluation. The twenty-nine patients in whom no precipitating factor was identified were followed for a mean of 32 months. Nineteen (66%) of these patients were normal at the time of the follow-up evaluation with no deficits, seven (24%) had a minor neurological deficit, and 3 (10%) had major neurological deficits. When their visual outcome was assessed, 22 (76%) had normal visual function, visual function was improved but not normal in six (21%) patients, and one (3%) patient remained blind. Six patients (21%) had residual ophthalmoplegia / paresis. All of the patients in the group with a precipitating factor who had follow-up remained hypopituitary requiring hormone replacement therapy, whereas 24 (83%) of the patients with no precipitating factor required replacement therapy. The presence or absence of a precipitating factor was not significantly associated with outcome ( $p = 0.725$ ), visual function ( $p = 0.580$ ), or residual ophthalmoplegia ( $p = 0.327$ ).

## 5.4. Discussion

Although the pathogenesis of pituitary apoplexy is not well understood, there have been numerous precipitating factors proposed that might trigger pituitary apoplexy. These factors have been described as precipitating or associated factors [Biousse et al 2001]. Associated factors suggest that they are not necessarily direct causes, but that their presence may make the tumor more susceptible to the development of pituitary apoplexy. Precipitating factors, however, suggest that these factors directly trigger the pathogenesis of apoplexy in pituitary tumors.

The majority of reported cases of precipitating factors for pituitary apoplexy are in the form of case reports, which makes it difficult to determine the proportion of patients with pituitary apoplexy who may have a precipitating factor. There is a lack of uniform agreement regarding what constitutes a precipitating factor. In addition, we cannot always be certain that there is no precipitating factor present simply because it may not have been recognized. In the current series, nine out of thirty-eight patients (24%) had a precipitating factor identified. The majority of patients who present with pituitary apoplexy do not have a precipitating factor, and there is a wide variation of incidence of reported precipitating factors ranging from 4% to 30% [Cardoso & Petersen 1984, Randeva et al 1999].

Biousse et al [2001] divide the precipitating factors into four categories: 1) those associated with reduced blood flow, 2) acute increase in blood flow, 3) stimulation of the pituitary gland, and 4) the anticoagulated state. The published case reports and

series in the English literature from 1990 to 2006 were reviewed, and 97 patients were found in whom a precipitating factor was reported. For the purposes of this discussion they were divided into stimulation of the pituitary gland (32 patients), surgery (40 patients), anticoagulant therapy (13 patients), head injury (3 patients), and other miscellaneous causes (eight patients) (Figure 5.1)

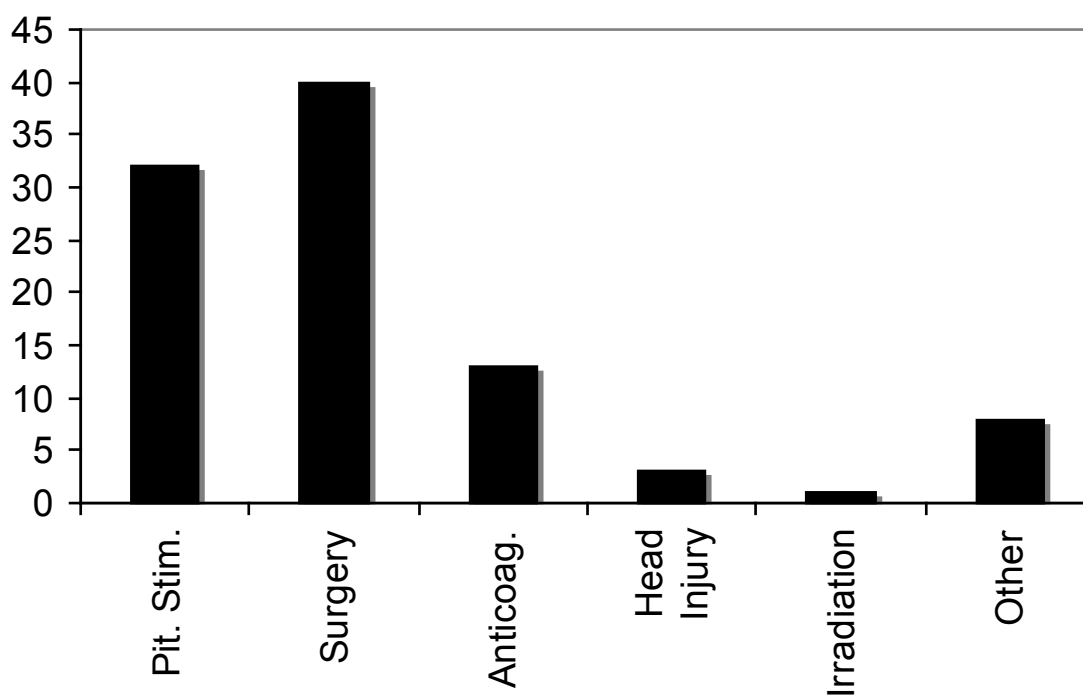


Figure 5.1. Bar graph showing the precipitating factors in pituitary apoplexy published in the English-language literature between 1990 and 2006. Pit. Stim. = stimulation of the pituitary tumor / gland, Anticoag. = anticoagulant therapy.

Stimulation of the pituitary gland or tumor may be the result of pregnancy, pituitary stimulation testing, treatment of prolactinomas with cabergoline or bromocriptine, or pituitary stimulation secondary to treating other conditions with gonadotrophin-releasing hormone or clomiphene. In the review, four patients were reported to have

had apoplexy in late pregnancy, possibly related to increased pituitary stimulation resulting from increased estrogens [Biousse et al 2001, de Heinde et al 2004]. Two of the patients in the current series had apoplexy shortly after childbirth, one of them after a caesarian section. The rapid growth of pituitary tumors is well described during pregnancy. It is possible that the relative ischemia related to outgrowing the blood supply and increased pituitary stimulation may combine to precipitate apoplexy. Fifteen patients with a known pituitary tumors developed pituitary apoplexy after pituitary stimulation tests in the literature review. None of the patients in the current series had pituitary stimulation tests as a precipitating factor. Stimulatory tests that have been implicated include thyrotropin-releasing hormone, corticotrophin-releasing hormone, gonadotrophin-releasing hormone, insulin, and luteinizing hormone-releasing hormone [Chapman et al 1985, Dokmetas et al 1999, Galvin & Stavern 2004, Hiroi et al 2001, Lee et al 2000, Matsuura et al 2001, Otsuka et al 1998, Riedl et al 2000, Rotman-Pikielny et al 2003, Szaboics et al 1997, Vassello et al 1994]. It has been speculated that the stimulation tests may have a vaso-active effect that initially results in ischemia and infarction that later may evolve into hemorrhage [Matsuura et al 2001]. The use of cabergoline and bromocriptine in the treatment of prolactinomas have also been described as precipitating factors [Cardoso & Petersen 1984, Knoepfelmacher et al 2004]. The use of gonadotrophin-releasing hormone analogs or agonists in patients for the treatment of prostate carcinoma and ovarian stimulation in patients who have an undiagnosed pituitary tumor can also result in pituitary apoplexy [Davis et al 2006, Engel et al 2003, Morsi et al 1996, Reznik et al 1997]. The treatment of infertility with clomiphene stimulation has also been implicated [Walker et al 1996].

Forty patients in whom surgery was implicated as a precipitating factor were found in the literature review. Twenty-two of these cases involved cardiac surgery, six pituitary surgeries for large tumors, 11 other surgical procedures, and one spinal anesthetic. In the current series, two patients developed apoplexy immediately after cardiac surgery, one after hip surgery, and one after orchidectomy for a testicular mass. Factors that may predispose patients with a pituitary tumor to apoplexy who undergo surgery include hypotension and fluctuations in blood pressure, transient increases in intracranial pressure, thrombotic events, dilution of blood from the use of crystalloids, and revascularization surgery [Abbott & Kirby 2004, Biousse et al 2001, Cardoso & Petersen 1984, Cohen et al 1997, Cummings et al 1997, Khandelwai et al 2005, Liberale et al 2006, Liu et al 2001, Mattke et al 2002, Peck et al 1980, Pliam et al 1995, Randeve et al 1999]. Patients undergoing cardiac surgery seem to be at higher risk than patients undergoing other types of surgery. This may be the result of the frequent use of anticoagulant therapy, cardiac bypass, and more severe hypotension in this type of surgery [Abbott & Kirby 2004, Alzetani et al 2002, Bhattacharyya et al 1999, Cummings et al 1997, Pliam et al 1995, Wiessman et al 1999]. Pituitary apoplexy has been reported in patients who have very large pituitary tumors and have undergone partial resection. This surgery may compromise the blood supply to the remaining tumor resulting in apoplexy, associated with a high mortality rate [Ahmad et al 2005, Lee & Reilly 2001]. Abdominal aneurysm surgery, hip and knee joint replacement surgery, spinal surgery, abdominal surgery, and large-volume liposuction have been associated with pituitary apoplexy [Acar & Mertol 2004, Cardoso & Petersen 1984, Cohen et al 2004, Galvin & Stavern 2004, Khandelwai et al 2005, Liberale et al 2006, Liu et al 2001, Mattke et al 2002]. Spinal anesthesia, on

the basis of lowering intracranial pressure and producing hypotension, has been implicated in precipitating pituitary apoplexy [Lennon et al 1998].

Thirteen patients in the literature review had anticoagulation or coagulopathy identified as a precipitating factor. In the current series, a woman with coagulopathy secondary to chronic liver disease had pituitary apoplexy. The use of an anticoagulant or thrombolytic agent for the treatment of acute myocardial infarction in a patient with an undiagnosed pituitary adenoma has been implicated as a precipitating factor in pituitary apoplexy [Fuchs et al 1998, Karotinsky et al 2002, Maiza et al 2004, Nagarajan et al 2002, Oo et al 1997, Skijarevski et al 2003, Tan et al 2007, Williamowicz & Houlden 1999]. Fluctuations of blood pressure and increased stress on the pituitary gland can also be precipitating factors in patients with myocardial infarction [Biousse et al 2001]. Anticoagulation with heparin for dialysis and idiopathic thrombocytopenia have also been implicated as precipitating factors [De la Torre et al 1998, Lenthal et al 2001, Maiza et al 2004].

Three cases of pituitary apoplexy after head injury were reported in the literature review. A possible mechanism postulated was that the intrasellar part of the tumor may be fixed to the bony structure of the sella. The suprasellar part is relatively free to move so that rotational forces will create a shearing strain between the intra- and suprasellar part of the tumor resulting in ischemic injury and apoplexy [Uchiyama et al 1999]. The raised intracranial pressure and episodes of hypotension that are often associated with a head injury can also be contributing factors. Carotid artery injury or vasospasm has also been associated with pituitary apoplexy [Itoyama et al 1990, Provenzale et al 1995].

In the current series a single patient who received gamma knife irradiation for Nelson's syndrome developed apoplexy within 12 hours; a similar case was published in the review of the literature. Two cases of pituitary apoplexy after coronary artery angiography and one after cerebral angiography have been described. The pathogenesis may relate to the use of heparin in coronary angiography and alterations in perfusion from blood pressure fluctuations [Louwerens et al 1996, Skijarevski et al 2003]. Other published reports of possible precipitating factors include gadolinium-enhanced MRI scans, subarachnoid hemorrhage, physical exertion, lymphocytic leukemia, metastatic endometrial carcinoma, and cellulitis [Biousse et al 2001, Proust et al 1995, Randeve et al 1999, Wichers et al 1997].

Biousse et al [2001] found that an altered level of consciousness was more common in patients with a precipitating factor compared to those without, but they were unable to explain this difference. The rest of the clinical presentation was similar in their two groups of patients. In the current series, there seems to be a somewhat more severe presentation in those patients with a precipitating factor. Thirty-three percent of patients in whom a precipitating factor was identified had a diminished level of consciousness compared with 14% in those without a precipitating factor. Blindness was present in 22% of patients on presentation with a known precipitating factor compared with 3% in those without, and a slightly lower percentage of those with a precipitating factor had normal vision. A higher proportion of patients in the precipitating factor group had ophthalmoplegia (33%) compared with those without (24%). No statistically significant difference was identified in the clinical features between those patients with and without a precipitating factor. However, the relatively

small sample size in statistical terms (although not in terms of pituitary apoplexy) limits the interpretation of statistical significance. Although most of the patients without a precipitating factor were hypopituitary (83%), all of those with a precipitating factor were found to be hypopituitary on endocrine testing.

The histopathological examinations of the tumors at the time of surgery showed differences between the two groups. Of importance is that the entire specimen is sent for histopathological examination so an incorrect diagnosis is minimized. Only one patient in the group of patients with a precipitating factor showed ischemic infarction alone. Eighty-three percent of patients had a picture of mixed hemorrhage and infarction or hemorrhage alone on histopathological examination. In the group of patients with no precipitating factor, the majority was found to have infarction alone (68%) on histopathological studies with a minority (38%) having a mixed picture of hemorrhagic infarction. Patients with hemorrhage or hemorrhagic infarction are 13.1 times more likely to have a precipitating factor compared to those with infarction alone. In Chapter 3 it was shown that patients who presented with histological features of infarction alone had less severe clinical features on presentation, a longer course before presentation, and a better outcome than those presenting with hemorrhagic infarction or frank hemorrhage. Therefore, logically it follows that a more severe clinical presentation and poorer outcome would be expected in patients in whom a precipitating factor is identified. The current series of patients was also analyzed for histopathological findings (Chapter 4) and a similar trend is shown except that the outcomes of those patients with hemorrhagic infarction or hemorrhage alone have improved compared to the earlier study, although they are still not as good as the infarctive group.

One of the major problems in pituitary apoplexy is that it most frequently occurs in a patient with an undiagnosed pituitary tumor and, therefore, the diagnosis may easily be missed or delayed. In patients who have a known pituitary tumor and are undergoing pituitary endocrine investigations, the diagnosis of pituitary apoplexy may be easier. In the majority of these patients, there is another primary illness, or surgery has been performed for another pathology, and the patient presents with neurological or visual impairment that is not obviously caused by the known pathology. In addition, pituitary apoplexy is not a common event, which may further delay the diagnosis or cause it to be missed altogether. Therefore, it is important when patients develop neurological / visual or endocrine disturbances after illnesses or surgery that cannot be explained by the primary diagnosis or complication, particularly when the diagnosis is known to be a precipitating factor of pituitary apoplexy, they should be evaluated promptly using MRI scans and endocrine assessment. This is particularly important because untreated apoplexy may result in death or major deficits.

The knowledge of precipitating factors that can result in apoplexy of a pituitary tumor may have some influence on the management of patients with or without known pituitary tumors. In a patient with a known pituitary tumor, there is a risk in performing pituitary stimulation tests [Vassallo et al 1994]. In patients who are to receive gonadotrophin-releasing hormone agonists in the treatment of prostatic carcinoma, an argument can be made for performing an MRI scan to exclude pituitary tumor. If a patient has a diagnosed pituitary tumor and is to undergo treatment that is a known precipitating factor such as anticoagulation or coronary artery surgery, the

risk should be made known to both the patient and treating physicians; in certain cases, other treatment options might be considered.

### **5.5. Conclusion**

Pituitary apoplexy may be associated with precipitating factors in a minority of cases. The most commonly associated precipitating factors are surgery, particularly coronary artery surgery, pituitary stimulation tests, and anticoagulation. The pathogenesis of pituitary apoplexy and the precipitating factors are not completely understood. The histology of apoplectic pituitary tumors in which precipitating factors are identified is predominantly hemorrhagic infarction or hemorrhage. The presence of a precipitating factor makes hemorrhage or hemorrhagic infarction 13.1 times more likely, and this may influence the severity of presentation and outcome. Care should be taken when performing stimulation tests on a patient with a pituitary tumor, placing a patient with a pituitary tumor on anticoagulant therapy, or undertaking coronary artery surgery or other surgery. In patients who have pathology or who undergo a procedure that is a known precipitating factor in pituitary apoplexy and who developed an impairment in their level of consciousness, visual deficits, or endocrine failure should undergo prompt MRI scan, endocrine evaluation, and hormone replacement therapy.

## **CHAPTER 6**

### **CONCLUSION**

6.1. Researching uncommon clinical problems is problematic so the methodology of setting up a website using a common protocol and having different institutions entering patients is a very useful tool for collecting data from more than a single institution. It allows for a wider experience in terms of patient numbers as well as encompassing the different possible approaches.

6.2. A study group of 62 patients with pituitary apoplexy from University of Cape Town and University of Virginia was retrospectively analyzed. In the majority of patients the pituitary adenoma was undiagnosed and the apoplexy was the first presentation. The diagnosis is easy to miss and a high index of suspicion is necessary in patients presenting with headache, visual acuity and field defects, ophthalmoplegia, or diminished level of consciousness. MRI scan is the imaging modality of choice. In this series 59 patients were treated surgically and in the majority a good outcome was achieved. High dose corticosteroid replacement is necessary in all patients. Emergency transsphenoidal decompression should be carried out on all patients with diminished level of consciousness, hypothalamic disturbance or severe visual impairment including blindness. In patients with mild or moderate visual impairment surgery should be performed as soon as possible (within the first week). There is evidence that some patients, in particular those with isolated ophthalmoplegia or those

who only present long after the ictus with mild or improving symptoms, may be managed conservatively. The majority of patients require long-term replacement therapy.

6.3. The GSH-UVA cohort of patients was divided on the basis of histopathology into 2 groups: infarction alone; or hemorrhage or hemorrhagic infarction. Patients who presented with pituitary apoplexy due to infarction alone in a pituitary adenoma were found to have a statistically significant more benign illness with a less severe presentation and better outcome than those in whom histopathological studies showed hemorrhagic infarction or hemorrhage alone.

6.4. Thirty-six patients who had MRI scans to diagnose pituitary apoplexy at UVA and underwent surgery were retrospectively reviewed to ascertain if MRI could predict histopathological findings. The histological features of infarction alone, or hemorrhage or hemorrhagic infarction on the histopathological examination was accurately predicted on the MRI. MRI can predict the histopathological diagnosis and this may help in management decisions and improving the outcome of these patients in the future.

6.5. In a minority of cases pituitary apoplexy may be associated with precipitating factors the most common of which are surgery, anticoagulation and pituitary stimulation tests. The histopathology of apoplectic tumors in which precipitating factors were identified are 13.1 times more likely to be hemorrhagic or hemorrhagic infarction and this may influence the severity and the outcome of pituitary apoplexy.

6.6. The uniqueness of this thesis is that this is the first time that it has been shown that MRI at the time of diagnosis can be used to predict the histopathology and consequently the severity as well as the outcome in pituitary apoplexy. In addition the presence of a precipitating factor may also help in predicting outcome in these patients. This has significant benefit in managing patients with pituitary apoplexy, including making a decision on conservative or surgical management.

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