Pituitary apoplexy

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Pituitary apoplexy (PA), a rare clinical syndrome secondary to abrupt hemorrhage or infarction, complicates 2–12% of pituitary adenomas, especially nonfunctioning tumors. Headache of sudden and severe onset is the main symptom, sometimes associated with visual disturbances or ocular palsy. Signs of meningeal irritation or altered consciousness may complicate the diagnosis. Precipitating factors (increase in intracranial pressure, arterial hypertension, major surgery, anticoagulant therapy or dynamic testing, etc.) may be identified. Corticotropic deficiency with adrenal insufficiency may be life threatening if left untreated. Computed tomography (CT) or magnetic resonance imaging (MRI) confirms the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components. Formerly considered a neurosurgical emergency, PA always used to be treated surgically. Nowadays, conservative management is increasingly used in selected patients (those without important visual acuity or field defects and with normal consciousness), as successive publications give converging evidence that a wait-and-see approach may also provide excellent outcomes in terms of oculomotor palsy, pituitary function and subsequent tumor growth. However, it must be kept in mind that studies comparing surgical approach and conservative management were retrospective and not controlled.

I. Introduction

BAILEY WAS THE first to describe a case of fatal pituitary tumor-associated hemorrhage in 1898 (1). The second description was an autopsy case of hemorrhagic pituitary infraction in a young acromegalic patient in 1905 (2). But the first full description was published in 1950, under the term "pituitary apoplexy" (3). Pituitary apoplexy (PA) is a clinical syndrome due to abrupt hemorrhaging and/or infarction of the pituitary gland, generally within a pituitary adenoma. Headache of sudden and severe onset is the main symptom, sometimes associated with visual disturbances or ocular palsy. PA can reveal the pituitary adenoma or occur during its follow up.

The outcome of acute apoplexy is variable and difficult to predict: clinical status may deteriorate dramatically (subarachnoid hemorrhage (SAH) from the apoplectic adenoma, or cerebral ischemia secondary to cerebral vasospasm), or the patient may recover spontaneously, with or without sequelae (visual defects, neurological disorders or pituitary insufficiency). PA sometimes completely destroys the adenoma, while in other cases a remnant may regrow. This explains why the optimal management of acute PA remains controversial. Indeed, PA was almost universally considered a neurosurgical emergency in the past (4–7), but reports of spontaneous clinical recovery and/or tumor disappearance have led some specialists to adopt a conservative approach in selected cases (8–21).

EPIDEMIOLOGY

PA is a rare event: according to recent epidemiological studies its prevalence is about 6.2 cases per 100 000 inhabitants (22) and its incidence 0.17 episodes per 100 000 per year (23). Between 2% and 12% of patients with all types of adenoma experience apoplexy (4, 6, 10, 12, 24–32), and the diagnosis of pituitary tumor was unknown at time of apoplexy in more than 3 out of 4 cases (12–16, 24, 27, 29, 31, 33–49) (Table 1). If the non functioning pitu-

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Abbreviations:

Table 1. Demographic, clinical, biochemical and evolutive characteristics of patients with pituitary apoplexy as reported in the main retrospective series published in the literature since 2000 and including at least 15 adults or 8 children. NF, non functional; GT, gonadotroph; NA, non available; VF, visual field; VA, visual acuity

First author (reference)	Year of publication	N	Mean age, years (Range)	Sex ratio (M/F)	Length of duration of the study	Number (%) of adenomas previously known	Type of secretion defined clinically and/or biochemically (%)					Precipitating factors (%)
							GH	PRL	ACTH	NF or GT	NA	
Biousse (33)	2001	30	51 (21–90)	14/16	1989- 2000	6 (20)	0	3 (10)	0	3 (10)	26 (80)	9 (30)
Chacko (34)	2002	41	40 (18–65)	28/13	1983–1995	NA	4 (10)	3 (7)	0	34 (83)	0	NA
Sibal (13)	2004	45	49 (16–72)	28/17	1983–2004	8 (18)	1 (2)	14 (31)	3 (7)	2 (4)	25 (56)	18 (40)
Ayuk (12)	2004	33	52 (27–79)	20/13	1994- 2004	1 (3)	0	0	0	1 (3)	32 (97)	10 (33)
Semple (27)	2005	62	51 (18–82)	38/24	1970- 2003	12 (19)	1 (2)	7 (11)	0	48 (77)	6 (10)	2 (4)
Lubina (40)	2005	40	51 (15–80)	27/13	1985- 2002	4 (10)	1 (2.5)	2 (5)	0	1 (2.5)	36 (90)	5 (13)
Gruber (14)	2006	30	53 (17–86)	23/7	1988- 2004	4 (13)	0	3 (10)	0	1 (3)	26 (87)	37
Khaldi (37)	2006	25	54 (20–79)	14/11	1980–2003	3 (12)	1 (4)	5 (20)	0	0	19 (76)	3 (12)
Semple (43)	2006	59	51 (NA)	34/25	1970–2003	NA	1 (2)	1 (2)	0	48 (81)	9 (15)	3 (5)
Dubuisson (29)	2007	24	56 (23–87)	16/8	1968–2004	6 (25)	1 (4)	3 (13)	1 (4)	1 (4)	18 (75)	12 (50)
Zhang (49)	2009	185	38 (16–65)	89/96	1990–2007	NA	14 (8)	117 (63)	6 (3)	0	48 (26)	47 (25)
Shou (45)	2009	44	43 (NA)	36/8	2006- 2006	NA	2 (5)	3 (7)	0	0	39 (89)	NA
Liu (39)	2010	65	48 (21–87)	30/35	2002–2006	NA	2 (3)	10 (15)	0	0	53 (82)	NA
Pal (41)	2011	32	57 (29–85)	23/9	1985- 2008	2 (6)	0	0	0	32 (100)	0	NA
Zhang (47)	2011	52	52 (18–79)	39/13	2001–2009	NA	3 (6)	12 (23)	1 (2)	1 (2)	35 (67)	NA
Seuk (44)	2011	29	42 (25–68)	21/8	1995–2009	6 (21)	2 (7)	3 (10)	1 (3)	23 (79)	0	NA
Moller-Goede (31)	2011	42	53 (21–85)	30/12	1980–2007	1 (2)	1 (2)	7 (17)	2 (5)	29 (69)	3 (7)	32 (76)
Leyer (15)	2011	44	53 (12–83)	27/17	1996- 2008	12 (27)	0 (0)	4 (9)	2 (4)	6 (14)	32 (73)	23 (52)
Chan (35)	2012	17	39 (NA)	6/11	1979–2012	17 (100)	0	0	17 (100)	0	0	2 (12)
Sarwar (42)	2013	25	34 (23–41)	3/22	2000–2011	25 (100)	0	25 (100)	0	0	0	8 (32)
Kinoshita (38)	2014	58	48 (16–75)	28/30	2006–2012	58 (100)	6 (10)	22 (38)	0	30 (52)	0	5 (9)
Vargas (46)	2014	47	51 (NA)	26/21	1999- 2013	9 (19)	NA	NA	NA	NA	47 (100)	NA
Bujawansa (16)	2014	55	58 (14–78)	35/20	1985- 2010	4 (7)	4 (7)	6 (11)	0	45 (82)	0	11 (20)
Jankowski (36)	2014	9	17 (14–23)	3/6	2008–2013	1 (11)	0	7 (78)	0	0	2 (22)	4 (44)
Jho (48)	2014	109	52 (18–87)	69/40	1992–2012	8 (7)	0	1 (1)	0	1 (1)	107 (98)	9 (8)
Total		1202	48 yr	707/495		187/756 (25)	44/1155 (4)	258/1155 (22)	33/1155 (3)	306/1155 (26)	563/1255 (45)	240/892 (27)

itary adenomas (NFPAs) (often incidentalomas) were already known and that a decision was made to manage them conservatively, the risk of PA was calculated to be between 0.2 and 0.6 events per 100 person-years in two meta-analyses (50, 51).

PA can occur at all ages but is most frequent in the fifth or sixth decade, with a male preponderance ranging from 1.1 to 2.3/1 (Table 1) (4, 7, 10, 12–16, 24, 27, 29, 31, 33–49, 52–54).

Subclinical (asymptomatic) apoplexy is much more frequent than acute apoplexy, as up to 25% of all pituitary tumors display hemorrhagic and/or necrotic areas (4–6, 38, 42, 55) either on imaging or at autopsy, but this subject is beyond the scope of this review.

PREDISPOSING AND PRECIPITATING FACTORS

Precipitating factors

Precipitating factors are identified in 10 to 40% of cases of PA (Table 1). Many single case-reports of PA have been published where the relationship with a potential precipitating factor has been suggested. The most relevant clinical situations associated with PA are summarized in Table 2.

Angiographic procedures, particularly cerebral angiography, have been reported to be associated with PA which began from few minutes to 7 hours after the procedure; PA may be related either to blood pressure (BP) fluctuations or to vasospasm (56–59). Among surgical procedures, orthopedic surgery and cardiac surgery seem more prone to be complicated by PA than gastrointestinal (GI) (60–62) or pulmonary (63) surgery or thyroidectomy (64). PA occurred from very early, in the operating theater, to 24–48h after orthopedic surgery (on the hip or shoulder more often than on the knee) (65–73). Proposed mechanisms include intra or postoperative hypotension, anticoagulation and/or microemboli leading to infarction. Cardiac surgery, because of BP fluctuations and anticoagulant therapy, is a very "classic" clinical situation leading to intra- or postoperative PA (60, 74–92). Cardiopulmonary bypass (CBP) is likely to be an important contributor by generating important variation in BP. This has led some authors to recommend, when the presence of pituitary adenoma is known before the cardiac procedure, to use off-pump technique which maintains pulsatile flow with an adequate systemic perfusion, as opposed to standard CBP (82). The temporal relationship between a head trauma (sometimes quite minor) and the onset of specific signs and symptoms also seems convincing that cranial trauma may be a cause of PA (93–100). Apoplexy can also occur after dynamic testing (insulin, TRH, GnRH or GHRH tests and much more rarely CRH): the period between the test and the beginning of PA (often few minutes only) is, once again, a good argument supporting that dynamic tests, particularly when different agents are combined, are clearly precipitating factors of PA in many instances (101–130). The suspected mechanism is the imbalance between the increased metabolic demand induced by the stimulation and the ability of increased blood

Table 1. Continued

Immunocytochemistry (%)						Clinical/biochemical characteristics at diagnosis (%)						Evolution		
GH	PRL	ACTH	FSH/LH	Necrosis or negative	NA	Headache	Vomiting	Unconsciousness	Abnormal VF/VA	Cranial nerves impairment	Hypopituitarism	Surgery (%)	Normal pituitary function (%)	Recurrence of the adenoma (%)
NA	NA	NA	NA	NA	30 (100)	30 (100)	NA	9 (30)	14/11 (47/37)	17 (57)	16 (53)	27 (90)	4 (12)	1 (3)
3 (7)	1 (2)	1 (2)	0	10 (25)	26 (63)	NA	NA	NA	NA	NA	28 (68)	41 (100)	NA	NA
2 (4)	2 (4)	3 (7)	2 (4)	21 (47)	15 (33)	43 (96)	35 (78)	10 (22)	20/18 (48/46)	22 (51)	34 (76)	27 (60)	7 (15)	5 (11)
1 (3)	1 (3)	0	8 (24)	5 (15)	18 (55)	32 (97)	17 (53)	NA	11/27 (36/82)	15 (46)	24 (72)	15 (46)	5 (15)	2 (6)
1 (2)	1 (2)	0	0	8 (13)	52 (84)	52 (84)	15 (24)	8 (13)	27/38 (43/61)	26 (43)	45 (73)	58 (93)	7 (12)	46 (74)
7 (18)	2 (5)	3 (7)	3 (7)	4 (10)	21 (52)	25 (63)	20 (50)	7 (17)	24/NA (61/NA)	16 (40)	17 (42)	34 (85)	6 (14)	15 (37)
4 (13)	2 (7)	NA	NA	NA	24 (80)	27 (90)	14 (47)	3 (10)	10/18 (33/60)	15 (62)	21 (70)	10 (33)	3 (10)	6 (20)
NA	NA	NA	NA	NA	25 (100)	24 (96)	17 (68)	10 (40)	14/17 (56/68)	20 (80)	NA	20 (80)	NA	NA
1 (2)	1 (2)	0	48 (81)	8 (13)	1 (2)	49 (83)	NA	9 (15)	39/39 (66/66)	24 (41)	48 (81)	34 (58)	9 (15)	NA
2 (8)	1 (4)	2 (8)	2 (8)	6 (25)	11 (46)	22 (92)	13 (54)	10 (42)	12/12 (50/50)	13 (54)	17 (71)	21 (87)	2 (8)	4 (17)
96 (52)	14 (8)	6 (3)	0	69 (37)	0	70 (38)	NA	NA	46/96 (25/52)	NA	101 (54)	185 (100)	159 (86)	23 (12)
2 (5)	0	0	0	12 (27)	30 (68)	42 (96)	29 (66)	1 (2)	33/31 (75/70)	28 (64)	NA	44 (100)	14 (32)	0
14 (22)	2 (3)	1 (2)	7 (11)	11 (17)	30 (46)	30 (46)	11 (17)	4 (6)	50/50 (77/77)	9 (14)	24 (37)	65 (100)	20 (31)	10 (15)
NA	NA	NA	NA	NA	NA	25 (78)	15 (47)	4 (12)	16/22 (50/69)	26 (81)	24 (75)	29 (90)	NA	4 (11)
NA	NA	NA	NA	NA	52 (100)	51 (98)	48 (92)	15 (29)	41/48 (79/92)	39 (75)	17 (33)	52 (100)	6 (11)	5 (10)
NA	NA	NA	NA	NA	29 (100)	29 (100)	NA	NA	23/26 (79/90)	21	NA	29 (100)	NA	NA
NA	NA	NA	NA	NA	42 (100)	5 (12)	NA	NA	16/ NA (38/ NA)	32 (76)	19 (45)	39 (93)	12 (29)	NA
5 (11)	1 (2)	1 (2)	6 (14)	11 (25)	20 (45)	41 (93)	26 (59)	12 (27)	19/24 (43/54)	22 (50)	35 (80)	39 (89)	12 (27)	4 (9)
0	0	11 (65)	0	6 (35)	0	12 (70)	10 (59)	NA	11/11 (65/65)	NA	NA	12 (70)	8 (47)	0
NA	NA	NA	NA	NA	25 (100)	7 (28)	NA	NA	NA	NA	3 (13)	2 (8)	NA	2 (9)
NA	NA	NA	NA	NA	58 (100)	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	47 (100)	35 (75)	NA	NA	34/34 (73/74)	10 (23)	40 (85)	36 (76)	20 (43)	12 (25)
NA	NA	NA	NA	NA	55 (100)	48 (87)	14 (25)	NA	20/NA (36/NA)	26 (47)	NA	33 (55)	8 (14)	NA
7 (78)		0	0	1 (11)	1 (11)	9 (100)	2 (22)	NA	3/0 (33/0)		2 (22)	8 (89)	6 (66)	2 (22)
13 (12)	3 (3)	1 (1)	0	81 (74)	11 (10)	95 (87)	36 (33)	14 (13)	43/NA (39/NA)	39 (36)	92 (84)	101 (93)	43 (39)	NA
						803/1101 (73)	322/661 (49)	116/691 (17)	VF:526 /1078 (49) VA: 567/832 (68)	420/867 (48)	607/944 (64)	961/1144 (84)	(28)	141/707 (20)

flow at the level of the pituitary adenoma (see paragraph "Pathophysiology" below). Reports of PA occurring after stimulation test are much rarer in the recent past, probably because the vast majority of endocrinologists are now convinced that many of these tests (TRH, GnRH) do not bring crucial information while they put the patient at risk of PA (121). In this setting we do not recommend preoperative stimulation tests in patients with pituitary macroadenomas particularly when they present suprasellar extension (131, 132) except CRH or Insulin tolerance test when useful for evaluating corticotropic axis. Treatment with GnRH agonists for prostate cancer has also been associated with PA, occurring from few minutes to 10 days after the injection of long-acting formulation (133–143).

PA may be observed in patients under anticoagulation therapy, sometimes very soon after the initiation of treatment, or after a prolonged period of treatment (31, 144–147); new classes of anticoagulant (dabitagran) (148, 149) may also be involved. Bleeding disorders have also been reported as associated with PA (150–152).These case reports suggest that these medications or conditions may favor the occurrence of PA. However, to our knowledge, there has been no prospective study looking at their specific role on the risk of PA and it is thus very difficult to propose any recommendation concerning authorization or contraindication for anticoagulation prescription in patients with a known pituitary adenoma.

The role of dopamine agonists (DA) treatment as precipitating factor is more controversial. As exemplified by case reports summarized in Table 2, PA may occur during treatment with DA, sometimes early after the initiation of treatment (eg, 1 week) but this is quite rare (153), suggesting a potential role of DA. However, in most cases, PA is reported to occur after a very prolonged period of treatment (55, 153–161) and the responsibility of DA is thus more questionable. Moreover, in prospective studies analyzing the effects of DA on macroprolactinomas, PA were very rarely or never observed (23, 156, 162–168) even when treatment was initiated at high dose (168), when high doses were used due to DA resistance (165, 169) or when pituitary adenomas were already hemorrhagic on MRI (42). In a review, PA was found to occur in 1 to 6% of macroprolactinomas treated with DA, a rate not higher than that of untreated macroprolactinomas (170). Finally, it must be pointed out that prolactinomas are, by themselves, more prone to bleeding (see next paragraph "Influence of adenoma subtype") even if this is generally asymptomatic. Indeed, in a study analyzing MRI characteristics at diagnosis (before any treatment), 16 out of 79 macroprolactinomas (20.3%) were identified as having pituitary hemorrhage and 3 of them presented with « classic apoplexy » (42). Some authors have even suggested that DA treatment may prevent macroprolactinomas from PA (31).

Contrary to previous studies, a recent publication suggests that diabetes and arterial hypertension do not predispose patients to pituitary apoplexy (31).

Influence of the adenoma subtype

PA is observed more frequently in patients with non functioning pituitary adenomas (Table 1) (7, 12–16, 22,

Table 2. Litterature review on the main predisposing or precipitating factors of pituitary apoplexy NA, non available; BRC, bromocriptine; CAB, cabergoline; CABG, coronary artery bypass graft; ITT, insulin tolerance test

Predisposing/ precipitating factors	First Author, Year of publication	Ref	Age	Sex	Tumor type	Drug used/type of intervention	Dose	Duration before apoplexy weeks/ days/hours/minutes (w/d/h/mn)
Angiography	Reichenthal, 1980	(57)	40	M	NA	Carotid angiography		15mn
	Suga, 1996	(59)	29	F	PRL	Cerebral angiography		6 h
	Louwerens, 1996	(56)	32	M	GH	Cerebral angiography		7 h
	Skljarevski, 2003	(58)	66	M	NF	Coronarography		Immediate post-procedure
Orthopedic Surgery	Lennon 1998	(69)	51	M	NA	Total hip replacement under spinal anesthesia		6 h
	Liu, 2001	(70)	45	M	NA	Laparoscopic anterior lumbar interbody fusion		1 h
	Galvin, 2004	(65)	48	M	NA	Total hip replacement (+lupus anticoagulant)		48 h
	Khandelwal, 2005	(67)	65	F	NA	Total knee replacement		24 h
	Thomason, 2009	(73)	70	M	NA	Total hip replacement		4d
	Goel, 2009	(66)	76	M	Necrosis	Total hip replacement		24 h
	Goel, 2009	(66)	61	M	Necrosis	Total knee arthroplasty		24 h
	Koga 2010	(68)	60	M	NF	Shoulder arthroplasty		During the procedure
	Madhusudhan, 2011	(71)	62	M	No operated	Shoulder afthroplasty		48 h
	Prescott, 2011	(72)	58	M	Not operated	Total hip replacement		10 h
Cardiac surgery	Peck, 1980	(74)	68	M	Not operated	Aortic valve replacement		48 h
	Slavin, 1984	(75)	57	M	Necrosis	CABG		<24 h
	Slavin, 1984	(75)	55	M	NF, hemorrhage, necrosis	Mitral Valve replacement		48 h
	Cooper, 1986	(78)	63	M	NF	CABG		63 h
	Cooper, 1986	(78)	55	M	PRL,FSH	CABG		55 h
	Cooper 1986	(78)	62	M	NF	Mitral and aortic valve replacement		12 h
	Khardori, 1987	(81)	62	M	Necrosis	CABG		8 h
	Shapiro 1990	(89)	60	?	NA	CABG		24 h
	Absalom, 1993	(76)	61	M	Hemorrhage	CABG		40 h
	Savage, 1994	(88)	72	M	Necrosis	CABG		Immediately post-procedure
	Savage, 1994	(88)	64	M	Necrosis	CABG		21 h
	Meek, 1998	(85)	56	M	Necrosis	Mitral valve repair		15mn
	Mattke, 2002	(84)	64	M	NA	CABG		20m
	Alzetani, 2002	(77)	72	M	Not operated	CABG		Immediate postop
	Glass, 2003	(79)	63	M	NA	CABG		4 h
	Abott, 2004	(60)	48	M	Necrosis	Aortic valve replacement		24 h
	Liberale, 2006	(83)	73	M	NA	Aortic abdominal aneurysm surgery		Immediate postop
	Mukhida 2007	(87)	71	M	Not operate	CABG		71 h
	Levy, 2007	(82)	58	M	NA	CABG		Postop (time not provided)
	Levy, 2007	(82)	65	M	NA	CABG		Postop (time not provided)
	Levy, 2007	(82)	68	M	NA	CABG		Postop (time not provided)
	Levy, 2007	(82)	65	M	NA	CABG		Postop (time not provided)
	Hidiroglu, 2010	(80)	47	M	NA	Cardiac surgery		2 h
	Yakupoglu 2010	(91)	74	M	Necrosis	Open cardiac surgery		6 h
	Tansel 2010	(90)	60	M	NA	CABG (anaphylaxis shock due to allergy to protamine)		During the procedure
	Mizuno, 2011	(86)	73	M	Necrosis	CABG		73 h
	Kocyigit, 2011	(92)	66	F	NA	CABG		66 h
Surgery Other	Yahagi, 1992	(62)	47	M	NA	Cholecystectomy		24 h
	Kato, 1996	(64)	38	F	GH	Thyroidectomy		3 h
	Abott 2004	(60)	66	M	NA	Laparotomy for resection of hepatic mass		48 h
	Mura 2014	(61)	85	M	Not operated	Laparoscopic/laparotomic resection of sigmoid colon		0 h
	Yoshino, 2014	(63)	78	M	NA	Pulmonary lobectomy and lymph node dissection for squamous cell carcinoma		128 h
Closed head trauma	Holness, 1983	(95)	39	M	NF	Minor head trauma motor vehicle		Immediate
	Tamasawa, 1988	(99)	34	M	GH	Fall from the back of a truck		Immediate
	Itoyama,1990	(97)	45	M	NA	Fall 2m		3 h
	Uchiyama 1999	(100)	66	M	NA	Fall 15m		15 h
	Uchiyama 1999	(100)	60	F	NA	Mild, (fall from his height)		1 h
	Horie 2002	(96)	56	F	NA	Traffic car accident		15mn
	Smidt 2007	(98)	30	M	NA	Minor head trauma		3w
	Dev, 2007	(94)	40	M	necrosis	Mild cranial trauma (road traffic)		1w
	Bao, 2007	(93)	79	M	Not operated	Mild cranial trauma (fall)		1 h

(*Continued*)

24, 27, 29, 31, 33–49, 52, 171, 172). This may be the result of selection bias as these adenomas are generally discovered late and are usually larger than functioning adenomas. Indeed, in the vast majority of cases, apoplexy complicates large macroadenomas (31). Other tumor types that have been reported to undergo apoplexy include prolactinomas and GH-secreting adenomas (12–16, 27, 29, 31, 33–49, 173).

Clinically silent ACTH adenomas may be particularly prone to necrosis, hemorrhage and cyst transformation. These complications occur in 30 to 64% of cases, compared with 6.8% to 20% in patients with prolactinomas and 2% to 14% in patients with all types of pituitary adenoma (38, 42, 174–176), and are generally revealed by MRI. Recurrent clinical apoplexy has been described in these patients (174, 176–179), and may be associated with a brisk and transient increase in ACTH/cortisol production, leading to hypertension, hyperglycemia, hypokalemia and edema.

It must be underlined that in many cases, if not obvious clinically, the potential functioning nature of the adenoma which underwent apoplexy is impossible to assess due to the extent of necrosis.

PATHOPHYSIOLOGY

The pathophysiology of PA is not fully understood, but it is noteworthy that most cases involve patients with macroadenomas (7, 26, 31, 180, 181).

Table 2. Continued

Predisposing/ precipitating factors	First Author, Year of publication	Ref	Age	Sex	Tumor type	Drug used/type of intervention	Dose	Duration before apoplexy weeks/ days/hours/minutes (w/d/h/mn)
Dynamic tests	Dunn, 1975	(107)	22	F	GH	TRH	400 μg	48 h
	Silverman, 1978	(126)	31	M	PRL	Chlorpromazine	25 mg	1.5 h
	Jordan, 1979	(112)	21	F	ACTH (Nelson)	Dexamethasone 8 mg	8 mg	The last day of the test
	Cimino, 1981	(104)	48	M	NF	GnRH/TRH	100 μg/200 μg	20mn.
	Drury, 1982	(106)	59	F	NF	GnRH/TRH	100 μg/200 μg	5mn
	Drury, 1982	(106)	66	M	GH	TRH	200 μg	10mn
	Drury, 1982	(106)	39	F	PRL	GnRH/TRH	100 μg/200 μg	2mn
	Drury, 1982	(106)	28	M	PRL	GnRH/TRH	100 μg/200 μg	15mn
	Korsic, 1984	(114)	56	M	FSH	GnRH	100 μg	2 h
	Bernstein, 1984	(102)	48	M	NF	GnRH/TRH/ITT	100 μg/200 μg/0.1 UI/kg	5mn
	Chapman, 1985	(103)	39	F	PRL	GnRH/TRH/ITT	100/200/0.15 UI/kg	0.5 h
	Lever, 1986	(116)	19	F	GH	TRH	200	2mn
	Shirataki, 1988	(125)	50	F	GH	BRC	2.5 mg	2mn
	Harvey, 1989	(111)	50	M	NF	ITT	0.15 UI/kg	0mn
	Arafah 1989	(101)	41	F	PRL	GnRH	100 μg	1 h
	Masson, 1993	(118)	54	F	GT	GnRH	100 μg	20mn
	Okuda, 1994	(120)	60	F	NF	GnRH/TRH/ITT	100/500/0.1U/kg	10mn
	Vassalo, 1994	(128)	81	M	NF	GnRH/TRH/liter-Dopa/ACTH	100 μg/200 μg/500 mg/250 μg	2 h
	Masago, 1995	(117)	48	M	FSH	GnRH/TRH/ITT	100 μg/500 μg/0.1UI/kg	15mn
	Masago, 1995	(117)	54	M	NF	GnRH/TRH	100 μg/500 μg	10mn
	Frankart, 1995	(109)	64	M	FSH-LH	GnRH/TRH	100 μg/200 μg	48 h
	Grunenberger, 1996	(110)	30	M	GH	GnRH/TRH/ /Glucagon	100 μg/250 μg/2 mg	24 h
	Szabolcs, 1997	(127)	54	M	NF	TRH	200 μg	1 h
	Otsuka, 1998	(121)	31	F	GH	GnRH/TRH/CRH/GHRH	100 μg/200 μg/100 μg/100 μg	2mn
	Dokmetas, 1999	(105)	28	F	GH	GnRH/TRH	100 μg/200 μg	88 h
	Sanno, 1999	(124)	55	M	NF	GnRH/TRH/CRH/GHRH	100/500/100/100	30mn
	Foppianni, 2000	(108)	43	F	NF	GnRH	100 μg	Few minutes
	Lee, 2000	(115)	34	M	GH	GnRH/TRH/ITT	100 μg/400 μg/0.15UI/kg	20mn
	Riedl, 2000	(122)	71	F	NF	GnRH/TRH/CRH/GHRH	NA	Immediate
	Matsuura, 2001	(119)	63	M	NF	GnRH/TRH/ITT	100 μg/500 μg/0.1 UI/kg	2 h
	Rotman-Pikielny 2003	(123)	19	F	ACTH	CRH	100 μg	48 h
	Wang, 2007	(129)	41	F	Necrosis	TRH	200 μg	2 h
	Yoshino, 2007	(130)	36	M	Necrosis	GnRH/TRH/ITT	100 μg/500 μg/5UI	24 h
	Yoshino, 2007	(130)	38	M	Necrosis	TRH	500 μg	2 h
	Kilicli, 2010	(113)	52	M	FSH LH PRL	GnRH/TRH	100 μg/200 μg	30mn
GnRH-agonists	Ando, 1995	(133)	83	M	NA	Goserelin	3.6 mg	9d
	Chanson, 1995	(134)	78	M	FSH	Triptorelin	3.75 mg	10mn
	Morsi, 1996	(135)	74	M	FSH, LH, GH	Leuprolide	7.5 mg	15mn
	Reznik, 1997	(136)	62	M	FSH, LH	Leuprolin	3.75 mg	4d
	Eaton, 2001	(137)	67	M	FSH, LH	Goserelin Androcur	3.6 mg 100 mg/j	4 h
	Hernadez-Morin, 2003	(138)	69	M	FSH, LH	Leuprolin Bicalutamide	11.25 mg 50 mg/j	30mn
	Massoud, 2006	(139)	70	M	FSH	Leuprolin	11.25 mg	10d
	Blaut, 2006	(140)	74	M	negative	Goserelin	3.6 mg	12 h
	Hands, 2007	(141)	60	M	LH	NA	NA	4 h
	Ito, 2011	(142)	78	M	FSH	Goserelin Bicalutamide	3.6 mg 80 mg/j	9d
	Huang, 2013	(143)	77	M	necrosis	Leuprolin	3.75 mg	Few hours
Dopamine agonists	Yamaji, 1981	(154)	46	M	GH	BRC	7.5 mg/d	48w
	Yamaji, 1981	(154)	55	F	GH	BRC	NA	24w
	Onesti, 1990	(55)	34	F	PRL	BRC	NA	NA
	Gittelman, 1991	(155)	19	F	NA	BRC	5 mg/d	48w
	Biller, 1996	(156)	26	F	PRL	CAB	0.5 mg/wk	12w
	Pinto, 1998	(157)	14	F	PRL	BRC	10 mg/d	24w
	Hanna, 1999	(158)	42	F	PRL	BRC	NA	NA
	Vella, 2001	(159)	30	M	PRL	CAB	0.5 mg/wk	20w
	Knoepfelmacher, 2004	(160)	17	M	PRL	CAB	1.5 mg/wk	52w
	Balarini Lima, 2008	(153)	57	M	PRL	CAB	3.5 mg/wk	7w
	Balarini Lima, 2008	(153)	27	M	PRL	CAB	1.5 mg/wk	12w
	Balarini Lima, 2008	(153)	15	F	PRL	CAB	1.5 mg/wk	32w
	Balarini Lima, 2008	(153)	52	F	PRL	CAB	NA	1w (1st); 8w (2^{nd})
	Chng, 2013	(161)	20	M	PRL	CAB	0.5	6w

The understanding of clinical and biochemical picture of patients with PA is helped by a better knowledge of the characteristics of pituitary gland vascularization. Pituitary vascularization is supported by a capillary network called hypophysial portal system coming from hypothalamus via the long portal veins and by direct arterial blood supply either from superior hypophysial arteries that descends along the pituitary stalk to the anterior pituitary gland or from inferior hypophysial arteries to the posterior pituitary, both originating from branches of the internal carotid artery (Figure 1). Moreover, the superior and inferior hypophysial circulations are anastomised. The venous drainage is directed via hypophysial veins to adjacent venous sinuses and then to jugular veins. By contrast with normal pituitary, the vascularization of pituitary adenomas are predominantly supported by a direct arterial blood supply rather than portal system (43, 182, 183) and contrast-enhanced imaging clearly shows that blood supply to pituitary adenomas is reduced compared with normal pituitary (184). Pituitary tumors have reduced angiogenesis as shown by reduced density of microvasculature (185, 186). In addition to the presence of fenestrated endothelial cells, which are characteristic of the normal capillaries of the anterior pituitary, prolactinomas contain arteries, ranging from well formed vessels with multiple layers of smooth muscle cells to abnormal terminal arte-

rioles, ie, vessels with fenestrated endothelium surrounded by a variable number of smooth muscle cells. Such arteries are not found in normal anterior pituitary (187).

Nevertheless, pituitary adenomas are prone to bleed and undergo infarction and necrosis, possibly because pituitary gland has this unique rich vascular structure and/or because pituitary tumors (which have a high energy requirement) may outgrow their blood supply or because ischemia (and thus infarction) occurs following compression of infundibular or superior hypophyseal vessels against the sellar diaphragm by the expanding tumor mass (180, 188) with intrinsically poor vascularity.

Moreover, as recently demonstrated, pituitary tumor cells are particularly sensitive to glucose deprivation (184).

In this setting, all clinical situations (see Paragraph "Precipitating factors" above) that acutely decrease systemic BP, such as cardiac, vascular or orthopedic surgery may decrease blood supply to the pituitary adenoma and precipitate apoplexy. Dynamic tests or hypoglycemia which acutely increase the metabolic needs of the tumor may also precipitate apoplexy, as well as severe vomiting/diarrhea with concomitant increased Valsalva pressure.

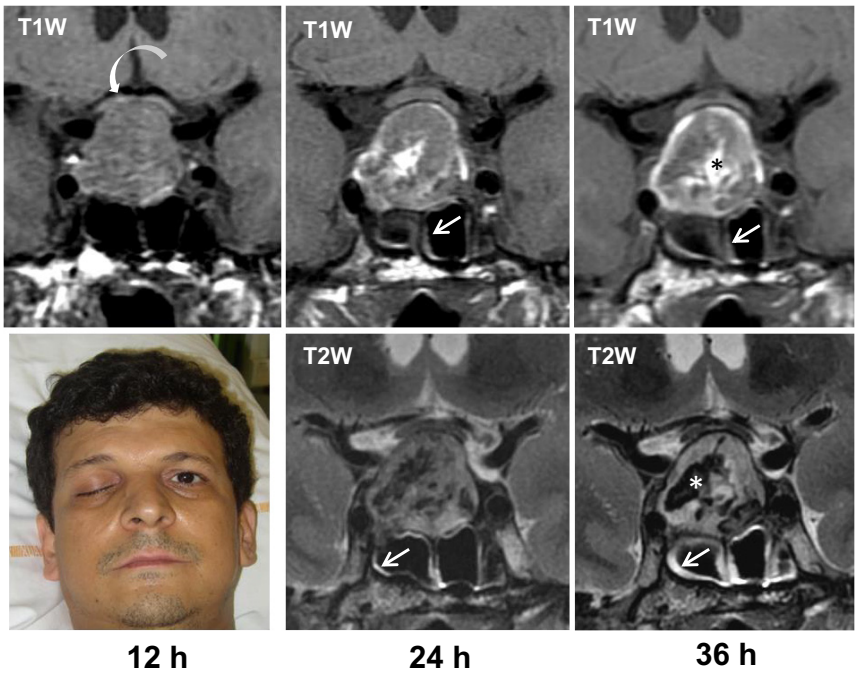
The inherent fragility of tumoral blood vessels may also explain the hemorrhagic tendency (189). Indeed, the vessels of pituitary adenomas show signs of incomplete maturation and poor fenestration, and their basal membranes are often ruptured (52, 190, 191). Immunohistochemical expression of vascular endothelial growth factor (VEGF) was found to correlate positively with the risk of pituitary hemorrhage (192). Pituitary Tumor-Transforming Gene (PTTG), which is correlated to vascularization and expression of VEGF (193) is also overexpressed in pituitary adenomas (194, 195). Fetal liver kinase 1 (FKL-1) a vascular marker is also expressed, particularly in NF pituitary adenomas, particularly in older subjects (196) as is nestin, another vascular marker (197).

To our knowledge, genetic markers of intracranial vascular malformations such as cranial aneurysms (198, 199) have not been studied in patients with PA.

Imaging studies and surgical exploration may reveal both hemorrhage and ischemic necrosis (10, 43, 200)

Whatever the mechanism, the extent of hemorrhage and necrosis will produce an increase in intrasellar pressure (26, 52, 201–203), which in turn leads to more or less pronounced compression of neighboring structures, thus explaining the broad clinical spectrum, from "classical" acute PA to totally silent necrotic and/or hemorrhagic adenomas found only on pathological examination.

Figure 1.



Serial MRI studies of a patient with pituitary apoplexy (mainly hemorrhagic).

Left row: 12 hours after onset of symptoms (sudden headache, fatigue and right third oculomotor nerve palsy; bottom), T1-weighted (T1W) MRI shows a pituitary mass abutting the optic chiasm (curved arrow) and yielding a heterogeneous signal (top).

Middle row: At 24 hours: T1W sequences show peripheral and central areas of spontaneous signal hyperintensity (top), while T2W sequences show mainly central hypointense areas (bottom); note also the typical thickening of the sphenoid sinus mucosa on both T1W and T2W sequences (arrows).

Right row: At 36 hours: T1W (top) and T2W (bottom) sequences show an increase in the hyperintense and hypointense areas (asterisk) and further thickening of the sphenoid sinus mucosa (arrows).

CLINICAL PRESENTATION

The clinical presentation of PA is highly variable and is largely determined by the extent of hemorrhage, necrosis and edema (Table 1).

Headache

Headache is the most prominent symptom of acute apoplexy and is present in more than 80% of patients (12–16, 27, 29, 31, 33–49, 54, 204, 205). Headache is also generally the initial symptom, with sudden and severe onset described "like a thunderclap in a clear sky" (206). It is probably due to dural traction or to extravasation of blood and necrotic material into the subarachnoid space, producing meningeal irritation. Headache is usually retro-orbital but can be bifrontal or diffuse. It is often associated with vomiting and nausea and can mimic migraine or meningitis (13, 24, 207). Headache may be subacute with slow development of symptoms.

Visual disturbances

Visual disturbances are present in more than half of PA patients (12–17, 24, 27, 29, 31, 33–49, 52, 55, 204). They are due to the sudden hemorrhage-related increase in tumor mass, leading to compression of surrounding structures (mainly the optic chiasm or optic nerves, from upward expansion of the tumor). Variable degrees of visual-field impairment may be observed, bitemporal hemianopsia being most common. Loss of visual acuity and blindness can occur, but are rare (24, 27, 32, 52, 55, 204).

Oculomotor palsies are also frequent, affecting 52% of patients in a compilation of studies (208), and are due to functional impairment of cranial nerves III, IV and VI. The third cranial nerve is the most frequently affected (half of cranial nerve palsies) and is characterized by ptosis, limited eye movements in adduction, and mydriasis (24, 204, 208) (Figure 2). This phenomenon can be due to intracavernous expansion of the tumor mass, a hematoma or, most frequently, to an abrupt pressure increase in the pituitary region (the cranial nerves are exquisitely sensitive to increased pressure) (203).

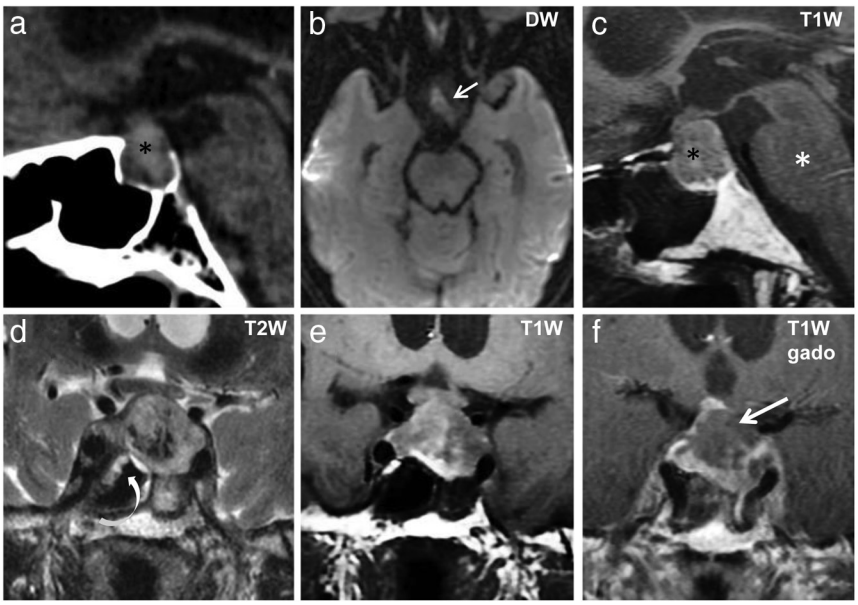
Other neurological signs

Signs or symptoms of meningeal irritation such as photophobia (40%), nausea, vomiting (57%), meningismus (25%) and, sometimes, fever (16%) may be misleading: an initial false diagnosis of meningitis may be made, especially as cerebrospinal fluid (CSF) examination may show hyperlymphocytosis (98, 209). Variable degrees of altered consciousness may be observed, ranging from lethargy to stupor or even coma (12–16, 27, 29, 31, 33–49). These signs are due to extravasation of blood or necrotic tissue into the subarachnoid space (210).

Cerebral ischemia can occasionally result from mechanical compression of the carotid artery against the anterior clinoid, or to cerebral vasospasm, and lead to focal neurological deficits such as hemiparesis or dysphasia, or to a pyramidal syndrome (211, 212). Stroke can be part of the differential diagnosis, at presentation or subsequently.

Less frequent manifestations include anosmia (due to olfactory nerve compression), epistaxis or CSF rhinorrhea (due to erosion of the bone of the sella turcica) and facial pain (due to compression of cranial nerve V). Accompanying acute adrenal insufficiency may lead to collapse and vital signs changes suggesting an incorrect diagnosis of myocardial infarction (MI).

Figure 2.



Imaging features 24 hours after symptom onset in a patient with pituitary apoplexy.

a- Reformatted sagittal CT scan showing a spontaneously hyperdense sellar mass, suggesting hemorrhage within a pituitary adenoma; b- Diffusion-weighted MRI (DW) at 24 hours demonstrates a sellar tumor with a hyperintense central area (straight arrow); c- T1-weighted MRI: sagittal section showing that the mass (black asterisk) is slightly hyperintense relative to the brain stem (white asterisk); d- T2-weighted MRI: coronal section showing the mass with central areas of signal hypointensity and thickening of the sphenoid sinus mucosa (curved arrow); T1-weighted MRI: coronal views; e- before gadolinium injection, the mass shows both hyper- and hypointense areas; f- after gadolinium injection, only the bottom part of the tumor is enhanced, the central part remaining hypointense, without enhancement (thick arrow).

Scoring system

The UK Pituitary Apoplexy Guidelines Development Group proposed a "Pituitary Apoplexy Score" based on the level of consciousness, visual acuity and field defects, and ocular palsies (Table 3) in order to enable more uniform clinical description of PA and, thus, better comparison of different management options (17).

ENDOCRINE DYSFUNCTION

Acute endocrine dysfunction may also be present, further complicating the clinical picture (Tableau 1). One or more anterior pituitary deficiencies are present at PA onset (12–17, 24, 25, 27, 29, 31, 33–49, 213) In retrospect, signs and symptoms consistent with endocrine abnormalities are often present before the apoplectic episode, such as sexual problems, menstrual disturbances, galactorrhea or fatigue (7, 24). These disorders are produced by mass effect on the normal pituitary. Multiple acute endocrine insufficiencies can occur, related either to destruction of the anterior pituitary or to increased intrasellar pressure on the pituitary stalk, impairing the release of hypothalamic and/or pituitary hormones (201, 204). Details about the various pituitary deficits found at presentation in the main series of PA published in the literature since 2000 (12, 13, 15, 27, 29, 31, 38, 40, 42, 45, 46, 49) are given in Table 4.

Table 3. Pituitary Apoplexy Score (from Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, Markey A, Plant G, Powell M, Sinha S, Wass J 2011 UK guidelines for the management of pituitary apoplexy. Clin Endocrinol (Oxf) 74:9–20) (17)

Variable	Points
Level of consciousness	
Glasgow coma scale 15	0
Glasgow coma scale 8–14	2
Glasgow coma scale <8	4
Visual acuity	
Normal 10/10 (or no change from prePA visual acuity)	0
Reduced -- unilateral	1
Reduced - bilateral	2
Visual field defects	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present unilateral	1
Present bilateral	2

Corticotropic deficiency

Corticotropic deficiency is the most common deficit observed in patients with PA, occurring in 50% to 80% of cases (12–15, 17, 24, 25, 27, 29, 31, 38, 40, 42, 45, 46, 49, 213). It is also the most life-threatening hormonal complication, potentially causing severe hemodynamic problems and hyponatremia (214, 215). As acute secondary adrenal insufficiency is very frequent in patients with apoplexy, empiric parenteral corticosteroid supplementation (if possible preceded by blood drawing for subsequent serum cortisol determination) should be given to all patients with signs of PA, without waiting for diagnostic confirmation.

Severe hypotension occurs when vessels become insensitive to endogenous or exogenous catecholamines in the absence of circulating cortisol (216). Hyponatremia may also be observed in patients with corticotropic deficiency, particularly in the acute setting (217–219)

Both hypotension and hyponatremia are not related to hypomineralocorticism as observed in primary adrenal insufficiency (Addison's disease), in which both mineralo- and glucocorticoid levels are insufficient (220). Mineralocorticoid levels are normal in ACTH-deficient patients. Hyponatremia is a direct consequence of glucocorticoid deficiency, and is related to inappropriate antidiuresis resulting from non suppressible AVP release (despite hypoosmolality) and probably, to a direct renal water excretion defect, both being consequences of cortisol deficiency. Other factors also probably contribute to hyponatremia in these patients. By irritating hypothalamus, PA can produce syndrome of inappropriate antidiuretic hormone (ADH) (SIADH) with hyponatremia (221); in that setting, serum bicarbonate measurement is useful for differentiating SIADH and corticotropic deficiency as it is lower in this latter condition (222). Hypothyroidism secondary to thyrotropic deficiency may also contribute to hyponatremia (223, 224). Nausea-vomiting and hypoglycemia (related to both ACTH/cortisol and GH/IGF-I deficiency) are non osmotic stimuli of AVP release. Blood samples for cortisol and ACTH should be obtained in the

Table 4. Percentages of pituitary deficiency at time of PA presentation in the main series published since 2000. NA, not available

First Author (Ref)	Year of publication	Number of patients	Any pituitary deficiency	Gonadotroph deficiency	Thyrotroph deficiency	Corticotroph deficiency	Somatotroph deficiency	Lactotroph deficiency	Diabetes insipidus
Sibal (13)	2004	45	76	76	57	60	NA	40	NA
Ayuk (12)	2004	33	72	72	37	50	NA	24	NA
Semple (27)	2005	62	73	40	55	61	6	2	8
Lubina (40)	2005	40	42	35	30	50	NA	NA	2
Dubuisson (29)	2007	24	71	67	67	62.5	58	58	0
Zhang (49)	2009	185	54		25	30	NA	NA	NA
Shou (45)	2009	44	NA	39	77	73	NA	NA	NA
Möller-Goede (31)	2011	42	45	43	14	7	NA	NA	2
Leyer (15)	2011	44	89	NA	NA	70	NA	NA	NA
Sarwar (42)	2013	25	13	1	9	13	NA	NA	NA
Kinoshita (38)	2014	58	NA	21	13	17	40	6	NA
Vargas (46)	2014	47	85	49	53	53	35	35	NA

acute phase prior to the administration of hydrocortisone (78, 220). A normal response of the pituitary-adrenal axis during critical illness, whatever its origin, is associated with a marked increase in plasma cortisol levels. For example, according to a recent study performed in critically ill patients with severe sepsis, compared with controls, baseline total cortisol was elevated two-fold (median, 463 nmol/L [interquartile range, IQR, 284–742] vs 245 [200299], $P < .001$) (225) and decreased slowly thereafter. In another study « normal » pituitary-adrenal axis response to stress resulted in mean cortisol level which peaked around 20 μg/dl (540 nmol/l) on the second day after admission in ICU and thereafter remained at an overall mean of 16.8 $\pm$ 7.8 μg/dl (464 $\pm$ 215 nmol/l) over a 7-day period in ICU (226). It must be underlined that these high levels are to a large extent explained by reduced cortisol breakdown, whereas cortisol production is only moderately increased (226, 227).

Thus if the increase in cortisol levels is limited, adrenal failure should be suspected. A threshold of 15 μg/dl (414 nmol/l) seems accurate for identifying patients with adrenal insufficiency in critical acute settings (78). Moreover, it is important to point out that, in our experience and according to the numerous papers reporting cortisol levels in patients with PA who ultimately proved to have corticotropic deficiency, cortisol levels are very low and the diagnosis is indisputable. Nevertheless, it is important to repeat that in patients with apoplexy, empiric parenteral corticosteroid supplementation should be given to all patients with signs of PA, without waiting for diagnostic confirmation

Other pituitary hormone deficiencies

Other pituitary defects do not raise the same concerns in the acute setting. According to reviews of the literature (52, 213) and compilation of important series (12, 13, 15, 27, 29, 31, 38, 40, 42, 45, 46, 49) (Table 4), 30%–70% and 40%–75% of patients with PA have thyrotropic deficiency and gonadotropic deficiency, respectively, at presentation. Replacement therapy can begin when the patient has recovered from the acute episode, based on hormonal status (213).

Almost all patients with PA have GH deficiency, but it is not often tested at diagnosis (12, 13, 15, 24, 25, 27, 29, 31, 38, 40, 42, 45, 46, 49, 189, 213, 228). Finally, PA is one of the rare circumstances in which a pituitary adenoma may be associated with low PRL levels, in 10%–40% of patient with PA (12, 13, 15, 17, 27, 29, 31, 38, 40, 42, 45, 46, 49, 213).

Diabetes insipidus

Diabetes insipidus is rare at PA onset, being present in less than 5% of patients. It may be masked by secondary adrenal failure (or hypothyroidism), however, in which case it will only emerge at the time of steroid replacement (or thyroid hormones) therapy (12, 13, 15, 27, 29, 31, 38, 40, 42, 45, 46, 49, 229, 230). Postoperative diabetes insipidus is more prevalent and may be either transient or permanent (17, 24).

Pituitary hypersecretion

PA can complicate a secreting pituitary adenoma. Prolactinomas are the most frequent, (12–16, 27, 29, 31, 33–49). As detailed above (see paragraph "Predisposing factors"), this is likely related to their frequent hemorrhagic nature; indeed, the imputability of DA treatment in triggering PA seems more disputable. PA also complicates, but more rarely (3 to 10% of cases) acromegaly or Cushing's disease secondary to pituitary corticotroph macroadenomas (Table 1).

In some cases, PA leads to resolution of pituitary hypersecretion by a secreting pituitary adenoma (8, 24, 123, 179, 231–239), eg, "fugitive acromegaly".

DIAGNOSTIC EVALUATION

Differential diagnosis

The clinical presentation of PA may raise two major differential diagnoses, namely SAH and bacterial meningitis. Other neurological events, such as cavernous sinus

thrombosis and midbrain infarction also need to be eliminated. Lumbar puncture is of little help in differentiating SAH and bacterial meningitis from PA, as the latter may be accompanied by a high red cell count, xanthochromia or pleocytosis, and by an increased CSF protein level, particularly when signs of meningeal irritation are present (209, 240, 241). CSF culture will rule out bacterial meningitis, and lumbar puncture is thus mandatory if this diagnosis is suspected. The best tools for diagnosing PA are computed tomography (CT) and magnetic resonance imaging (MRI). By revealing a pituitary tumor, even if no necrosis or hemorrhage is found, these imaging methods offer confident diagnostic confirmation.

Diagnosis thus relies on a combination of clinical manifestations (eg, sudden headache and visual disturbances) and the detection of a pituitary adenoma, whether before or after PA onset.

Imaging

Before discussing imaging features it is important to understand that the underlying pathophysiological process in PA can be simple infarction (ie, with little or no hemorrhagic component), hemorrhagic infarction, mixed hemorrhagic infarction and clot, or pure clot (189, 200). This explains why imaging rarely shows pure hemorrhage or infarction but rather mixed features (211).

Computed tomography

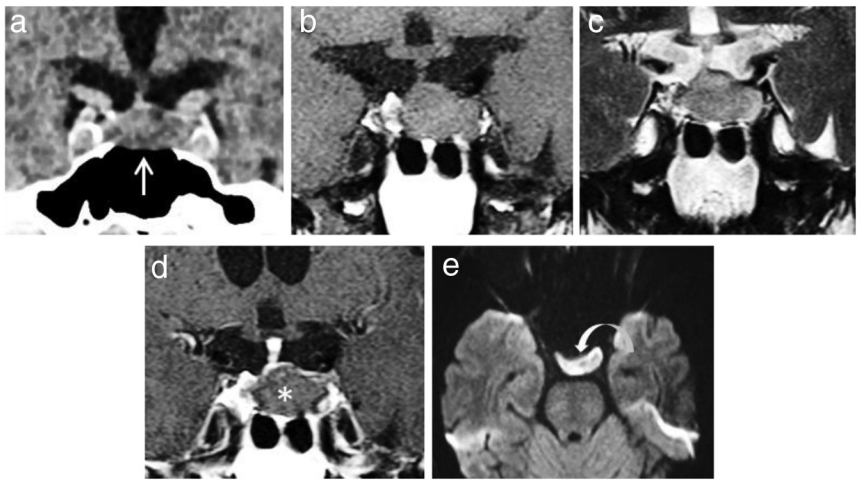
Given its wide availability, CT is usually the initial emergency examination for patients with severe headache of sudden onset. It has two interests: it rules out SAH and it shows an intrasellar mass in 80% of cases, with hemorrhagic components in 20 to 30% of cases (12, 13, 55, 242). After a few days, blood density decreases and may be more difficult to detect. After administration of contrast medium, the pituitary tumor shows inhomogeneous enhancement (243, 244), occasionally with ring enhancement (245, 246).

Magnetic resonance imaging

MRI is now the imaging procedure of choice (7, 13, 24, 55), even in the first days after symptom onset, as it can detect fresh bleeding (Figure 2). T1- and T2-weighted sequences are both interesting. T1 (longitudinal relaxation time) and T2 (transversal relaxation time) have specific characteristics according to each tissue. T1, T2 and proton density determine the contrast of MR images. The choice of technical parameters as TR (time to repeat) and TE (time to echo) allows to obtain images more or less dependent on T1 or T2. On T1W images, the water (CSF) is black, the gray matter is darker than the white matter; on T2W images, the water (CSF) is hyperintense, the white matter is darker than gray matter. MRI can identify hemorrhagic and necrotic areas and show the relationship between the tumor and neighboring structures such as the optic chiasm, cavernous sinuses and hypothalamus (247). As conventional (T1/T2) MRI sequences may not demonstrate an infarct for 6 hours, and small infarcts may be hard to appreciate on CT for days (Figure 3), diffusion weighted imaging (DWI), which provides information about consistency of macroadenomas, is very useful early in the PA process. Indeed, increased DWI signal in ischemic tissue is observed within a few minutes after arterial occlusion. In case of ischemic apoplexy, DWI can show increased signal intensity (Figures 2 and 3) relative to normal gray and white matter (248).

In the very first hours after onset, frank hyperintensity on T1-weighted sequences (T1W) may be absent, either because of infarction or because the hemorrhage is still in the form of deoxyhemoglobin (246).

Figure 3.



CT scan and MRI images of an ischemic form of pituitary apoplexy during the very first hours after the beginning of symptoms.

a) Coronal CT scan. Discrete hypodensity of a pituitary mass and thinning of the sellar floor (white arrow). b,c,d) T1, T2 and contrast enhanced T1W images. The mass is T1 isointense and T2 hyperintense; a rim enhancement is visible after contrast administration, but the central part of the mass (astrerisk) does not enhance. These images give no indication about the pathologic process. e) Axial DWI shows marked hyperintensity of the lesion (curved arrow) thus confirming the ischemic origin of the apoplexy (Courtesy of Dr C. Magnin)

A specific pattern of alternating subtly T1W hyperintense and hypointense areas within the sellar mass may suggest apoplexy (Figure 2 and 4) before the T1W hyperintense signal more characteristic of blood becomes visible (Figure 5).

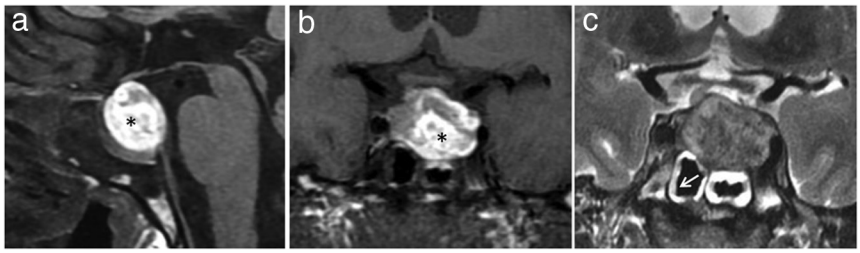
Sequential MRI procedures are able to demonstrate the gradual increase in the T1W hyperintense signal, from the periphery towards the center of the mass, corresponding to the transformation from deoxyhemoglobin to methemoglobin (in methemoglobin the iron is in the ferric state and as such, is paramagnetic explaining why it appears hyperintense on T1WI) (249); in parallel, T2W sequences demonstrate irregular hypointense areas towards the center of the tumor. Sometimes, the entire lesion can exhibit high signal intensity or a fluid-filled space, possibly associated with a fluid level inside the lesion; in this case the upper compartment appears hyperintense while the lower compartment appears isointense (Figure 6).

T2*W MRI, which is a gradient-echo sequence, is even more sensitive. The signal is dependent on T2 and on heterogeneity of magnetic field. It is generally used to detect deposits of hemosiderin even lately after an hemorrhagic event. Thus T2*W MRI can detect intratumoral hemorrhage in pituitary adenomas: it yields a dark "rim," "mass," "spot," or "diffuse" aspect or combinations thereof, which can be useful for assessing both recent and old intratumoral hemorrhage (250).

Thickening of the sphenoid sinus mucosa, predominantly in the compartment just beneath the sella turcica (Figures 2 and 4), was first described by Arita et al on MRI performed during the acute phase of PA (251). A histological study showed that the subepithelial layer of the sphenoid sinus mucosa was markedly swollen. This thickening of the sphenoid mucosa, confirmed in another study in up to 80% of patients with PA of variable severity, was shown to correlate with higher grades of PA and with worse neurological and endocrinological outcomes (28). This thickening does not indicate infectious sinusitis nor rule out transsphenoidal surgery, but is likely vascular in nature, from an increase in pressure in the venous system draining the sinus area – an indirect result of the tumor and the increased intrasellar pressure.

If conservative treatment is chosen, spontaneous shrinkage of the sellar mass may be observed within a few weeks (184, 252) (Figure 6)

Figure 4.

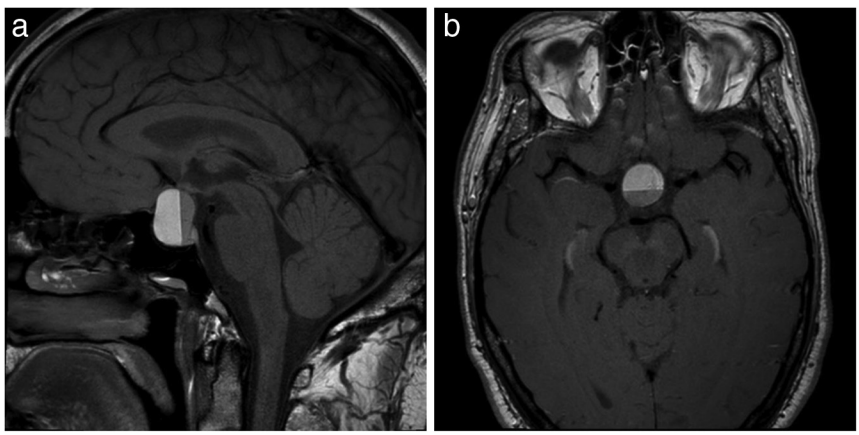


Typical aspect of hemorrhagic pituitary apoplexy on MRI, four days after symptom onset.

a- sagittal, and b- coronal T1W sequences showing a frankly hyperintense pituitary mass (asterisk),

c- on coronal T2W sequences, the lesion is hypointense and the sphenoid sinus mucosa appears hyperintense and thickened (arrow).

Figure 5.



MRI in a patient with pituitary apoplexy, showing a fluid level inside the pituitary lesion; the upper compartment is hyperintense while the lower compartment is isointense (T1-weighted sequences, sagittal (A) and axial (B) views.

MANAGEMENT OF PITUITARY APOPLEXY

A matter of debate

The course of PA is highly variable. Histological features may be important for prognostication: simple tumor infarction alone tends to produce less severe clinical features at presentation, some of which may be present before diagnosis, and have a better outcome than hemor-

rhagic infarction or frank hemorrhage (43).

In mild forms, headache, visual abnormalities and pituitary deficiencies (if not present before onset of PA) develop slowly and persist for several days or weeks. In the most acute and severe forms, blindness, coma, neurological signs and hemodynamic problems may occur within hours. If the correct diagnosis is not made promptly and decompresssion and corticosteroid treatment is not performed, death may ensue as a result of adrenal failure and/or neurological complications. Acute PA is thus a true medical emergency. Most cases, however, fall between these two extremes, with headache and visual disturbances developing over several days.

Recovery of neurological, ophthalmological and endocrine function is also highly variable. Altered consciousness improves after decompression; altered visual fields and acuity also tend to improve after surgery, particularly when they were normal before the acute episode. Permanent sequelae may occur, however, particularly in cases with evidence of optic nerve atrophy. Ophtalmoplegia generally resolves but this may take several weeks. Endocrine function often remains at least slightly altered.

The treatment aims are to improve symptoms and relieve compression of local structures, particularly the optic pathways. Surgical decompression is the most rapid means of achieving these goals (12–16, 27, 29, 31, 33–49). The dramatic picture presented by many patients probably explains why PA is considered a neurosurgical emergency and has almost always been treated surgically in the past (7, 180, 253, 254). However, surgery may also be harmful, with a risk of postoperative CSF rhinorrhea, posterior pituitary damage (risk of permanent diabetes insipidus) and an increased likelihood of hypopituitarism due to removal of or damage to normal pituitary tissue. Fortunately, in experienced pituitary centers, these complications are very rare and this does not prevent to propose surgery when symptoms are severe and rapidly installed and/or when the tumor is large.

As some patients recover normal visual and endocrine function following conservative steroid-based management, the optimal management of acute PA is controversial. At all events, PA must be managed by an expert multidisciplinary team including an ophthalmologist, neuroradiologist, endocrinologist and neurosurgeon (17).

Steroid therapy is mandatory

As corticotropic deficiency is present in the vast majority of patients at PA onset and may be life-threatening, whether treated surgically or conservatively, corticosteroids should be administered intravenously (IV) as soon as the diagnosis is confirmed: it will consist of hydrocortisone 50 mg every 6 hours (52, 255), or a bolus of 100–200 mg followed by 50–100 mg every 6 hours IV (or intramuscularly (IM)) (220, 256–258), or 2–4 mg/h by continuous intravenous (IV) administration (17). Patients in shock should initially receive 5% dextrose (to prevent hypoglycemia) in normal saline IV (17, 213, 214)

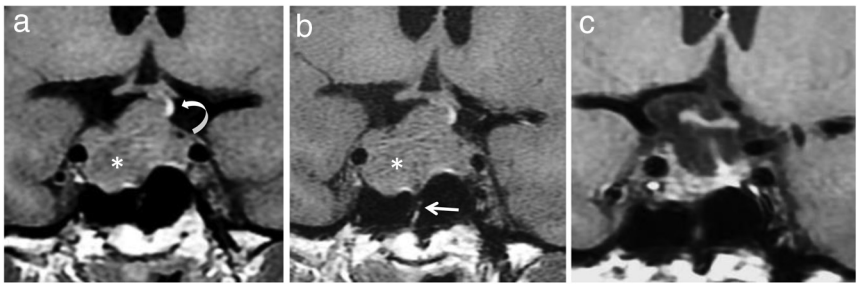
Surgical approach

If surgical management is chosen, the transsphenoidal approach is almost always recommended because it allows good decompression of the optic pathways and neuroanatomic structures in contact with the tumor, and because it is associated with low postoperative morbidity and mortality (17).

Transsphenoidal surgery now usually involves transnasal septal displacement rather than the classical sublabial transseptal approach (259). Some neurosurgeons prefer to use an the operative microscope, others prefer the use of an endoscope.

Even if surgical complications are rare, particularly in experienced hands, CSF leakage and diabetes insipidus (sometimes permanent) may occur (29, 31, 260, 261). Surgical pa-

Figure 6.



Serial imaging studies in a patient with ischemic pituitary apoplexy.

a. Two days after symptom onset, T1W image shows an heterogeneous pituitary mass (asterisk). Note the ectopic position of the posterior pituitary represented by a T1 hyperintense nodule below the optic chiasm (curved arrow)

b. 48 hours later, T1W image does not show any hyperintense area within in the pituitary mass, suggesting purely necrotic apoplexy. Note the slight thickening of the sphenoid sinus mucosa (straight arrow).

c. Four months later, after conservative management, T1WI demonstrates a spontaneous shrinkage of the tumor.

pers dealing with PA rarely mention the complication rate. Nevertheless, it seems that endocrine outcome after elective pituitary surgery is poorer in patients with PA than in patients without PA. Indeed, in a study comparing patients operated from pituitary adenomas complicated or not with PA, those with PA had a worse endocrine outcome with a frequency of hypopituitarism increasing (from 45% at presentation to 71% during follow-up, odds ratio (OR) = 4.7, CI,1.30–25.33, $P = .013$) in the PA group, while it did not change in the control group (from 48% at presentation to 55% during follow-up, OR = 1.5, CI = 0.68–3.41, $P = .362$) (31). Much of this, however, is secondary to damage to the normal gland from the initial apoplectic event.

Another important point is that, in this acute setting, the operation may be performed by an on-call neurosurgeon rather than by a skilled pituitary neurosurgeon, as underlined in UK guidelines (17), and this may increase the risk of adverse events.

Conservative approach

Reports of spontaneous clinical improvement and shrinkage (or disappearance) of apoplectic pituitary adenomas suggest that a conservative approach may be appropriate in selected cases. Pelkonen et al (1978) were among the first to propose a conservative approach, after observing not only spontaneous recoveries but also cases in which the apoplexy appeared to cure hormonal hypersecretion (GH, ACTH, etc.,) (8). Other authors subsequently also advocated a conservative approach (9, 10).

In 1995, Maccagnan et al reported the results of a prospective study in which they treated pituitary apoplexy with high-dose steroids (11). Only patients whose visual impairment or altered consciousness failed to improve underwent surgery. Conservative steroid treatment was possible in 7 of 12 patients, leaving only 5 patients who needed surgery. Visual deficits resolved in 6 of the 7 patients and improved in the remaining patient. Importantly, the post-treatment prevalence of pituitary hormone deficiency and the incidence of tumor regrowth were similar in conservatively and surgically treated patients.

Surgical or conservative management?

The risk-benefit ratio of conservative treatment vs surgery must be carefully evaluated, in terms of not only visual outcome and pituitary function but also subsequent tumor growth. Indeed, what is the point of conservative treatment during the acute phase of pituitary apoplexy if surgery will ultimately be necessary? On the other hand, the potentially serious complications of surgery need to be taken into account (19).

Five large retrospective studies have compared the outcomes of conservatively and surgically treated patients with pituitary apoplexy (12–16). As their authors acknowledged, these studies suffered from a selection bias due to their retrospective design: indeed, the patients in the conservative group generally had less severe ocular defects than those in the surgical group (Table 5). In the study by Bujawansa et al (16), retrospective calculation of the Pituitary Apoplexy Score (PAS, see above), (17, 262) showed that patients treated with early surgery had lower mean PAS values than those treated conservatively.

Outcome of ocular palsies

In published series (Table 5), oculomotor palsies resolved completely in 75% to 100% of patients without surgery, and in 31% to 57% of patients with surgery (12–16). This lack of benefit of surgery is not surprising, as ocular palsies carry spontaneously a relatively good prognosis even if it may take several weeks or months to resolve (18).

Outcome of ocular defects

Surgical decompression normalizes visual acuity in about one-half of cases and improves it in another 6% to 36% of cases (13–15). Visual field defects normalize after surgery in 30%–60% of cases and improve in another 50% (Table 1). Unfortunately, visual outcome is poorer in patients with more severe disorders such as monocular or binocular blindness, irrespective of whether management is conservative or surgical (14, 32, 263).

The outcome of visual acuity or field defects is similar with conservative treatment: in studies comparing the two strategies, visual acuity normalized after conservative management in 60%–100% of patients and improved in 25%, while visual field defects normalized in 50%–100% of cases and improved in 25% (12–16) (Table 3). One study, in which patients with contraindications to surgery (anesthetic risk) were treated with steroids alone, showed that blindness resolved in about 50% of patients treated with conservative and surgical approaches (14).

It has been argued that conservatively treated patients may have less severe visual defects than surgically treated patients, and that this might explain why the improvement is at least as good in the former as in the latter (16, 17, 52). The number of patients with visual defects was effectively higher in the surgical groups of published series (12–15). Visual defects were also more severe, notably in Gruber's study, in which the proportions of patients with very poor visual acuity and $> 50\%$ field loss were clearly higher in the surgical group (14). Nevertheless, it remains that visual deficits either resolved or improved substantially in almost all the patients in both the surgical and conservative treatment groups (Table 3).

Table 5. Main characteristics of patients with pituitary apoplexy at presentation and outcome after conservative or surgical management in 5 retrospective comparative studies

Author (reference)	Ayuk *et al.* (12)			Gruber *et al.* (14)			Sibal *et al.* (13)			Leyer *et al.* (15)			Bujawansa *et al.* (16)		
Type of management	Conservative	Surgery	P	Conservative	Surgery	P	Conservative	Surgery	P	Conservative	Surgery	P	Conservative	Surgery	P
N	18	15	-	20	10	-	18	27	-	25	19	-	22	33	-
Mean age (y) (range)	NA	NA	-	54 (23–84)	46 (17–70)	-	45.7 (25–72)	50.7 (25–72)	0.4	58 (29–81)	50 (12–83)	-	NA	NA	-
Male/Female	NA	NA	-	16/4	7/3	-	9/9	19/8		10/15	7/12	-	NA	NA	-
AT PRESENTATION															
Number (%) with decreased visual acuity	NA	NA	-	11 (55)	7 (70)	-	4/15 (26)	14/24 (58)	0.01	8 (32)	16 (84)	-	NA	NA	-
Number (%) with visual field defect	6 (33)	7 (46)	ns	4 (20)	6 (60)	-	4/17 (24)	16/25 (64)	0.01	5 (20)	14 (74)	-	10 (45)	13 (39)	-
Number (%) with ocular palsy	7 (39)	8 (53)	ns	12 (60)	3 (37)	-	8/17 (47)	14/26 (54)	0.6	12 (48)	10 (53)	-	15 (68)	18 (54)	-
Number (%) with hypopituitarism	13 (87)	15 (83)	ns	15 (75)	9 (90)	-	13/18 (72)	21/24 (87)	0.39	20/23 (87)	15/17 (88)	-	NA	NA	-
OUTCOME															
Decreased visual acuity															
- Complete resolution	NA	NA	-	5/11 (45)	4/7 (57)	-	3/4 (75)	8/14 (57)	-	6/8 (75)	7/16 (44)	-	NA	NA	-
- Partial/near complete resolution	NA	NA	-	4/11 (36)	2/7 (28)	-	1/4 (25)	5/14 (36)	-	1/8 (12)	1/16 (6)	-	NA	NA	-
- No improvement	NA	NA	-	2/11 (19)	1/7 (15)	-	0	1/14 (7)	-	1/8 (12)	6/16 (37)	-	NA	NA	-
Visual field defect															
- Complete resolution	6/6 (100)	4/7 (57)	ns	2/4 (50)	2/6 (33)	-	3/4 (75)	7/16 (43)	-	4/5 (80)	8/14 (57)	-	6/10 (60)	4/13 (31)	ns
- Partial/near complete resolution	0	NA	-	1/4 (25)	3/6 (50)	-	1/4 (25)	8/16 (50)	-	NA	1/14 (7)	-	NA	NA	-
- No improvement	0	NA	-	1/4 (25)	1/6 (17)	-	0	1/16 (7)	-	NA	4/14 (29)	-	NA	NA	-
Ocular palsy															
- Complete	7/7 (100)	5/8 (63)	ns	10/12 (83)	2/3 (66)	-	6/8 (75)	9/14 (64)	-	11/12 (92)	6/10 (60)	-	15/15 (100)	15/18 (83)	ns
- Partial/near complete resolution	0	NA	-	2/12 (17)	1/3 (33)	-	2/8 (25)	4/14 (29)	-	1/12 (9)	1/10 (10)	-	0	3/18 (17)	-
- No improvement	0	NA	-	0	0	-	0	1/14 (7)	-	0	2/10 (20)	-	0	0	-
Endocrine impairment															
- Normal function	NA	NA	-	1 (5)	2 (20)	-	2 (11)	5 (19)	-	9 (37)	3 (16)	-	2/22 (9)	3/33 (9)	ns
- Corticotropic deficiency	13/18 (72)	13/15 (87)	ns	(68)	(60)	-	NA	NA	-	NA	NA	-	NA	NA	-
- Thyrotropic deficiency	9/15 (60)	13/15 (87)	ns	(70)	(68)	-	NA	NA	-	NA	NA	-	NA	NA	-
- Gonadotropic deficiency	15/18 (83)	10/15 (67)	ns	(80)	(86)	-	NA	NA	-	NA	NA	-	NA	NA	-
Tumor growth															
- Recurrence of pituitary adenoma	1 (5)	1 (6)	-	0	6 (60)	-	4 (22)	1 (4)	-	4/24 (16)	0	-	NA	NA	-

NA, non available.

Outcome of pituitary function

One of the main arguments in favor of the surgical approach is that surgical decompression can improve pituitary function, which is frequently impaired. After surgery, pituitary function recovers partially or completely in more than 50% of cases (24, 52, 201). Various series suggest that only about 20% of PA patients do not require replacement therapy after surgery (52). But is conservative treatment really less effective than surgery in terms of functional pituitary outcome? In the five studies which compared the two approaches, the proportions of patients with post-treatment hypocortisolism, hypothyroidism and hypogonadism were roughly the same in the surgical and conservative treatment groups (12–16).

Whatever the management approach, the endocrine prognosis is poor in patients with pituitary apoplexy, who frequently suffer irreversible pituitary damage. However, in our opinion, endocrine outcome is not a primary criterion when choosing between surgical and conservative treatment, as the two approaches seem to have the same impact on functional pituitary recovery. Nevertheless, it must be emphasized that in the absence of controlled studies, comparisons between the two approaches are hazardous.

Outcome of the pituitary tumor

Another major argument in favor of the surgical approach is that surgery not only relieves the symptoms of pituitary apoplexy but also removes the pituitary tumor. However, tumor shrinkage is frequent following apoplexy, many patients having no visible tumor remnant after the episode (Figure 6). Very few studies have compared the "completeness" of tumor disappearance between patients receiving surgery and conservative treatment for apoplexy. Recently, a long-term follow-up study showed a recurrence rate of 11.1% an average of 6.6 years after surgery (41). In four of the five comparative studies in which this information is available (Table 5), the incidence of tumor regrowth was low and similar with the two approaches in one study (12), while it was higher after surgery in another (14) and lower after surgery in two others (13, 15)! Thus, the respective merits of the two approaches in terms of tumor control are currently difficult to judge.

Whatever the therapeutic method which is used, long term surveillance of these patients is recommended as these adenomas (often non functioning) may recur (Table 1).

Can imaging help to choose between conservative and surgical treatment?

There are few data on the value of CT or MRI for prognostication or decision-making during the acute phase of PA. Compared to CT, MRI allows more precise evaluation of adjacent anatomical structures (optic apparatus, cavernous sinus, etc.,) (52, 243, 247) and provides earlier diagnosis (248). In one study the size of the adenoma and its extension were similar in surgically and conservatively treated patients (12). MRI did not predict the likelihood or severity of ocular paresis or field defects. Even when the tumor was very large, conservative management was accompanied by tumor shrinkage (12). A single large hypodense area within the tumor on CT might be associated with better subsequent tumor shrinkage than are several small hypodense areas (11). In another study, MRI findings were found to be associated with clinical status and outcome: patients with simple infarction had less severe clinical features and better outcomes than those with hemorrhagic infarction or hemorrhage (211).

UK guidelines for the management of pituitary apoplexy

Guidelines were recently proposed in the UK for the management of patients with pituitary apoplexy (17). They recommend surgical decompression in case of "significant neuro-ophtalmic signs or reduced level of consciousness". This seems a very reasonable option. A management algorithm is proposed in these guidelines. If surgery is chosen, then its timing is important. Visual defects used to be considered a neurosurgical emergency, but there seems to be no difference in outcome when surgery is performed in the first three days or during the first week after symptom onset (32, 205, 264). In contrast, the prognosis of visual defects is less favorable when surgery takes place more than a week after onset: in one study, 86% of cases improved or resolved when surgery took place within 8 days, vs 46% between 9 and 34 days (24).

The higher number of patients treated conservatively by the same team nowadays (29.9%) (21) compared as in the past (2.7%) (7) may be related to the lower rates of ophtalmoparesis and visual field defects in the current series which may be explained by earlier diagnosis enabled by MRI.

Conclusion

Pituitary apoplexy, due to sudden hemorrhaging and/or infarction of the pituitary gland, generally within a pituitary adenoma, can be difficult to diagnose. A CT or MRI scan confirms the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components. Corticotropic deficiency may be life-threatening if left untreated, and glucocorticoids must therefore always be introduced immediately. Owing to the highly variable course of this syndrome and the lack of randomized prospective studies, optimal management of acute pituitary apoplexy remains controversial. Some authors advocate early transphenoidal surgical decompression for all patients, whereas others adopt a conservative approach for selected patients, namely those without visual acuity or field defects and with normal consciousness. The size of the tumor on MRI is also an important part of the clinical decision-making process. If conservative treatment is chosen, then careful monitoring of visual signs and symptoms is necessary, and surgical decompression is recommended if visual disorders do not improve or if they deteriorate. However, clinical deterioration can be rapid and patients may not be able to be hospitalized for observation which may limit this approach.

Re-evaluation of pituitary function and the tumor mass in the months following the acute apoplectic episode is mandatory to determine whether or not the pituitary defect is permanent, to determine the possible hypersecretory nature of the adenoma, and to initiate follow-up of a possible tumor remnant.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed for articles published from January 1970, to December 2014, with the terms « pituitary apoplexy », « pituitary hemorrhage, « pituitary infarction ». Articles identified by these searches and relevant references cited in those articles were reviewed. Only articles published in English were included. Review articles and book chapters are also cited to provide readers with more details and more references than this Review has room for. We largely selected those published in the past 15 years, but did not exclude commonly referenced and seminal older articles.

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