NOTE

A Case of Ruptured Dissecting Aneurysm 5 Years after Pituitary Microsurgical Treatment of Cushing's Disease: Autopsy Findings in the Hypothalamic-Pituitary-Adrenal Axis

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Abstract. The patient was a 26-year-old man with Cushing's disease who underwent transsphenoidal microscopic surgery for a pituitary microadenoma. His postoperative course was uneventful, but he died suddenly five years after the operation. At autopsy, a ruptured dissecting aneurysm with marked atherosclerosis was observed in the aorta. In the pituitary, a small focus of adrenocorticotropic hormone (ACTH) producing adenoma, possibly residual adenoma, was detected and Crooke's degeneration was observed in the non-tumorous pituitary gland. But immunohistochemical patterns of pituitary hormones in the non-tumorous pituitary gland were normal and the adrenal cortex was unremarkable. In the hypothalamus, corticotropin-releasing hormone immunoreactivity was not detected and arginine vasopression was sporadically positive. Considering these findings, this patient may have developed subclinical hypercortisolism due to the residual adenoma at the time of autopsy, despite clinical remission. Cushing's syndrome is considered to be a risk factor dissecting aneurysm, and in this case the metabolic changes in Cushing's disease may have influenced the development of the dissecting aneurysm. Periodic cardiovascular re-evaluations should therefore be performed when there is clinical remission of Cushing's syndrome.

Key words: Cushing's syndrome, Transsphenoidal microsurgery, Corticotropin-releasing hormone (CRH), Arginine vasopressin (AVP), Adrenocorticotropic hormone (ACTH), Dissecting aneurysm.

CUSHING'S syndrome is characterized by an overproduction of cortisol. Approximately 60 to 70% of cases are due to autonomous hypersecretion of adrenocorticotropic hormone (ACTH) in the pituitary, i.e. Cushing's disease. Since Hardy first reported the procedure in 1969 [1], transsphenoidal microsurgery for removal of the pituitary adenoma has become the treatment of choice for a majority of patients with Cushing's disease [2-4]. Transsphenoidal microsurgery is certainly a successful and safe treatment for the vast majority of patients with pituitary microadenoma, but it is also true that a few patients who were initially considered to be in remission after surgical treatment, later develop a recurrence of the disease [3, 5-6]. It is very important to examine the postoperative clinical course, including the rate of recurrence and the occurrence of other disorders in patients who undergo microsurgery of the pituitary for Cushing's disease.

The influence of the hypothalamus in the pathogenesis of Cushing's disease remains an unresolved and challenging issue [7], and morphological examinations of the hypothalamic-pituitary-adrenal axis after transsphenoidal microsurgery have not been reported to the best of our knowledge. We report an autopsy case of ruptured...
dissecting aneurysm 5 years after pituitary microsurgical treatment for Cushing’s disease, and describe the histopathologic and immunohistochemical examinations of the hypothalamic-pituitary-adrenal axis.

**Case Report**

A 26-year-old man was referred to the Tohoku University Hospital in March, 1986 for evaluation of a two year history of hypertension and a one year history of obesity and general fatigue. He had truncal obesity, a “moon face”, hypertension (180/150 mmHg), a buffalo hump and skin striae. A diagnosis of Cushing’s disease was made on basis of the following endocrinological data: The plasma cortisol level was high (17–24 µg/dl) with loss of circadian rhythm; 24 h urinary excretion of 17-hydroxycorticosteroid (17-OHCS) and 17-ketosteroid (17-KS) were increased (11.5 mg/day and 15.9 mg/day, respectively) and 17-OHCS production was increased when metyrapone was administered; dexamethasone suppression test was abnormal, i.e. 8 mg of dexamethasone administration could not completely suppress the plasma cortisol level; the plasma adrenocorticotropic hormone (ACTH) level was high (144 pg/ml) with loss of circadian rhythm and responded dramatically to corticotropin-releasing hormone (CRH) administration. A right side pituitary microadenoma was revealed by enhanced computed tomography (CT) scan. The results of bilateral inferior petrosal venous sampling indicated a high ACTH level on the same side as the microadenoma (right: 595 pg/ml, left: 129 pg/ml). Transsphenoidal microsurgery was subsequently performed in June, 1986 and a 0.5 cm microtumor was verified on the right side. Histopathologically this tumor was diagnosed as a basophilic adenoma consistent with Cushing’s disease. Tumor cells showed ACTH immunoreactivity, and Crooke’s hyaline degeneration was observed in non-tumorous corticotrophs. After selective adenomectomy, the clinical and physical symptoms of Cushing’s disease were lessened, but moderate hypertension (150/100 mmHg) remained throughout the postoperative clinical course. Plasma ACTH and cortisol levels became low due to the microsurgery (<10 pg/ml and <0.5 µg/dl, respectively), and dexamethasone supplementation (0.5 mg/day) was maintained for 3 years. Plasma ACTH and cortisol levels rose to normal in 1989 (35 pg/ml and 10 µg/dl, respectively), and dexamethasone supplementation was then stopped. After 1989, no hormonal abnormalities, including plasma ACTH and cortisol levels, or adverse results of findings in dexamethasone suppression test (1 mg), were detected. In May, 1991, the patient suddenly complained of severe back pain, became hypotensive and died three days later.

**Autopsy findings**

At autopsy, a dissecting aneurysm was observed. It was classified as type A, extending from the ascending aorta to the common iliac arteries. External ruptures into the pericardial and peritoneal cavities (500 ml and 1600 ml, respectively) were considered to be the cause of death. Atherosclerosis, which was characterized by fibrofatty intimal plaques, was observed in the aorta and the medial muscular arteries including coronary and renal arteries. Microscopically, arteriolosclerosis, which was marked by proliferative and/or hyaline thickening of the small arterial walls was observed, especially in the kidneys, peri-adenals and subarachnoid region. In the pituitary, a small basophilic adenoma measuring 0.3 cm was observed at the same site as at surgery with scar formation (Fig. 1). Morphological findings in this adenoma were considered to be similar to those in the surgically removed adenoma. Immunohistochemically, these tumor cells were positive for ACTH (polyclonal antibody, INC STAR) (Fig. 2). In the non-tumorous portions of the pituitary gland, Crooke’s hyaline degeneration was observed (Fig. 3A). However, immunohistochemical patterns of pituitary hormones including ACTH (Fig. 3B), growth hormone (GH) (polyclonal antibody, DAKO, Glostrup, Denmark), thyroid-stimulating hormone (TSH) (polyclonal antibody, DAKO), prolactin (PRL) (polyclonal antibody, DAKO), follicle-stimulating hormone (FSH) (polyclonal antibody, DAKO) and luteinizing hormone (LH) (monoclonal antibody, Nichirei, Tokyo, Japan) were normal in the pituitary. No histopathological changes were observed in the hypothalamus. Immunohistochemically, CRH (kindly provided by Dr. A. Sasaki, Department of Medicine, Tohoku University School of Medicine, Sendai, Japan [8]) was negative in the hypothalamus, while immunoreactivity
for arginine vasopressin (AVP) (kindly provided by Dr. K. Naruse, Department of Medicine, Tokyo Women's Medical College, Tokyo, Japan) (Fig. 4), and growth hormone-releasing hormone (GRH) (kindly provided by Dr. A. Sasaki [9]) was observed. The adrenal glands were unremarkable, without any evidence of adrenocortical hyperplasia.
Discussion

Despite recent advances in clinical investigations, the possibility of an initiating role being played by hypothalamic factors in the pathogenesis of pituitary tumors is still controversial. Recent investigations revealed that some patients with Cushing's disease do not have a discrete solitary adenoma, but instead have multiple microadenomas [10]. Moreover in a few cases, no apparent

Fig. 3. A: Crooke's hyaline degeneration in non-tumorous pituitary gland at the time of autopsy. In this figure, a large number of basophils were not granulum positive for periodic acid Schiff (PAS) stain in the cytoplasm. They were considered to indicate Crooke's hyaline degeneration. Arrows represent examples of Crooke's hyaline degeneration (PAS-alcian blue stain, original magnification × 320). B: Immunohistochemical examinations of ACTH in non-tumorous pituitary gland at autopsy. Immunohistochemical pattern of ACTH was almost normal in the non-tumorous pituitary gland (original magnification × 320).

Fig. 4. Immunohistochemical examination of AVP in the hypothalamus. Some paraventricular nuclei were positive for AVP (original magnification × 130).
pituitary lesions have been observed [10]. In these cases, excessive hypothalamic CRH production or factors derived from sources other than the pituitary gland may be involved in the pathogenesis of Cushing’s disease, as was proposed by Krieger [11]. In addition, pituitary microsurgery is followed by recurrence of symptoms after a period of remission in a number of cases [4–6]. Mampalam et al. [4] reported that 9 of 216 patients who had transsphenoidal microsurgery for Cushing’s disease had a recurrence of the disease within an average of 3.8 years after surgery. The vast majority of these patients are considered to have a residual adenoma, but pathologic evaluation of the hypothalamic-pituitary-adrenal axis after microsurgical treatment for Cushing’s disease has not been reported.

In our case, at the time of autopsy a pituitary adenoma immunohistochemically positive for ACTH was present in the same site as at surgery. In the hypothalamus, no apparent morphological changes were observed. AVP expression was observed, but no hypothalamic CRH hyperproduction was immunohistochemically observed. Andoh et al. [12] examined immunohistochemistry of CRH and AVP in the hypothalamus in 73 autopsy cases, and demonstrated that AVP expression was observed in all cases but hypothalamic CRH immunoreactivity was often negative. Therefore, in this case in which AVP immunoreactivity was observed but CRH was negative, it was difficult to determine whether CRH production was suppressed due to this residual adenoma or within normal variations. But, at least, hyperproduction of CRH was considered to be unlikely. Clinically, this patient was in remission from Cushing’s syndrome. The pattern of distribution of ACTH immunoreactivity in the non-neoplastic pituitary gland was normal at the time of autopsy, and no adrenal morphological changes, including cortical hyperplasia, were observed. However, Crooke’s hyaline degeneration was clearly observed in pituitary cells at autopsy. It is uncertain when Crooke’s degeneration diminished, according to normalization of the plasma cortisol level after pituitary microsurgery. The Crooke’s degeneration observed may indicate a residue, but it is also possible that this patient became slightly hypercortisolic at the time of autopsy, despite clinical remission.

Cushing’s syndrome is established as a risk factor for dissecting aortic aneurysm, but only five cases with dissecting aneurysm in Cushing’s syndrome [13–17] have been reported so far. An excess of plasma cortisol has been demonstrated to cause arteriosclerosis, hypertension and dissecting aneurysm in investigations in many experimental models. This patient’s ruptured aneurysm may not be directly related to the Cushing’s disease. However, this patient was very young (31 years old) at the time of the onset of the dissecting aneurysm. Thus, the metabolic changes in Cushing’s disease may have influenced the development of arteriosclerosis, hypertension and the dissecting aneurysm in this case. It is therefore considered that patients in clinical remission from Cushing’s syndrome should not only have periodic endocrinological but also cardiovascular reevaluations if hypertension persists.

Acknowledgements

The authors appreciate the technical assistance of Mrs. Fumiko Date, Department of Pathology, Tohoku University School of Medicine, Sendai, Japan, and suggestions from Dr. Noriaki Andoh, Department of Pathology, Tohoku University School of Medicine, Sendai, Japan.

References


