Pituitary Apoplexy After Thyrotropin-releasing Hormone Stimulation Test in a Patient with Pituitary Macroadenoma

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Pituitary apoplexy is a rare complication of pituitary tumors. We report a case of a 41-year-old female with acromegaly due to a pituitary macroadenoma, who developed pituitary apoplexy after a thyrotropin-releasing hormone (TRH) 200 μg intravenous injection stimulation test. Neither emergency computed tomography (CT) scans nor magnetic resonance imaging (MRI), performed 6 hours and 12 hours, respectively, after the active episode, disclosed the evidence of acute hemorrhage or infarction. Two days later, the pituitary mass, removed by transsphenoidal approach, showed ischemic necrosis and acute hemorrhage. The TRH test is generally safe for evaluating pituitary function, but pituitary apoplexy may occur after the procedure. CT and MRI may miss the diagnosis of pituitary apoplexy, especially if performed immediately after the acute episode. [*J Chin Med Assoc* 2007;70(9):392–395]

Key Words: acromegaly, pituitary apoplexy, thyrotropin-releasing hormone, TRH

Introduction

Pituitary apoplexy is an uncommon clinical syndrome caused by sudden hemorrhage or infarction of pituitary tumors. It is characterized by acute onset of headache, accompanied by vomiting and frequently followed by visual deterioration and ophthalmoplegia. Apoplexy is usually spontaneous, but it may be associated with numerous pathologic states and medications, such as head trauma,[1–3] arterial hypertension,[2] increased intracranial pressure,[1–3] radiotherapy,[1,3] diabetic ketoacidosis,[2–4] anticoagulation,[1–3] estrogens,[1,2] and bromocriptine.[1,2,5] The possible relationship between the predisposing conditions and the occurrence of pituitary apoplexy may be pituitary necrosis, hemorrhage, or vasculopathy, although the exact mechanism is unclear.[1,3–5] Pituitary apoplexy associated with dynamic testing of the pituitary gland is extremely rare.[6–8] Patients with this medical emergency need prompt diagnosis for appropriate management. Computed tomography (CT) and magnetic resonance imaging (MRI) play important roles in confirming the diagnosis by revealing a pituitary tumor with hemorrhage and/or necrotic components. In this report, we present a patient who developed pituitary apoplexy 2 hours after injection of thyrotropin-releasing hormone (TRH). CT and MRI studies failed to demonstrate pituitary hemorrhage or infarction.

Case Report

A 41-year-old female presented to our clinic for further evaluation of her goiter, which was discovered recently. However, acromegaloid picture, accompanied by 5-year history of dysmenorrhea followed by 2-year history of amenorrhea made the presence of pituitary tumor highly probable. Thus, she was admitted to the hospital for investigation of pituitary tumor with acromegaly.

At the time of admission, the patient's blood pressure was 145/93 mmHg and heart rate was 91 beats per minute. Smooth respiratory pattern, goiter (grade II), galactorrhea, increased size of hands and feet, as well as coarse facial contours were noted. Visual acuity was 6/12 in both eyes, and visual field examination

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Table 1. Pituitary hormones and relative biochemical data

	Pre-op	3 d post-op	17 d post-op	2 mo post-op
GH (N < 5 ng/mL)	353	4.11		3.96
IGF-1 (N 100–276 ng/mL)	1,076	869		686
PRL (N 3–26 ng/mL)	4.03	0.13	0.11	
TSH (N 0.4–4 μIU/mL)	1.19	0.34	1.25	0.42
Free T4 (N 0.8–1.9 ng/dL)	1.39	0.85	1.26	1.37
T3 (N 82–179 ng/dL)	147	56.79	152	119
ACTH (N 9–52 pg/mL)	AM 29, PM 14.5	AM 27		
TgAb (N < 60 U/mL)	6.2			
TPOAb (N < 60 U/mL)	24.7			
Cortisol (AM) (N 5–25 μg/dL)	18.42	15.8	10.2	9.264
Cortisol (PM) (N < 5 μg/dL)	7.73			
LH (IU/L)	0.24	0.18	0.78	
FSH (IU/L)	1.33	0.07	0.72	
E2 (pg/mL)	16.58	16.09	20.58	24.10
ADH (N 0.4–2.4 pg/mL)	0.97			
Plasma osmolality (mOsm/kg)	290			
Urine osmolality (mOsm/kg)	193			
iPHT (N < 50 pg/mL)	42.05			
Ca (N 8.4–10.6 mg/dL)	9.6			

op = operation; GH = growth hormone; N = normal; IGF-1 = insulin-like growth factor-1; PRL = prolactin; TSH = thyroid-stimulating hormone; T4 = thyroxine; T3 = triiodothyronine; ACTH = adrenocorticotropic hormone; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; LH = luteinizing hormone; FSH = follicle-stimulating hormone; E2 = estradiol; ADH = antidiuretic hormone; iPTH = intact parathyroid hormone.

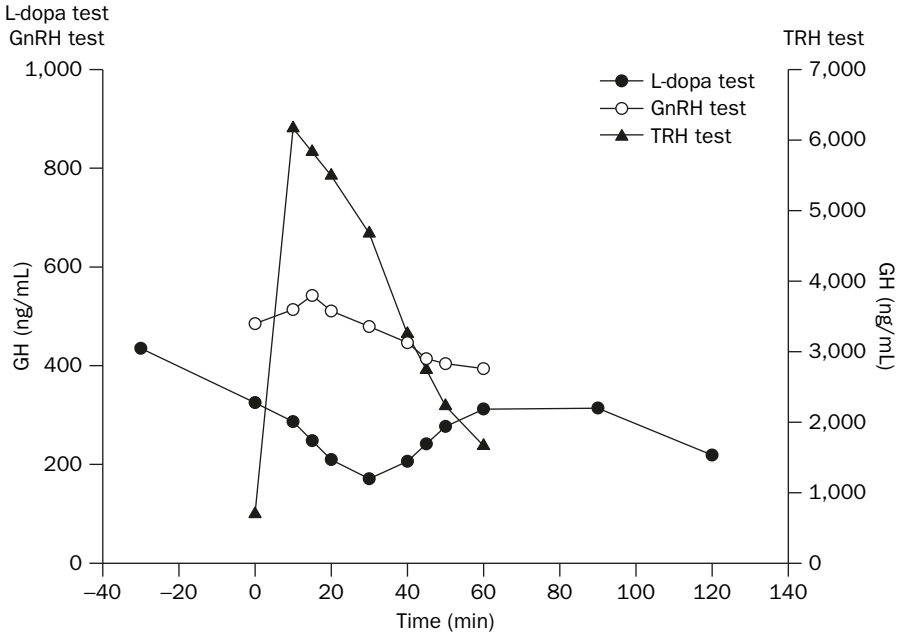

Figure 1. Serum growth hormone (GH) levels during L-dopa, gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) tests.

signified a bitemporal upper field defect. Extraocular muscle movements were normal. Fasting plasma glucose level was 154 mg/dL, and diabetes pattern was also noted by oral glucose tolerance test (OGTT). Basal growth hormone (GH) level (353 ng/mL) was high, and there was no suppression of GH during the OGTT. The basal endocrine function test results are shown in Table 1. Paradoxical GH responses to L-dopa, gonadotropin-releasing hormone (GnRH) and TRH are demonstrated in Figure 1. Plain skull X-ray

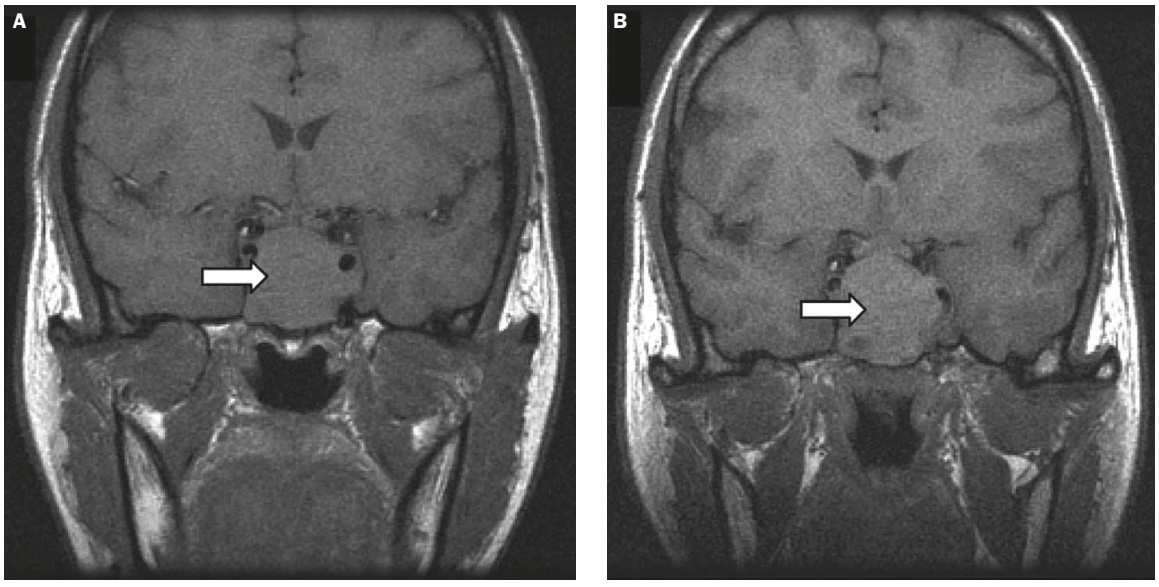

Figure 2. Magnetic resonance imaging coronal T1-weighted images show pituitary macroadenoma (arrow) without evidence of pituitary apoplexy: (A) before thyrotropin-releasing hormone (TRH) test; (B) after TRH test.

films illustrated erosion and destruction of pituitary fossa. MRI performed the day before TRH stimulation test revealed a lobulated pituitary macroadenoma ($38 \times 31 \times 25$ mm) with suprasellar extension, compression of optic chiasm, and invasion of left cavernous sinus (Figure 2A). About 2 hours after a bolus injection of 200 μg TRH, the patient had a sudden and intense headache, cold sweating, visual disturbance, ptosis, and diplopia. Blood pressure was 157/82 mmHg, heart rate was 50 beats per minute, and glucose level was 94 mg/dL. Emergency CT showed neither intratumoral hemorrhage nor infarction. Since pituitary apoplexy was highly suspected clinically, MRI was performed 12 hours after the episode, which disclosed no hemorrhage within the tumor (Figure 2B), but slight increase in tumor size (from 15.26 cm^3 to 16.15 cm^3) compared with the previous MRI image. The patient was administered hydrocortisone (300 mg/day) intravenously, and her headache and diplopia partially improved.

Two days later, the tumor was removed by transsphenoidal approach. Microscopic study indicated a picture of pituitary adenoma with fresh hemorrhage and ischemic necrosis. Immunohistochemically, the tumor was positive for GH, follicle-stimulating hormone, and alpha-subunit. On the second postoperative day, the symptoms mentioned above had all subsided except for diplopia. The follow-up hormone levels are shown in Table 1. One month after the operation, the patient was well without steroid hormone replacement. Three months after operation, her extraocular muscle movements were nearly normal, and the diplopia had disappeared.

Discussion

The very high basal GH level, up to 353 ng/mL in our case, confirmed the diagnosis of active acromegaly. However, acromegalic patients have both increased plasma levels of GH and a deranged pattern of GH secretion. About 50–80% of acromegalic patients will have GH > 50% of the basal level after TRH stimulation, and less frequently in response to GnRH.[9–11] In addition, half of acromegalic patients may have a paradoxical response to L-dopa.[9,10] Elevation and suppression of GH after TRH and L-dopa disclosed abnormal GH secretion dynamics in our case.

Pituitary apoplexy is a rare clinical syndrome caused by sudden hemorrhage or infarction of the pituitary gland. Headache is the initial and leading symptom of pituitary apoplexy.[12] Ocular palsy is also frequent, due to functional impairment of cranial nerves III, IV and VI.[2,13] Though apoplectic symptoms frequently occur within minutes or hours after pituitary apoplexy, it has been reported that they may transpire several days later.[6] The possible causes of pituitary apoplexy have been reported, but the precise mechanism of apoplexy is not fully understood.[1,3,6–8] Pituitary stimulation tests are extremely rare causes of pituitary apoplexy.[6–8] In a review of 22 reports of pituitary apoplexy after a pituitary function test, TRH was responsible for 15 cases

of apoplectic events.[8] Direct vasospasm effect may be the cause of TRH-induced pituitary apoplexy. In our case, the pituitary apoplexy was noticed shortly after TRH injection, which was quite similar to other reports.[6–8] This supported a causal relationship rather than spontaneous occurrence.

CT is useful in the acute setting (24–48 hours), and the most reliable CT sign of pituitary apoplexy is the presence of a homogeneously dense lesion showing little or no enhancement of a high density fluid level inside the tumor.[1,2] However, CT often fails to show a small hemorrhage or infarction. MRI is superior to CT in these aspects.[14] Randeva et al reported that MRI correctly demonstrated 88% of pituitary tumors with hemorrhage, but it was only 21% for CT.[13] One limitation of MRI scans is their inability to detect fresh bleeding, so they are performed at least 12 hours after the onset of symptoms to eliminate false-negative scan taken during the hyperacute stage.[15] Also, MRI has been shown to be useful for identifying blood components in the subacute setting (4 days to 1 month).[2]

Although TRH test is a generally safe test for evaluation of pituitary function, pituitary apoplexy may occur after the procedure, especially in patients with a large adenoma. CT and MRI are good techniques for brain imaging, but occasionally, these examinations may miss the diagnosis of pituitary apoplexy, especially when performed immediately after the acute episode.

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