www.jkns.or.kr

J Korean Neurosurg Soc 42 : 83-88, 2007

Clinical Article

Jae-Hyun Lee, M.D.
Jae-Hyoo Kim, M.D.
Kyung-Sub Moon, M.D.
Sung-Pil Joo, M.D.
Jung-Kil Lee, M.D.
Soo-Han Kim, M.D.

Department of Neurosurgery
Chonnam National University
Hospital & Medical School
Gwangju, Korea

Pituitary Apoplexy : Surgical Experience with 16 Patients

Objective : Pituitary apoplexy, resulting from an acute infarction or hemorrhage mainly in pituitary adenomas, is a rare yet major clinical event with neurological, ophthalmological and hormonal emergent consequences. The authors review our surgical experience with a series of 16 cases of pituitary apoplexy.

Methods : The cases of pituitary apoplexy, operated via trans-sphenoidal approach in our hospital between 1998-2005, were retrospectively analyzed in terms of their clinicoradiological features, pathological findings and surgical outcomes.

Results : The mean age of patients (9 male and 7 female) was 47.1 years. The average time of presentation after onset of symptom was 8.9 days. Pituitary apoplexy occurred as an initial manifestation of pituitary adenoma in all patients. Headache was the most common presenting symptom (94%). Visual disturbance was found in 56% of patients. Thirty-one percent of the patients had hypopituitarism. On magnetic resonance imaging, this entire catastrophic event accompanied with macroadenoma in a mean size of 22.5 mm. Only four patients needed postoperative hormone replacement therapy. Three of them showed preoperative hypopituitary function, and one patient in normal pituitary function. There was no specific complication in any of these patients.

Conclusion : Early trans-sphenoidal decompression with high-dose corticosteroid replacement showed good outcomes of pituitary apoplexy.

KEY WORDS : Pituitary apoplexy · Pituitary adenoma · Transsphenoidal approach (TSA).

INTRODUCTION

Pituitary apoplexy is a rare but potentially life-threatening clinical syndrome caused by rapid enlargement of a pituitary tumor due to hemorrhage or infarction[13,14]. It usually presents with a sudden onset of headache, nausea and vomiting, visual disturbances and altered level of consciousness[8]. The frequency of pituitary apoplexy presenting with classical symptoms is about 0.6-9% in the series of surgically treated pituitary adenomas[7,12,13]. But, hemorrhage or infarction of pituitary adenomas may be detected incidentally on imaging study, and these patients may have mild or no symptoms. Subclinical pituitary apoplexy is more common and has been reported in 25% of surgically removed pituitary adenomas[9]. Urgent surgical decompression of pituitary fossa is a preferred treatment but delayed decompression may also restore neuro-ophthalmic function. In addition, conservative medical therapy may offer an alternative option for patients without progressive neuro-ophthalmic signs. There were no specific postoperative complications.

The authors performed a retrospective analysis to evaluate clinical presentation, postoperative courses, and pathological findings in a series of patients surgically treated for symptomatic pituitary apoplexy during last 8 years.

MATERIALS AND METHODS

Based on the data for brain tumor patients, 234 pituitary adenomas had been operated between 1998 and 2005. The definition of pituitary apoplexy used in this study included only patients with apoplectic onset symptoms, appropriate radiological and histopathological confirmation of hemorrhage or necrosis in pituitary adenoma. During the this period, 16 patients (9 males and 7 females, 6.8%) were surgically treated for acute presentation of pituitary apoplexy. Using retrospective analysis of hospital records and video-tapes for these 16 patients, the authors reviewed the detail of clinical presentations, radiologic findings, endocrine studies, pathologic findings, postoperative complication and outcomes.

• Received : August 23, 2006
• Accepted : July 13, 2007
• Address for reprints :
Jae-Hyoo Kim, M.D.
Department of Neurosurgery
Chonnam National University
Hospital & Medical School
8 Hak-dong, Dong-gu
Gwangju 501-757, Korea
Tel : +82-62-220-6606
Fax : +82-62-224-9865
E-mail : herhuz@hanmail.net

Table 1. Common presenting symptoms and signs in 16 patients with pituitary apoplexy

Symptoms and signs	Number of patients (%)
Headache	15 (94%)
Nausea/vomiting	7 (44%)
Decreased visual acuity	6 (38%)
Visual field deficit	6 (38%)
Ocular palsy	4 (25%)
Diplopia	2 (13%)
Altered consciousness	1 (6%)

Table 2. Neuroophthalmological evaluation in 16 patients with pituitary apoplexy

Symptoms and signs	Number of patients (%)	
Decreased visual acuity	6 (38%)	
Extraocular movement abnormality	4 (25%)	
III nerve palsy		2 (13%)
III+IV nerves palsy		1 (6%)
III+VI nerves palsy		1 (6%)
Visual field defect	6 (38%)	
Bitemporal hemianopsia		4 (25%)
Temporal hemianopsia+anopsia		1 (6%)
Temporal upper quadrantanopsia		1 (6%)

Table 3. Hormonal expression and secretion characteristics in patient with apoplexy

Hormone expression*	No.	Hormone secretion†	No.
FSH	4	Hyperfunction	2
GH	2	Prolactin	1
Prolactin	1	GH	1
FSH/LH	1	Hypofunction	5
TSH	1	ACTH	2
Can't check‡	7	TSH	1
		Panhypopituitarism	2
		Normal function	9

*hormonal expression in immunohistochemical study, †hormonal status in laboratory findings, ‡unconfirmed specimen in immunohistochemical study due to complete hemorrhage or necrosis

All patients underwent assessment of anterior pituitary function on admission and subsequent follow-up in department of endocrinology. Assessment of anterior pituitary function was made by measuring random serum levels of Free T4, T3, TSH, LH, FSH, PRL, ACTH, cortisol, GH and IGF-1 or combined pituitary stimulation test (Cocktail test). The presence of hypopituitarism was defined by proven biochemical deficiency of at least one endocrine axis. The degree of visual disturbance was assessed by Snellen visual acuity and automated visual field testing (Humprey perimetry).

RESULTS

Clinical features

In apoplexy group (9 males and 7 females), the mean age at diagnosis was 47.1 (range : 24-69) years. The average length of time from onset of symptoms until presentation in our department was 8.9 days, with a range from 1 day to 30 days. In 14 patients, no precipitating factors were identified. Apoplectic symptoms occurred after removal of angiolipoma of the thigh under general anesthesia in one patient and a pituitary stimulation test in another. Unfortunately, there were no imaging studies demonstrating any hemorrhage in pituitary adenoma before these procedures. However, these preoperative procedures could be regarded as precipitating factors based on the consecutive symptom after procedure.

The main presenting symptoms and signs are listed in Table 1. Headache, typically of sudden onset, was the most common complaint, occurring in all but one patient. Headache was frequently associated with nausea, vomiting and visual symptoms in 44% of patients. Neuroophthalmological evaluation was performed in all cases and revealed visual disturbance in 9 cases. Ocular movement abnormalities were present in 4 patients; oculomotor palsies in 2, multiple cranial nerve palsies in 2 (oculomotor and trochlear nerves : 1, oculomotor and abducens nerves : 1). On visual field examination, bitemporal hemianopsia was found in 6 patients included 1 case of right temporal hemianopsia and left anopsia and 1 case of both temporal upper quadrantanopsia. Decreased visual acuity was present in 6 cases (Table 2). One patient demonstrated stuporous mental status at presentation due to hyponatremia.

Table 4. Radiologic classification of tumor size and extension based on the classification system from Hardy, modified by Wilson in patients with apoplexy

	A	B	C	D	E
I	–	–	–	–	–
II	4	2	1	–	–
III	4	1	–	–	1
IV	1	2	–	–	–

Sella turcica destruction I; focal bulging, II; diffuse bulging, III; focal destruction, IV; diffuse destruction : Extrasellar extension A; suprasellar cistern only, B; up to 3rd ventricle floor, C; in or above 3rd ventricle, D; intradural lateral extension, E; extradural lateral extension

Table 5. MRI and operative findings

MRI		No.	Operative findings	No.
T1	T2			
High	low	7	hemorrhage with/without necrosis	6
High	high	5	necrosis with cystic fluid	4
Low	high	4	cystic fluid	6

Table 6. Postsurgical outcomes of visual and cranial nerve function of patients with visual disturbances

	Normal	Improved	Unchanged	Worse
Visual acuity	3	3	0	0
Visual field	6	0	0	0
Cranial nerve palsy	3	1 (VI)	0	0

Table 7. Postsurgical endocrine outcomes of patients with apoplexy

Initial endocrine function	Follow-up endocrine function		
	Hyperpituitarism	Normal function	Hypopituitarism (HRT*)
Hyperpituitarism (n=2)	1	1	0
Normal function (n=9)	0	6	3 (1)
Hypopituitarism (n=5)	0	2	3 (3)

* hormone replacement therapy

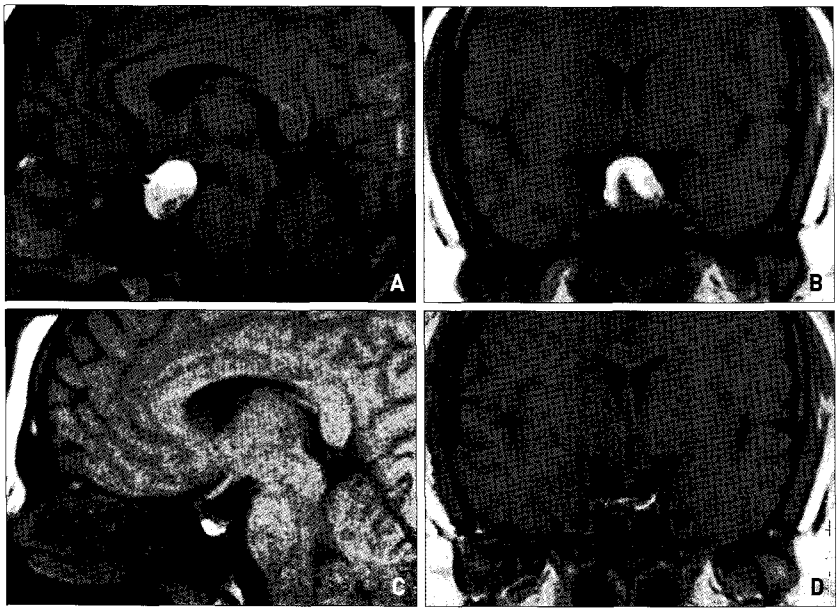

Fig. 1. Magnetic resonance image (MRI) scans of a 69-year-old man who presented with headache and left ptosis. A, B : Preoperative MRI scans show a 2.1×1.7×2.1 cm sized pituitary macroadema with suprasellar extension and hemorrhage. C, D : Postoperative MRI scans was obtained 3 months later revealing decompression of optic nerve and nearly total removal of tumor.

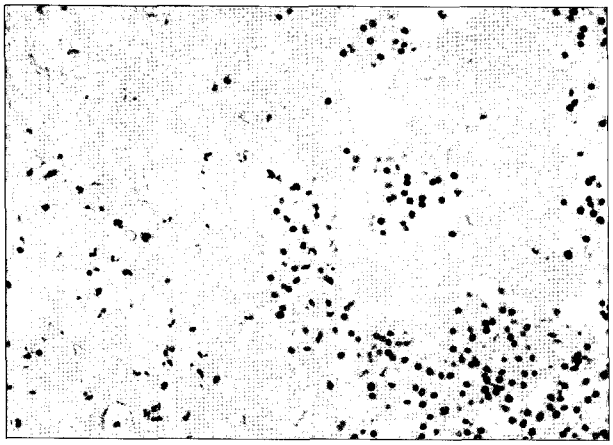

Fig. 2. Microscopic feature of pituitary apoplexy. Photomicrograph shows tumor cell with coagulative necrosis and hemorrhage (H&E, ×200).

Endocrine findings and pathologic findings

The results of pituitary function test at presentation were available in all patients. In considerable portion of apoplectic patients (15 patients), preoperative assessments of pituitary hormone were substituted by measurement of random serum levels of hormone because the patients were needed urgent or early operation. Fourteen patients had clinically nonfunctioning pituitary adenomas. Five patients showed deficiency of one or more pituitary hormones; corticotrophin deficiency was found in 2, thyrotrophin deficiency with adrenal insufficiency in 1 and panhypopituitarism in 2. Nine patients had normal pituitary functions, and two patients had hyperpituitarism; hyperprolactinemia was found in 1 and increased somatomedin-C in 1.

The pituitary decompression via transsphenoidal approach was performed within 14 days after admission. Tumor cell type was defined by immunohistochemistry only in 9 of 16 cases, because of extensive hemorrhagic or necrotic changes. FSH was positive in 5 patients, GH in 2, TSH in 1, LH in 1, prolactin in 1 (Table 3).

Radiologic features and operative findings

All patients with apoplexy underwent magnetic resonance imaging (MRI) as a primary investigation (Fig. 1). The tumors were all macroadenomas, with an average size of 22.5 mm (Average size=a+b+c/3, a and b : maximal perpendicular diameters of the tumor on axial images, c : diameter on coronal or sagittal images). According to Hardy classification, IIA and IIIA were the most common types (Table 4). Definitive hemorrhagic changes on MRI study were found in 12 cases; early subacute stage of hemorrhage in 7, late subacute stage of hemorrhage in 5. The cystic or necrotic degeneration of pituitary adenoma was in 4 (Table 5).

On operation, hemorrhage with/without necrosis was detected in 6 cases (Fig. 2), necrosis with cystic fluid in 4 cases. However, there was no evidence of apoplexy except simple liquified cystic fluid in 6 cases (Table 5).

Outcome

The average length of follow-up in this series was 14.5 months (range, 1mo-5yr) and there was no death. The patient's most recent clinical state at follow-up was assessed and divided into the following group : no symptoms in 12 patients; non-disabling symptoms (requiring hormonal replacement) in 4 patients. Visual acuity was assessed on follow up period in 11 patients and was normal in 8, improved but not normal in 3. None was worse. Visual fields at follow-up were normal in all patients. Cranial nerve function returned

Table 8. Summary of 16 patients with pituitary apoplexy

Patient	Age (yr) /Sex	Chief complaint	Precipitating factors	Delay to surgery	Visual symptoms			Endocrine study	
					decreased acuity	field defect	ocular palsy	Preop	Postop
1	24/M	headache	-	6d	-	-	-	normal	normal
2	44/M	headache	-	5d	-	-	-	Cortisol : 0.1ug/dl	Panhypopituitarism
3	53/F	headache	-	2w	+	+	+ (III)	normal	GH : 0.4ng/ml
4	59/F	headache	-	8d	+	-	+ (III,IV)	T4 : 0.2ng/dl	normal
5	54/M	headache	-	2w	+	+	-	normal	normal
6	54/M	headache	-	1m	-	-	-	normal	normal
7	37/F	blindness	-	4d	+	+	-	normal	normal
8	29/F	headache	-	8d	-	-	-	Panhypopituitarism	normal
9	55/M	headache	-	11d	-	-	-	normal	T4 : 0.5 ng/dl
10	65/F	stuporous mentality	-	1d	+	+	-	Cortisol : 0.29 ug/dl	Cortisol : 5.8 ug/dl
11	69/M	headache	previous general anesthesia	9d	-	-	+ (III)	Panhypopituitarism	Panhypopituitarism
12	34/M	headache	cocktail test	1d	-	-	-	normal	Panhypopituitarism-> normal
13	48/F	headache	-	9d	-	-	-	normal	normal
14	33/M	headache	-	7d	-	+	-	Prolactin : 5322 ng/ml	Prolactin : 2180 ng/ml
15	66/M	headache	-	4d	+	-	+ (III,VI)	IGF-1 : 525 ng/ml	IGF-1 : 210 ng/ml
16	30/F	headache	-	12d	+	+	-	normal	normal

M : male, F : female, d : day, w : week, m : month, normal : normal pituitary function

Table 9. Summary of 16 patients with pituitary apoplexy

Patient	Hardy classification	MRI findings		Operative findings	Immunohistochemical stain	Complication
		T1	T2			
1	IIA	high	low	necrosis with cystic fluid	FSH	-
2	IVA	high	low	hemorrhage	GH	-
3	IIA	low	high	necrosis with cystic fluid	-	toxic hepatitis
4	IIA	high	low	cystic fluid	-	-
5	IIIA	high	high	necrosis with cystic fluid	FSH	-
6	IIIA	low	high	cystic fluid	TSH	-
7	IIIB	high	low	cystic fluid	FSH	-
8	IIB	high	high	cystic fluid	-	-
9	IIIA	high	high	cystic fluid	FSH, LH	-
10	IVB	low	high	cystic fluid	FSH	remnant mass -> radiotherapy
11	IIIA	high	high	necrosis with cystic fluid	-	-
12	IIB	high	low	hemorrhagic necrosis	GH	-
13	IVB	low	high	hemorrhage	-	-
14	IIIE	high	low	hemorrhage	Prolactin	remnant mass -> bromocriptine medication
15	IIA	high	low	hemorrhagic necrosis	-	-
16	IIC	high	high	hemorrhaghic necrosis	-	-

to normal in 75% of patients demonstrating ocular palsy preoperatively (Table 6). Data on postoperative endocrine function were available in all patients (Table 7). It was assessed by cocktail test in 9 patients and by random serum level of pituitary hormone in 7 patients and followed up in the department of endocrinology. Among 9 patients with normal endocrine function before operation, 3 showed postoperative hypopituitarism (hypothyroidism, panhypopituitarism, hypothyroidism and growth hormone deficiency in each patient) but only one required hormonal replacement during follow-up period. On the other hand, among 5 patients who showed preoperative hypopituitarism, 3 needed continuous hormonal replacement. Two patients had remnant mass on follow-up imaging study. One of them received radiotherapy, the other with prolactinoma, subtotally removed due to active tumor bleeding, was managed with bromocriptine. Diabetes insipidus after operation was not present in any patients. Toxic hepatitis, as a postoperative complication, was developed in one patient and recovered completely. There was no recurrence and no need for additional radiotherapy or reoperation (Table 8, 9).

DISCUSSION

The definition of pituitary apoplexy has not always been uniform, with most common factors being a characteristic clinical diagnosis associated with appropriate pathological features on histology. Mohr and Hardy[9] found 64 (9.6%) to have hemorrhage or necrosis at surgery in a review of 664 patients with pituitary adenomas. However, only 4 had clinical presentation of pituitary apoplexy. According to Ostrov et al.[11], only 3 had clinical pituitary apoplexy among 12 patients with pituitary adenomas who had intratumoral evidence of hemorrhage on CT or MRI. These asymptomatic hemorrhage or infarction has been called subclinical pituitary apoplexy. All patients in this study revealed sudden onset symptoms in correspondence with clinical apoplexy. In surgically confirmed cases, the incidence of pituitary apoplexy in pituitary adenoma was 6.8%. The fact that all patients in this study had macroadenomas on radiopathological findings proves previous series noting that pituitary apoplexy typically occurs in pituitary macroadenomas. All of the patients in this study did not have a known pituitary tumor. Pituitary apoplexy occurred as an initial manifestation of pituitary adenoma in all cases. The other diseases, such as subarachnoid hemorrhage, can induce sudden headache and aneurysms can be present in patients with pituitary tumors. For this reason, the correct diagnosis should be performed even in outpatient department to differentiate other conditions including subarachnoid hemorrhage, meningitis, migraine, optic neuritis, and stroke[4,6].

Although the majority of cases of pituitary apoplexy are spontaneous, many precipitating factors have been suggested. Biousse et al.[2] reported multiple factor as precipitants of apoplexy into four categories : 1) reduced blood flow in the gland, 2) acute increase in blood flow in the pituitary gland, 3) stimulation of the pituitary gland, 4) the anticoagulated state. Reduced blood flow may be associated with fluctuations in blood pressure, including hypotension often associated with surgery, changes in intracranial pressures associated with head injuries or after radiation. One of our patients seems to have had an association with surgery, another followed by cocktail test.

Although various theories have been proposed in the literature, the pathogenesis of apoplexy from pituitary adenoma is poorly understood. A well described theory is that with rapid growth, the tumor outstrips its blood supply, resulting in ischemic necrosis and then hemorrhage[3,4,12]. Second theory is compression of trabecular arteries arising from the superior hypophyseal artery by the diaphragm sellae due to tumor growth[3,10]. The other theory is intrinsic vasculopathy in pituitary adenoma susceptible to infarction and hemorrhage[3].

Clinical presentation of pituitary apoplexy may vary from patient to patient, but according to most reports, headache (often frontal or orbital) is the most common symptom. Clinical presentation depends on the predominant mechanism of tumor expansion, blood extravasation into subarachnoid space, or pituitary tissue injury. In this study, 94% of patients were presented with a sudden onset of headache and 56% of patients with visual disturbance. These clinical features are similar to those previously reported[1,3,5,12,13].

Signs and symptoms from hypopituitarism are less frequent than headache and visual disorders and are usually detected by laboratory investigations. One patient had acromegaly as the evidence of hypersecretion of growth hormone. Another patient showed increased prolactin level (5322 μg/L) on laboratory findings without prominent hyperprolactinoma symptom. Pituitary adenomas are classified as functional (hormone-secreting) or nonfunctional, which still may be positively stained for pituitary hormones. In this study, several adenomas demonstrated immunoreactivities for FSH, GH, prolactin or TSH, but majority of these tumors never secreted the over-expressed hormone (except, acromegaly and prolactinoma). Other large series of patients with pituitary apoplexy reported 33% incidence of PRL-, GH- or ACTH-secreting adenomas among their patients[1,12].

MRI has the great advantage as an imaging tool for demonstration of features of hemorrhage, compression of the optic chiasm, the suprasellar extension and invasion into

the cavernous sinuses[8]. In this study, all pituitary apoplexy was macroadenoma with an average size of 225 mm. Early subacute stage was dominant in stage of hemorrhage.

The two principles of management of pituitary apoplexy have been trans-sphenoidal decompression and immediate institution of high-dose corticosteroid replacement[1,3]. There is a consensus that high-dose corticosteroid replacement therapy and careful management of fluid and electrolyte balance are mandatory. Randeva et al.[12] strongly advocate early trans-sphenoidal surgery for pituitary apoplexy, with particular urgency in patients with deteriorating vision. They argued that the procedure had a low morbidity and mortality and that they reliably reversed or improved the neuro-ophthalmological deficits and furthermore noted that this improvement was more likely in those patients operated within 8 days (73%) compared with those operated on later (42%). Therefore, they thought that early but not emergency surgery resulted in better outcome. Even late surgery for pituitary apoplexy was described as having satisfactory results in improved visual function.

There has been a marked improvement in outcome in pituitary apoplexy over the past 30 years that reflects the progress in surgical and endocrine management. The visual outcome was assessed at follow-up period. In visual acuity, 50% of patients was normal, 50% improved but not normal and in visual fields all were normalized which is similar to other series[7,12]. Ocular paresis has a good prognosis with normalization in 75%. Among five patients who had hypopituitarism before operation, two restored in normal pituitary function and the remainder required replacement therapy as in the previously published series[12,14]. Diabetes insipidus (DI) is much less common, probably because the blood supply of the posterior pituitary is different from that of the anterior. There was no DI in this study. The overall outcome was good, with 75% of patients alive with no symptoms and 25% alive with minor nondisabled symptoms. The mortality was zero as a consequence of the apoplexy.

CONCLUSION

Patients presenting with sudden headache, progressive visual disturbance, altered consciousness should be highly suspicious for pituitary apoplexy. An MRI scan is the imaging procedure of choice. Early trans-sphenoidal decompression with high-dose corticosteroid replacement show good outcome of pituitary apoplexy.

References

1. Bills DC, Meyer FB, Laws ER Jr, Davis DH, Ebersold MJ, Scheithauer BW, et al : A retrospective analysis of pituitary apoplexy. **Neurosurgery 33** : 602-608, 1993
2. Biousse V, Newman NJ, Oyesiku NM : Precipitating factors in pituitary apoplexy. **J Neurol Neurosurg Psychiatry 71** : 542-545, 2001
3. Cardoso ER, Peterson EW : Pituitary apoplexy : a review. **Neurosurgery 14** : 363-373, 1984
4. Ebersold MJ, Laws ER Jr, Scheithauer BW, Randall RV : Pituitary apoplexy treated by transsphenoidal surgery. A clinicopathological and immunocytochemical study. **J Neurosurg 58** : 315-320, 1983
5. Kim JK, Park BJ, Cho KT, Lee SK, Cho MK, Kim YJ : Surgical Outcomes of Pituitary Apoplexy. **J Korean Neurosurg Soc 38** : 450-455, 2005
6. Maccagnan P, Macedo CL, Kayath MJ, Nogueira RG, Abucham J : Conservative management of pituitary apoplexy : a prospective study. **J Clin Endocrinol Metab 80** : 2190-2197, 1995
7. McFadzean RM, Doyle D, Rampling R, Teasdale E, Teasdale G : Pituitary apoplexy and its effect on vision. **Neurosurgery 29** : 669-675, 1991
8. Milazzo S, Toussaint P, Proust F, Touzet G, Malthieu D : Ophthalmologic aspects of pituitary apoplexy. **Eur J Ophthalmol 6** : 69-73, 1996
9. Mohr G, Hardy J : Hemorrhage, necrosis, and apoplexy in pituitary adenomas. **Surg Neurol 18** : 181-189, 1982
10. Onesti ST, Wisniewski T, Post KD : Clinical versus subclinical pituitary apoplexy : presentation, surgical management, and outcome in 21 patients. **Neurosurgery 26** : 980-986, 1990
11. Ostrov SG, Quencer RM, Hoffman JC, Davis PC, Hasso AN, David NJ : Hemorrhage within pituitary adenomas : how often associated with pituitary apoplexy syndrome? **AJR Am J Roentgenol 153** : 153-160, 1989
12. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, Wass JA : Classical pituitary apoplexy : clinical features, management and outcome. **Clin Endocrinol (Oxf) 51** : 181-188, 1999
13. Semple PL, Webb MK, de Villiers JC, Laws ER Jr : Pituitary apoplexy. **Neurosurgery 56** : 65-72; discussion 72-73, 2005
14. Sibal L, Ball SG, Connolly V, James RA, Kane P, Kelly WF, et al : Pituitary apoplexy : a review of clinical presentation, management and outcome in 45 cases. **Pituitary 7** : 157-163, 2004