Case Report

Pituitary Apoplexy Associated with Endocrine Stimulation Test: Endocrine Stimulation Test, Treatment, and Outcome

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Pituitary apoplexy is a rare clinical syndrome attributable to hemorrhage or hemorrhagic infarction of pituitary tumors or pituitary glands. The features of pituitary apoplexy associated with the endocrine stimulation test remain to be elucidated and the importance of surgical treatment has not been discussed enough. We report two rare patients who were treated successfully by endoscopic endonasal transsphenoidal surgery within several hours after onset of pituitary apoplexy associated with the endocrine stimulation test. Their postoperative course was uneventful. We reviewed earlier reports on this clinical entity, document its features especially as related to the endocrine stimulation test, discuss the significance of immediate surgical treatment, and present our treatment outcomes. Performing only conservative treatment is not recommended. We suggest that the necessity of endocrine stimulation test should be assessed on a case-by-case basis and in patients subjected to the test, and neurosurgical support should be sought.

1. Introduction

Pituitary apoplexy is a life-threatening clinical syndrome thought to be attributable to hemorrhage or hemorrhagic infarction of pituitary tumors or pituitary glands [1]. Suggested precipitating factors are hypertension, anticoagulation, and bromocriptine therapy, and pregnancy [2–27]. There are few reports on the occurrence of pituitary apoplexy as a complication of the endocrine stimulation test, and its features remain to be elucidated. We report two rare patients with pituitary apoplexy associated with the endocrine stimulation test who were treated successfully by surgery and present a review of the literature. We also discussed about the necessity of neurosurgical support.

2. Case Presentation

2.1. Case 1. A 56-year-old woman with a one-year history of visual disturbance was admitted to our hospital for the evaluation of a suprasellar tumor. Physical examination at admission revealed visual disturbance (temporal hemianopia on the left side) but no other neurological disorders or endocrinological symptoms. Her baseline levels of pituitary hormones were normal. Computed tomography (CT) and magnetic resonance imaging (MRI) studies demonstrated a pituitary adenoma with suprasellar extension and superior displacement of the optic chiasm. To evaluate her hormonal responses we performed combined endocrine stimulation tests with growth hormone-releasing hormone (GRH, 100 μg), thyrotropin-releasing hormone (TRH, 250 μg), luteinizing hormone-releasing hormone (LH-RH, 100 μg), and corticotrophin-releasing hormone (CRH, 100 μg). Fifteen minutes after the intravenous bolus injection she complained of severe headache, and this was followed by vomiting, progressive visual disturbance, and left oculomotor paralysis. She was alert but her symptoms gradually worsened. Emergency CT and MRI revealed intratumoral hemorrhage (Figures 1(a)–1(d)). Four hours after onset, her
left visual acuity was reduced to total blindness; there was temporal hemianopia in the right visual field. At emergency endoscopic endonasal transsphenoidal surgery was (ETSS) performed 5 hr after onset. Partially, tumor was solid and reddish-brown, different from the typical feature of pituitary adenoma. The tumor was totally removed. Pathological examination revealed hemorrhagic and necrotic area in nonnecrotic papillary-patterned tumor tissue (Figure 1(e)). Postoperatively, her headache, nausea and left oculomotor paralysis resolved, and her vision returned to the preonset level. Because of her diabetes insipidus (DI) she received transient desmopressin replacement therapy. She was able to resume her normal life.

2.2. Case 2. A 73-year-old man with an 8-month history of visual disturbance was referred to our hospital. Five years earlier, when he was diagnosed with suprasellar tumor, he was asymptomatic and without visual disturbance. In the intervening five years, his tumor gradually enlarged and became symptomatic. At admission to our hospital, visual field examination revealed temporal hemianopia on the left side. He had no other neurological disorders or endocrinological symptoms. His baseline pituitary hormone levels were normal. CT and MRI demonstrated a pituitary adenoma with suprasellar extension and superior displacement of the optic chiasm. For preoperative endocrine evaluation we performed combined endocrine stimulation tests with growth hormone releasing peptide-2 (GHRP2, 100 μg), TRH (250 μg), LH-RH (100 μg), and CRH (100 μg). Twenty minutes after the intravenous bolus injection he complained of progressive visual disturbance. He was alert and experienced neither headache nor nausea. Emergency CT and MRI performed one hr after onset showed no evidence of intratumoral hemorrhage (Figures 2(a)–2(c)), two hr after onset his left visual acuity was reduced to total blindness. There was no visual disturbance on the right side. He underwent ETSS 5 hr after onset, and the tumor was totally removed. Same as Case 1, tumor was partially solid and reddish-brown. Pathological examination revealed papillary-patterned adenoma with diffuse hemorrhage and necrosis (Figure 2(d)). His postoperative course was uneventful. One month after the operation his visual disturbance resolved completely, and he required no hormone replacement therapy.
Figure 2: Case 2. CT scan performed 1 hour after onset demonstrates no evidence of intratumoral hemorrhage or acute enlargement of the tumor size (a), T1-weighted MRI performed after onset shows a pituitary tumor extending into the suprasellar cistern. There was no evidence of intratumoral hemorrhage or acute infarction (b), after onset gadolinium-enhanced T1-weighted MRI showing uniform enhancement of the pituitary tumor (c), and pathological examination revealed papillary-patterned adenoma with diffuse hemorrhage and necrosis (d).

3. Discussion

Pituitary apoplexy is a rare clinical syndrome thought to be attributable to hemorrhage or hemorrhagic infarction of pituitary tumors or pituitary glands. It is characterized by the sudden onset of headache, vomiting, visual impairment, and decreased consciousness. Reported precipitating factors of pituitary apoplexy are hypertension, anticoagulation and bromocriptine therapy, pregnancy, and angiography [1, 22]. Although pituitary apoplexy associated with the endocrine stimulation test has been reported (Table 1), its features remain to be elucidated [2–27]. Of the 32 previously-reported patients and our two patients with pituitary adenomas who experienced pituitary apoplexy, 16 (47%) had non-functioning, 8 (23.5%) GH-secreting, 5 (14.7%) prolactin (PRL)-secreting, 3 (8.8%) follicle-stimulating hormone (FSH)-secreting, and 2 (5.9%) had adrenocorticotropic hormone (ACTH)-secreting adenomas. This proportion is similar to the frequency among the types of pituitary adenomas [28]. This suggests that there is no strong correlation between the types of pituitary adenoma and the elicitation of pituitary apoplexy by the endocrine stimulation test. On the other hand, there appears to be a relationship between the size of pituitary adenomas and pituitary apoplexy associated with the endocrine stimulation test. Our review of the literature showed that 93% of previously reported patients manifested extrasellar extension of their pituitary tumors. TRH (26 cases, 76.4%) and LH-RH (23 cases, 67.6%) were the hormonal stimulants most commonly associated with the elicitation of pituitary apoplexy. Although the precise mechanisms of pituitary apoplexy associated with TRH- and LH-RH stimulation remain unclear, it has been suggested that TRH elevates the serum level of norepinephrine, and that vasospasm or pressor effects may be precipitating factors [3, 15, 29]. Others proposed that TRH directly activates the tumor cells, or that LH-RH stimulation increases metabolic activity leading to vascular accidents [6, 12, 15, 18, 29]. Interestingly, the number of hormonal stimulants used in the endocrine stimulation test has no bearing on the elicitation of pituitary apoplexy; the Spearman correlation was $\rho = -0.40$ with a $P$ value of 0.6 (Table 1(a)). Excluding the two patients reported here, the incidence of pituitary apoplexy among patients subjected to the endocrine stimulation test with four stimulants was 0 in our department. Because this
Table 1
(a) Reported cases of pituitary apoplexy associated with endocrine stimulation test: diagnosis, extension, and stimulation test

| Case no. | Author       | Year | Age/sex | Diagnosis       | Extension       | Stimulation test              |
|----------|--------------|------|---------|-----------------|-----------------|------------------------------|
| 1        | Dunn et al.  | 1975 | 22/F    | GH secreting   | Uncertain       | TRH, glucose, insulin        |
| 2        | Silverman et al. | 1978 | 31/M    | PRL secreting  | Extrasellar     | Chlorpromazine               |
| 3        | Jordan et al. | 1979 | 21/F    | ACTH secreting | Uncertain       | Dexemethasone                |
| 4        | Cimino et al. | 1981 | 48/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH                   |
| 5        | Drury et al. | 1982 | 59/F    | Nonfunctioning | Extrasellar     | TRH, LH-RH, glucagon         |
| 6        | Drury et al. | 1982 | 66/M    | GH secreting   | Intrasellar     | TRH                          |
| 7        | Drury et al. | 1982 | 39/F    | PRL secreting  | Extrasellar     | TRH, LH-RH                   |
| 8        | Drury et al. | 1982 | 28/M    | PRL secreting  | Extrasellar     | TRH, LH-RH                   |
| 9        | Bernstein et al. | 1984 | 48/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH, insulin          |
| 10       | Korsic       | 1994 | 56/M    | FSH secreting  | Extrasellar     | LH-RH                        |
| 11       | Chapman et al. | 1979 | 39/F    | PRL secreting  | Extrasellar     | TRH, LH-RH, insulin          |
| 12       | Lever et al. | 1986 | 19/F    | GH secreting   | Intrasellar     | TRH                          |
| 13       | Shirataki et al. | 1988 | 50/F    | GH secreting   |Extrasellar      | Bromocriptine                |
| 14       | Harvey et al. | 1989 | 50/M    | Nonfunctioning | Uncertain       | Insulin                      |
| 15       | Arafah et al. | 1990 | 41/F    | PRL secreting  | Extrasellar     | LH-RH                        |
| 16       | Masson et al. | 1993 | 54/F    | FSH secreting  | Extrasellar     | LH-RH                        |
| 17       | Okuda et al. | 1994 | 60/F    | Nonfunctioning | Extrasellar     | TRH, LH-RH, insulin          |
| 18       | Vassallo et al. | 1994 | 81/M    | Nonfunctioning | Uncertain       | TRH, LH-RH, L-Dopa           |
| 19       | Masago et al. | 1995 | 48/M    | FSH secreting  | Extrasellar     | TRH, LH-RH, insulin          |
| 20       | Masago et al. | 1995 | 54/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH                   |
| 21       | Szabolcs et al. | 1997 | 54/M    | Nonfunctioning | Extrasellar     | TRH                          |
| 22       | Otsuka et al. | 1998 | 31/F    | GH secreting   | Extrasellar     | GRF, TRH, LH-RH, CRH         |
| 23       | Dökmetaş et al. | 1999 | 28/F    | GH secreting   | Extrasellar     | TRH                          |
| 24       | Sanno et al. | 1999 | 55/M    | Nonfunctioning | Extrasellar     | GRF, TRH, LH-RH, CRH         |
| 25       | Lee et al.   | 2000 | 34/M    | GH secreting   | Extrasellar     | TRH, LH-RH, insulin          |
| 26       | Riedl et al. | 2000 | 71/F    | Nonfunctioning | Extrasellar     | GRF, TRH, LH-RH, CRH         |
| 27       | Matsuura et al. | 2001 | 63/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH, insulin          |
| 28       | Rotman et al. | 2003 | 19/F    | ACTH secreting | Extrasellar     | CRH                          |
| 29       | Yoshino et al. | 2007 | 36/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH, insulin          |
| 30       | Yoshino et al. | 2007 | 38/M    | Nonfunctioning | Extrasellar     | TRH, insulin                 |
| 31       | Wang et al.  | 2007 | 41/F    | GH secreting   | Extrasellar     | TRH, LH-RH, insulin, L-Dopa  |
| 32       | Kılıç et al. | 2010 | 52/M    | Nonfunctioning | Extrasellar     | TRH, LH-RH, insulin          |
| 33       | Our cases    | 2011 | 56/F    | Nonfunctioning | Extrasellar     | GRF, TRH, LH-RH, CRH         |
| 34       | Our cases    | 2011 | 73/M    | Nonfunctioning | Extrasellar     | GHRP2, TRH, LH-RH, CRH       |

(b) Reported cases of pituitary apoplexy associated with endocrine stimulation test: treatment and outcomes of the 23 cases, for whom detailed treatments and outcomes were available

| Case no. | Treatment     | Interval from onset to surgery | Outcomes                        |
|----------|---------------|--------------------------------|---------------------------------|
| 1        | Medication    | —                              | GH reduction, DI                |
| 2        | Craniotomy    | Undocumented                   | Panhypopituitarism              |
| 3        | Craniotomy    | Undocumented                   | Visual disturbance, hemiparesis, aphasia |
| 9        | Transsphenoidal surgery | The same day (8.5 hours) | Visual disturbance, hemiparesis, aphasia |
| 11       | Craniotomy    | 3 days later                   | Recovered completely            |
| 13       | Transsphenoidal surgery | 11 days later | Recovered completely            |
| 14       | Transsphenoidal surgery | Undocumented | Hypopituitarism                 |
| 17       | Craniotomy    | The same day and 17 days after | Recovered completely            |
| 18       | Medication    | —                              | Hyopituitarism                  |
| 19       | Craniotomy    | The same day (7 hours)         | Recovered completely            |
test is convenient and the incidence of test-elicited pituitary apoplexy is low, it is used widely to investigate the reserve function of the pituitary in patients with pituitary adenoma. Nonetheless, based on earlier reports and our experience with the two patients reported here, we think that the necessity for performing the endocrine stimulation test must be evaluated on a case-by-case basis.

Among the 34 patients, detailed treatments and outcomes were available in 23 (Table 1(b)); 20 patients underwent surgery, and the other 3 were treated conservatively [3, 4, 7, 8, 11, 13–15, 17–23, 26, 27, 29]. Of the latter, all went surgery, and the other 3 were treated conservatively come swer ea v ail able in 23 (Table 1(b)); 20 patients under- necessity for performing the endocrine stimulation test must be considered carefully and that they be performed with neurosurgical support.

| Case no. | Treatment          | Interval from onset to surgery | Outcomes                                      |
|----------|--------------------|--------------------------------|-----------------------------------------------|
| 20       | Craniotomy         | 5 days later                   | Hypopituitarism                               |
| 22       | Transsphenoidal surgery | 4 days later               | Hypopituitarism                               |
| 24       | Transsphenoidal surgery | 2 weeks later            | Hypopituitarism                               |
| 25       | Transsphenoidal surgery | 9 days later                | Hypopituitarism                               |
| 26       | Transsphenoidal surgery | 2 days later                | Visual disturbance, ophthalmoplegia          |
| 27       | Transsphenoidal surgery | 1 day later (30 hours)     | Improved to the level of preoperative state   |
| 28       | Medication         | —                             | Hypopituitarism                               |
| 29       | Transsphenoidal surgery | The same day and 21 days after | Hypopituitarism                               |
| 30       | Transsphenoidal surgery | 7 days later                | Hypopituitarism                               |
| 31       | Transsphenoidal surgery | 2 days later                | Ophthalmoplegia                               |
| 32       | Transsphenoidal surgery | The same day                | Recovered completely                          |
| 33       | Transsphenoidal surgery | The same day                | Visual disturbance                            |
| 34       | Transsphenoidal surgery | The same day                | Recovered completely                          |

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