

NOTE

Pituitary Apoplexy Induced by a Combined Anterior Pituitary Test: Case Report and Literature Review

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Abstract. We report the case of a 31-year-old woman with a pituitary adenoma who suffered symptomatic pituitary apoplexy. The patient developed a severe headache 2 min after undergoing a combined anterior pituitary function (CAP) test. Emergent computed tomography revealed a hemorrhagic pituitary tumor with evidence of a small subarachnoid hemorrhage. The headache improved spontaneously within half a day. Transsphenoidal surgery was performed 4 days later. Histologic examination demonstrated that the tumor was an eosinophilic adenoma with areas of diffuse hemorrhage. Although pituitary apoplexy caused by endocrinological testing has been reported in only 28 patients, apoplexy caused by a CAP test has been reported in only 1 patient. All of the previous cases had pituitary macroadenomas, 69% of which were involved in suprasellar extension. Non-functioning adenomas (24%) and prolactinomas (24%) were the most often affected by endocrine stimulation tests. With respect to the stimulants of pituitary adenomas, gonadotropin-releasing hormone (76%), TSH-releasing hormone (69%), and insulin (34%) were primarily responsible for the apoplexy. This case report with the literature review suggests that routine testing on pituitary function should be ordered cautiously given the risk of possible apoplexy.

Key words: Pituitary adenoma, Pituitary apoplexy, Endocrinologic stimulation tests, Combined anterior pituitary (CAP) test, Acromegaly

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PITUITARY apoplexy is characterized by the sudden onset of headache, vomiting, visual impairment, diplopia, changes in the level of consciousness, and hormonal dysfunction. This condition is considered to be caused by hemorrhage or hemorrhagic infarction of a preexisting pituitary adenoma [1, 2]. Although pituitary apoplexy following dynamic pituitary function testing has been previously reported [3–24], the etiology of the apoplexy has not been clarified. We report a patient with macroadenoma who developed pituitary apoplexy following dynamic pituitary

function tests, and discuss the causality of the manifestation of apoplexy from previous reports.

Case Report

A 31-year-old woman with a 1-year history of visual disturbances was referred to our hospital for evaluation of a suprasellar tumor detected by magnetic resonance imaging (MRI). The patient had experienced a weight gain of 10 kg and gradual enlargement of her feet and fingers over a 3-year period. She had suffered from amenorrhea since the age of 28 years, but suffered neither polyuria nor polydipsia. Physical examination revealed the following: height, 162 cm; weight, 66 kg; no typical acromegalic features but her feet and fingers were slightly enlarged; blood pressure, 110/70 mm Hg;

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heart rate, 60 bpm, regular; no focal abnormalities neurologically except bilateral hemianopsia; neither goiter, lymphadenopathy nor pretibial edema were observed. Skull roentgenogram demonstrated marked expansion of the sella. MRI revealed a large heterogeneous pituitary mass (area, 7.4 cm²) involving the optic chiasm and the left cavernous sinus (Fig. 1). Basal levels of various hormones are summarized in Table 1a. Serum GH, insulin like growth factor-1 (IGF-1), ACTH and PRL concentrations were increased. In contrast, gonadotropins and thyroid hormones were partially disturbed.

Combined anterior pituitary (CAP) testing with 1 µg/kg body weight of CRH, GH releasing hormone (GRF), gonadotropin releasing hormone (GnRH) and 200 µg of TRH were planned to evaluate the patient's preoperative hormonal responses. But when 20 µg of CRH, GRF, and GnRH, and 100 µg of TRH were actually administered during the 2 min after the injection, the patient complained of a severe headache followed by nausea and a feeling of chest oppression. The patient was alert and had no focal symptoms or progressive visual disturbances.



Fig. 1. Pituitary magnetic resonance imaging (MRI). Cranial MRI revealed a large pituitary mass involving the optic chiasm and left cavernous sinus. There was heterogeneous enhancement of the tumor with gadolinium.

Table 1a. Basic endocrinologic data on admission

ACTH	77.2 pg/mL (4.4–48)	TSH	0.53 µU/mL (0.55–4.8)
GH	53.1 ng/mL (0.28–8.7)	FT3	3.31 pg/mL (4–5.8)
PRL	61.3 ng/mL (<30)	FT4	0.86 ng/dL (1.03–2.21)
LH	0.45 mIU/mL (1.5–5)	F	12.5 µg/dL (5–21)
FSH	2.24 mIU/mL (4–10)	IGF-I	629 ng/mL (150–214)

FT3, free triiodothyronine; FT4, free thyroxine; F, cortisol; IGF-1, insulin like growth factor-1; values in parenthesis indicate normal values.

Table 1b. Results of combined anterior pituitary (CAP) test

		basal value	peak value	peak time (min)
ACTH	(pg/mL)	44.8	71.3	30
F	(µg/dL)	6.8	9.3	30
GH	(ng/mL)	61.2	147.2	30
TSH	(µU/mL)	0.71	8.13	30
PRL	(ng/mL)	59.3	110.7	15
LH	(mIU/mL)	1.61	6.52	60
FSH	(mIU/mL)	0.26	4.04	90

F, cortisol.



Fig. 2. Emergent cranial computed tomography (CT). Emergent CT revealed pituitary bleeding not only within the tumor but also around the tumor and in the subarachnoid space, suggesting pituitary apoplexy.

Emergent computed tomography (CT) revealed that the pituitary mass had enlarged (area, 8.7 cm²), and there was evidence of bleeding not only within the tumor but also around the tumor and in the subarachnoid spaces (Fig. 2). The severe headache continued for about half a day. Because the symptoms have gradually improved, emergent surgery was not performed. The results of the pituitary stimulation tests are shown in Table 1b, and reflect a hyperresponse of GH to GRH and poor responses of LH and FSH to GnRH.

Four days after the CAP test, transsphenoidal surgery was performed. There was evidence of a small hemorrhage around the tumor in the subarachnoid space. The tumor was soft and yellow and contained blood. The tumor was evacuated with a regular microsurgical suction tube, but was not resected because of the presence of tight adhesions to the cavernous sinus. Histological examination revealed that the tumor was an eosinophilic pituitary adenoma. Postoperatively, the patient's visual disturbance resolved and the PRL concentration was normalized, but since the gonadotropin response to GnRH remained attenuated and the basal GH

concentration was still as high as 10–15 ng/mL, she has been treated with self-injection of octreotide (100 µg/day) and replacement of estrogen and progesterone. Half a year after the surgery, her GH level has been lowered to 3–5 ng/mL, and the IGF-1 level has settled to below 200 ng/mL one year after the start of the octreotide injection.

Discussion

The classic definition of pituitary apoplexy is the acute, life-threatening loss of pituitary function. Hemorrhagic infarction causing apoplexy most commonly occurs in the presence of a pituitary tumor but may also occur spontaneously in a normal gland [1, 2]. Since 1975, pituitary apoplexy induced by pituitary function testing has been reported in 28 patients (Table 2) [3–24]. All of the reported cases have involved macroadenomas, including 69% (20 of 29 patients) with suprasellar extension of the tumor. Another common characteristic is the acute onset of symptoms after pituitary stimulation. Pituitary apoplexy developed within 3 days after the administration in all of the patients, and occurred within 30 min in 70% of the patients.

The relationship between the type of tumor and the stimulants with respect to the development of apoplexy has not been discussed in previous reports. We therefore analyzed this relationship in previous reports (Table 3). Of the apoplectic adenomas, prolactinomas (24%) and growth hormone producing adenomas (21%) were the most common, whose sequence was in keeping with that of frequency in pituitary adenomas [25]. Interestingly, apoplexy occurring in patients with non-functioning adenomas was also common (24%). Bills *et al.* reported that 94% of patients with pituitary apoplexy had pituitary tumors demonstrable by CT, and that null cell adenomas occurred more frequently (52%) than functioning adenomas [1]. Among various stimulants, TRH is most likely to cause infarction and hemorrhage probably because of its vasoactive properties [10, 12, 18]. In our review of the literature, GnRH, TRH and insulin stimulation were associated with the development of pituitary apoplexy (Table 3). With respect to GnRH, therapy with goserelin or triptorelin for the treatment of prostate cancer

Table 2. Literature review of cases of pituitary apoplexy after pituitary function testing to assess pituitary adenoma

Author (Year)	Age/Gender	Tumor	Size	Stimulants	Onset of apoplexy
Dunn (1975)	22/F	GH-oma	macro	Glc(25 g)+Ins(0.3 U/kg)+TRH[400]	2 d
Silverman (1978)	31/M	PRL-oma	macro+SS	Chlorpromazine(25 mg)	90 m
Jordan (1979)	21/F	ACTH-oma	macro	Dexamethasone(20 mg)	3 d
Cimino (1981)	48/M	non-F	macro+SS	GnRH[100]+TRH[200]	20 m
Drury (1982)	59/F	non-F	macro+SS	Gluca(1.5 mg)+GnRH[100]+TRH[200]	5 m
	66/M	GH-oma	macro	TRH[200]	10 m
	39/F	PRL-oma	macro+SS	GnRH+TRH	2–3 m
	28/M	PRL-oma	macro+SS	GnRH+TRH	15 m
Bernstein (1984)	48/M	non-F	macro	GnRH[100]+TRH[200]+Ins(0.1 U/kg)	5 m
Korsic (1984)	56/M	FSH-oma	macro+SS	GnRH[100]	2 h
Chapman (1985)	39/F	PRL-oma	macro+SS	GnRH[100]+TRH[200]+Ins(0.15 U/kg)	30 m
Yatsuzuka (1986)	20/M	PRL-oma	macro	GnRH[100]+TRH[500]+Ins(0.1 U/kg)	?
	36/M	PRL-oma	macro+SS	GnRH[100]+TRH[500]+Ins(0.1 U/kg)	?
Lever (1986)	19/F	GH-oma	macro	TRH[200]	2 m
Shirataki (1988)	50/F	GH-oma	macro+SS	Bromocriptine (2.5 mg)	2 h
Harvey (1989)	50/M	?	macro	Ins(0.15 U/kg)	during
Arafah (1989)	41/F	PRL-oma	macro+SS	GnRH[100]	60 m
Kimura (1989)	14/M	non-F	macro+SS	GnRH+TRH+Ins	20 m
Yada (1992)	60/F	?	macro+SS	GnRH[100]+TRH[500]+Ins(5 U)	10 m
Masson (1993)	54/M	FSH-oma	macro+SS	GnRH[100]	20 m
Fujiwara (1993)	67/F	GH-oma	macro+SS	ACTH+GnRH	30 m
Haakens (1994)	48/M	FSH-oma	macro+SS	GnRH[100]+TRH[500]+Ins(0.1 U/kg)	15 m
Vassallo (1994)	54/M	non-F	macro+SS	GnRH[100]+TRH[500]	10 m
Frankart (1995)	69/M	?	macro	GnRH[100]+TRH[200]+CRH[100]+GRH[1/kg]	30 m
Masago (1995)	81/M	?	macro+SS	GnRH[100]+TRH[200]+levodopa(500 mg)	2 h
	64/M	FSH-oma	macro	GnRH[100]+TRH[200]	2 d
Abe (1995)	48/M	non-F	macro+SS	GnRH+TRH+Ins	4 m
	74/F	non-F	macro+SS	GnRH	2–3 m
Current patient	31/F	GH-oma	macro+SS	GnRH[20]+TRH[100]+CRH[20]+GRH[20]	2 m

Glc, glucose; Ins, insulin; GnRH, gonadotropin releasing hormone; GRH, growth hormone releasing hormone; Gluca, glucagon; non-F, non-functioning tumor; SS, suprasellar extension; macro, macroadenoma; d, day; h, hour; m, minute; brackets include the value of μg .

Table 3. Summary of literature review of cases of pituitary apoplexy associated with endocrinologic testing

Pituitary tumor (Number of cases)	GH-oma (6)	PRL-oma (7)	FSH-oma (4)	ACTH-oma (1)	non-F (7)	unknown (4)	total (29)
Hypothalamic stimulants							
GnRH	2	6	4	–	6	3	21
TRH	4	5	2	–	6	3	20
GHR	1	–	–	–	–	1	2
CRH	1	–	–	–	–	1	2
Others							
Glucose	1	–	–	–	–	–	1
Insulin	1	3	1	–	3	2	10
Glucagon	–	–	–	–	1	–	1
Dexamethasone	–	–	–	1	–	–	1
Bromocriptine	1	–	–	–	–	–	1
Levodopa	–	–	–	–	–	1	1
Chlorpromazine	–	1	–	–	–	–	1

GnRH, gonadotropin releasing hormone; GRH, growth hormone releasing hormone; non-F, non-functioning tumor.

induced apoplexy in occult pituitary macroadenomas [26, 27]. White *et al.* reported that the mechanism responsible probably involved an increase in intracellular glycoprotein subunit synthesis or vasoconstriction rather than a sudden increase in gonadotropin synthesis [28]. In the cases we reviewed, post-stimulation hormonal excess is most likely not responsible for the development of apoplexy, because of the high incidence of non-functioning tumors. The lack of an association between the time at which stimulated hormone release peaks and the time of onset of pituitary apoplexy also supports this. Abe *et al.* described two patients with non-functioning pituitary adenomas with apoplexy induced by hormonal stimulation, whose resected tumors had *in situ* DNA strand breaks, suggesting the presence of apoptotic cells [24].

The CAP testing is a screening test used in patients with suspected pituitary dysfunction. In our patient, because the basal concentrations of TSH and gonadotropins were suppressed while those of GH, PRL and ACTH were high, the CAP test was planned for preoperative estimation of the pituitary gland. Simultaneous administration of four hypothalamic releasing hormones and measurement of the release of target pituitary hormones permit the assessment of pituitary reserve in an ambulatory care setting [29]. TRH, GnRH and insulin are each capable of inducing apoplexy when administered alone [7, 9, 12, 14, 24]. But in most cases it is difficult to determine which hormone caused the apoplexy, because the hormones are usually given in combination. Haakens *et al.* first reported a case of pituitary apoplexy associated with CAP testing of a non-functioning tumor [20]. In apoplexy caused by CAP testing, the effects of GRH and CRH should not be neglected, but there have been no reports of pituitary apoplexy caused by either GRH or CRH alone. Because CRH has begun to be used commonly, the potential for CRH to cause apoplexy should be investigated. In the present case, although the CAP testing was actually performed with only less than half of the regular doses, the apoplexy crisis occurred within 2 min. This finding

indicates that the apoplexy which followed pituitary function testing may be independent of the administered doses. Based on the characteristics of our patient and our literature review, it appears that a common clinical feature of these cases is the increased size of the macroadenoma which often involves the suprasellar region. In our patient, radiographic findings indicated mild enlargement of the adenoma after CAP testing. Lever *et al.* described pituitary enlargement on CT examination after TRH injection [12], and Yada and Abe *et al.* also reported pituitary enlargement after GnRH, TRH and insulin combined testing [17, 24]. These findings suggest that TRH may directly affect the intrasellar pressure. Among the other stimulants, the contribution of glucose or glucagon to apoplexy is unknown, but the fact that dexamethasone or bromocriptine alone caused apoplexy suggests that even the pituitary suppressive testing might affect the intrasellar pressure. Of 29 patients including ours, 22 were surgically treated and 7 patients were treated conservatively. Of the 7 patients, 5 had spontaneous remissions, 1 was treated with glucocorticoid and 1 received bromocriptine. Although 25 of the 29 patients (87%) reported improvement, 4 patients (13%) had persistent focal symptoms (amaurosis, aphasia, hemiparesis, etc.). To prevent life-threatening complications resulting from the endocrinologic examination, it is necessary to diagnose apoplexy quickly and determine if surgery is indicated. Bills *et al.* demonstrated that surgical treatment within a week of the onset of apoplexy resulted in significant recovery of visual acuity [1].

In summary, we described a patient with pituitary apoplexy induced by CAP testing with small doses. Our findings suggest that careful consideration of the benefit of CAP testing is necessary for all macroadenomas. Furthermore, I hope that the review of the reports of pituitary apoplexy caused by various stimulants will be helpful in clarifying the mechanism responsible for this complication. To evaluate dynamic pituitary function both non-invasively and precisely even in patients with suprasellar extension of the tumor, a new alternative testing method is desirable.

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