NOTE

Infarction Followed by Hemorrhage in Pituitary Adenoma due to Endocrine Stimulation Test

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Abstract. A 63-year-old man, who presented with visual field loss due to pituitary tumor, received an intravenous bolus injection of thyrotropin and gonadotropin releasing hormones and insulin as a preoperative evaluation. He complained of severe headache and nausea 2 hours after injection. Emergent CT scan showed no evidence of intratumoral hemorrhage. The next day, his visual field became null. MR images revealed heterogeneous mixed intensity lesions. Under diagnosis of pituitary apoplexy, he underwent transsphenoidal tumor removal 30 hours after onset. Intraoperative and pathological findings showed tumor hemorrhage and adjacent necrotic change. Fourteen cases with sufficient clinical detail in the literature are reviewed: All of the cases had macroadenoma with suprasellar extension. Testing agents were gonadotropin and thyrotropin releasing hormones in 92.9% and 85.7% of cases, respectively. Headache was an initial symptom and started within two hours in all cases but one. Half of the cases showed no change on CT scan. However, tumor hemorrhage was evidenced in 92.9% of cases with or without necrosis due to ischemic change, intraoperatively or pathologically. It is speculated that pituitary apoplexy often starts with infarction possibly due to vasoactive effect of testing agents and later develops into hemorrhage. Therefore, it is necessary to observe patients closely at least a few hours after endocrine stimulation test, and MR imaging may make an earlier diagnosis for the pituitary apoplexy since CT scan often shows no density change in the pituitary adenoma.

Key words: Pituitary apoplexy, Endocrine stimulation test, Macroadenoma, Neuroimaging
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PITUITARY apoplexy is a well-known syndrome caused by the sudden expansion of preexisting pituitary tumor due to hemorrhage and/or infarction. Its clinical characteristics are sudden onset of severe headache, nausea, confusion, visual disturbance and ophthalmoplegia. Although endocrine stimulation test is known to be one of the precipitating factors associated with pituitary apoplexy, its pathogenesis has been unclarified. We report a case of adenoma infarction followed by hemorrhage, which occurred after bolus injection of hypothalamic hormones and

insulin as a preoperative evaluation to pituitary macroadenoma. The purpose of this report is to elucidate the clinical characteristics of pituitary apoplexy and its pathomechanism after endocrine stimulation test.

Case report

A 63-year-old man was referred to our hospital with a two-month history of visual field defect and decreased visual acuity. He had no other neurological disorders or endocrinological symptoms in the physical examination. On admission his height was 168 cm and his weight 64.4 kg. Blood pressure was 130/90 mmHg, pulse 60 bpm. Visual acuity was 20/20 in the right eye and 8/20 in the left. Visual

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field examination revealed nasal hemianopia on the left side. Extraocular movements were normal. Baseline levels of anterior pituitary hormones were as follows: growth hormone (GH) 0.21 ng/ml, prolactin (PRL) 23.53 ng/ml, thyroid-stimulating hormone (TSH) 1.17 μ U/ml, follicle-stimulating hormone (FSH) 15.39 mIU/ml, luteinizing hormone (LH) 1.10 mIU/ml, adrenocorticotrophic hormone (ACTH) 47.8 pg/ml.

Plain skull X-ray images revealed a "ballooning" and "double floor" of sellae turcica. Magnetic resonance (MR) images showed a pituitary tumor with suprasellar extension (Fig. 1A, B, C), and computed tomography (CT) scan showed a slightly high density mass at the sellae turcica (Fig. 2A).

As preoperative endocrine evaluation, he received an intravenous bolus injection of 500 μ g thyrotropin releasing hormone (TRH), 100 μ g gonadotropin releasing hormone (GnRH), and 6.5 units regular insulin (0.1 units/kg). Two hours after the injection, he complained of severe headache and nausea that persisted all day long. Emergent CT scan images six hours after onset showed no evidence of intratumoral hemorrhage or increase of tumor size (Fig. 2B). Neither his visual field nor acuity deteriorated. Then the next day, he woke up to find that his left vision was null. The light reflex had disappeared in his left eye. Emergent MR imaging was performed at 24 hours after onset revealed a lesion of heterogeneous high and low signal- intensity in the tumor (Fig. 3A,

Fig. 1. A, B: Coronal and sagittal T1-weighted MR images show isointense pituitary macroadenoma with suprasellar extension and displacement of optic chiasm.
C: Sagittal Gd-DTPA enhanced MR image shows the homogeneous enhancement of pituitary macroadenoma.

Fig. 2. A: Plain computed tomography (CT) scan images show a slightly high-density mass lesion in the suprasellar cistern.
B: Emergent CT scan images (6 hours after onset) show neither intratumoral hemorrhage nor expansion of pituitary adenoma.

Fig. 3. Emergent axial (A) and coronal (B) MR images reveal a lesion of heterogeneous high- and low signal-intensity in the pituitary macroadenoma.

Fig. 4. Photograph of specimen stained with hematoxylin and eosin (X150). Hemorrhage and adjacent necrotic area is seen in the papillary chromophobe adenoma.

B). Thirty hours later, the tumor was removed via transsphenoidal approach. Incision of dura mater revealed obvious intratumoral hemorrhage, and the pituitary macroadenoma was subtotally removed. Histological examination revealed hemorrhage and adjacent necrotic area in the papillary type chromophobe adenoma. The adenoma was not especially vessel-rich, and the necrotic area was compatible with an infarction. (Fig. 4)

After the operation, headache and nausea improved. Visual field and acuity improved to the level of preoperative state at a 6-month postoperative ophthalmological examination. Postoperative MR

image showed a near total removal of the adenoma.

Discussion

The cause of pituitary apoplexy is considered to be an endocrine stimulation test in this case, since the headache and subsequent ophthalmological deterioration occurred immediately after the test.

Although causes of pituitary apoplexy are not sufficiently elucidated, there are many precipitating factors such as bromocriptine therapy, estrogen treatment, radiation therapy, head trauma, anticoagulant therapy, pregnancy, angiography, cerebral aneurysm, lumbar puncture, myelography, pneumoencephalography, increased intracranial pressure, nasal catarrh and open heart surgery [1, 2]. While endocrine stimulation test is included as one of the causes, how frequently the pituitary apoplexy occurs due to the test is unknown.

We reviewed the 13 cases in the literature, that had details of the following clinical data. 1. Hypothalamic hormones and/or insulin were used as the endocrine stimulating agents. 2. Pituitary apoplexy was confirmed in operative and/or pathological findings. A total of 14 cases including our own were reviewed and their clinical features are summarized (Table 1) [1-12]. Patients were 9 males and 5 females, from 28 to 71 years of age (mean, 49.6 years). The diagnoses were 7 nonfunctioning adenomas,

Table 1. Reported cases of pituitary apoplexy with pathological and/or operative evidence after endocrine stimulation test Abbreviations. F: female, M: male, TRH: thyrotropin-releasing hormone, GnRH: gonadotropin-releasing hormone, GRF: growth hormone releasing factor, CRH: corticotropin releasing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, GH: growth hormone, CT: computed tomography, MRI: magnetic resonance imaging, T1WI: T1-weighted image, SAH: subarachnoid hemorrhage, ○: no description about doses.

Case		Clinical profiles				Stimulating agents					
No.	Author	Year	Age/ Gender	Diagnosis	Suprasellar extension	Visual symptom	TRH (μ g)	GnRH (μ g)	Insulin (unit/kg)	GRF (μ g)	CRH (μ g)
1.	Bernstein	1984	48/M	not described	+	+	200	100	0.1		
2.	Korsic	1984	56/M	FSHoma	+	+		100			
3.	Chapman	1985	39/F	PRLoma	+	—	200	100	0.15		
4.	Masson	1993	54/M	FSHoma	+	+		100			
5.	Okuda	1994	60/F	non-functioning	+	—	500	100	0.1		
6.	Masago	1995	48/M	non-functioning	+	+	500	100	0.1		
7.	Masago	1995	54/M	non-functioning	+	+	500	100			
8.	Szabolcs	1997	54/M	non-functioning	+	—	200				
9.	Otsuka	1998	31/F	GHoma	+	+	100	20		20	20
10.	Dökmets	1999	28/F	GHoma	+	+	200				
11.	Sanno	1999	55/M	non-functioning	+	—	500	100		100	100
12.	Lee	2000	34/M	GHoma	+	—	400	100	0.15		
13.	Riedl	2000	71/F	non-functioning	+	+	○	○		○	○
14.	Our case	2001	63/M	non-functioning	+	+	500	100	0.1		

3 GH secreting, 2 FSH secreting, 1 PRL secreting and 1 without description. Although all cases had macroadenoma with suprasellar extension, 5 cases had no visual disturbance. This suggests that pituitary apoplexy may occur even in macroadenomas that are not large enough to compress the optic pathway or induce visual symptoms.

With respect to the endocrine stimulating agents, GnRH (92.9%), and TRH (85.7%) were most commonly used. The combinations of testing agents used were as follows: TRH+GnRH+insulin (6 cases), TRH+GnRH+GRF+CRH (3 cases), TRH+GnRH (2 cases), GnRH (2 cases), and TRH (1 case).

Initial symptoms were as follows: headache in all (100%) cases, visual symptoms in 4 (28.6%) cases, nausea in 4 (28.6%) cases, vomiting in 4 (28.6%) cases and chest discomfort or oppression in 2 (14.3%) cases. Deteriorated consciousness, confu-

sion, sweating and burning sensation were noted in 1 (7.1%) case each. Although visual acuity and field impairment as well as ophthalmoplegia are confirmatory signs for pituitary apoplexy, only headache without other ophthalmologic impairment is common as the first clinical sign of pituitary apoplexy after endocrine stimulation tests.

The interval from administration of agents to onset of initial symptom ranged from 2 minutes to 2 hours, but 1 case of Dökmets *et al.* reported an apoplexy at 88 hours after hormone function test [4]. Considering the most common time of occurrence of pituitary apoplexy, it is necessary to observe patients closely at least for a few hours after endocrine stimulation test.

In literature review, tumor hemorrhage was evidenced in 13 (92.9%) cases during operation or in pathological study, and was much more common than infarction alone. However, in our case, CT

Clinical features of pituitary apoplexy				Evidence of pituitary apoplexy	
Initial symptom	Time to onset	CT scan/Time	MRI	Hemorrhage on surgery	Pathology
headache, blurred vision	5 min	no change/day 0	—	not described	infarction
headache, confusion	120 min	heterogeneous/day 1	—	not described	hemorrhage
headache	40 min	low density/day 3	—	+	infarction & hemorrhage
headache, vomiting	20 min	low/day 0	—	+	not described
headache, sweating, nausea	10 min	high with SAH/day 0	—	+	hemorrhage
				with SAH	
headache, blurred vision	15 min	no change/day 0	—	+	hemorrhage
burning sensation, headache, blurred vision, chest discomfort	10 min	no change/day 0	—	not described (necrotic)	hemorrhage
headache, vomiting	60 min	high/day 1	—	+	hemorrhage
headache, nausea chest oppression	2 min	high with SAH/day 0	—	+	not described
				with SAH	
headache, nausea, vomiting, visual disturbance, deteriorated consciousness	88 hours	high/day 5	—	+	hemorrhage
headache	30 min	no change/day 0 high with SAH/day 1	—	+	necrosis
				with necrosis	
headache, vomiting	20 min	no change/day 0 (enhanced CT)	heterogeneous	+	infarction & hemorrhage
headache	during test	no change/day 1	high intensity	not described	hemorrhage
headache, nausea	120 min	no change/day 0	high intensity	+	infarction & hemorrhage

scan did not reveal either density or size changes in the initial study. In the literature as well, the CT findings obtained within 5 days after onset of initial symptoms were as follows: high density in 4 cases, low density in 2, mixed density in 1 and no change in 7. It should be noted that CT scans at acute stage fail to demonstrate specific signs of pituitary apoplexy in about half of the cases. On the contrary, MR imaging was performed in 3 reported cases including our own case without any change on CT scans. All of them showed high and/or mixed intensity on T1-weighted images. Thus CT scan is often useless in detecting early changes of pituitary apoplexy, while MR imaging is useful in early diagnosis of pituitary apoplexy. In addition, it is worthwhile to try diffusion weighted MR imaging which is superior to conventional MR imaging diagnosing at acute phase of cerebral infarction [13].

Various hemorrhagic and ischemic pathomecha-

nisms have been suggested for the development of pituitary apoplexy [14]. Fragile vascular walls of adenomas more readily rupture and cause intratumor hemorrhage. Large adenoma may outgrow their blood supply and develop areas of ischemic necrosis. The trabecular arteries (branches of the superior hypophyseal artery) may be compressed by the adenoma and diaphragm sellae. These mechanisms may result in primary ischemia and secondary necrosis of the tumor. Finally the infarction may be followed by intratumoral hemorrhage [14]. Although similar underlying pathomechanisms may be applicable, the details of pituitary apoplexy after hormone stimulation test have yet to be specified. In this study, based on chronological neuroimaging data and pathological findings, it is clearly demonstrated that the pituitary apoplexy following endocrine stimulation tests often starts with infarction and later develops into hemorrhagic type. The initial ischemic change may

be due to the vasoactivities of GnRH and TRH, which are commonly used. This hypothesis is supported by the report of Bernstein *et al.*, which suggested that TRH might induce vasospasm and subsequent infarction in the pituitary tumor [1]. However, this mechanism is not applicable to all patients with pituitary apoplexy following hormone stimulating tests. Okuda *et al.* reported a case of the primary pituitary hemorrhage induced within ten minutes after bolus injection of TRH. Neither necrosis nor infarction was demonstrated in either the anterior pituitary lobe or the tumor in their patho-

logical study [8]. However, it is worthwhile to emphasize that the incidence of infarction preceding the hemorrhagic event is unexpectedly high in pituitary apoplexy due to hormone stimulation test.

In conclusion, headache alone is a common symptom of pituitary apoplexy after hormone stimulation test, hence it is necessary to observe patients closely at least a few hours after the test. MR imaging may help to make an earlier diagnosis of pituitary apoplexy since infarction often precedes hemorrhage and CT scan will often show no density change in the pituitary adenoma.

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