Endocrinological evaluation of ACTH-secreting pituitary microadenomas: their location and \( \alpha \)-melanocyte stimulating hormone immunoreactivity

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- It has been hypothesized by Lamberts and coworkers in their analysis of 15 cases that adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas may be derived from either the anterior lobe or the intermediate lobe. The intermediate lobe type of Cushing's disease is thought to be controlled through a hypothalamic pathway and is characterized by hyperprolactinemia, suppressibility of cortisol with bromocriptine, and lower sensitivity to dexamethasone. The authors investigated the validity of this hypothesis in 125 cases of ACTH-secreting pituitary microadenomas by analyzing the endocrine findings, the locations of the microadenomas, and \( \alpha \)-melanocyte stimulating hormone (\( \alpha \)-MSH) immunoreactivity in the adenoma cells. No significant differences in the basal hormone levels, cortisol suppressibility with bromocriptine, sensitivity to dexamethasone, and recurrence rate were observed between patients with the microadenoma adjacent to the posterior lobe (considered typical of the intermediate lobe-derived tumor) or those with the microadenoma located in the anterior lobe. The locations of the microadenoma were not correlated with \( \alpha \)-MSH immunoreactivity in the adenoma cells. No significant differences in endocrine findings were noticed between adenomas positive or negative for \( \alpha \)-MSH. Thus, Cushing's disease cannot be simply divided into either the anterior lobe type or the intermediate lobe type by endocrinological evaluation as described by Lamberts, et al.

Key Words: Cushing’s disease • adenoma • adrenocorticotropic hormone • Lamberts’ hypothesis • pathogenesis

The pituitary gland is derived from two embryological sources: Rathke's pouch (the epithelial element) and the infundibular process of the diencephalon (the neural part). The former develops mainly into the anterior lobe, and the latter into the posterior lobe. The intermediate lobe develops from the posterior wall of Rathke's pouch and is adjacent to the posterior lobe. In most species, the cells in the intermediate lobe are known to synthesize and secrete pro-opiomelanocortin (POMC)-related peptides, and to be anatomically distinct and functionally different from the corticotrophs in the anterior lobe. The cells in the intermediate lobe are neurally controlled by dopaminergic inhibition, while the corticotrophs in the anterior lobe are under negative feedback regulation by glucocorticoids. In addition, POMC is processed differently in the two lobes. Adrenocorticotropic hormone (ACTH) is the final product in the anterior lobe. It is further cleaved to \( \alpha \)-melanocyte stimulating hormone (\( \alpha \)-MSH) and corticotropin-like intermediate peptide in the intermediate lobe. In the human pituitary, however, the intermediate lobe exists only in the fetal period or during pregnancy and is considered to be anatomically and functionally absent in the normal adult.

Although there is no evidence of a functional intermediate lobe in the adult human pituitary, it was hypothesized by Lamberts, et al., that human ACTH-secreting pituitary adenomas may be derived either from the anterior pituitary lobe or from the intermediate lobe. They regarded the presence of neural tissues in the adenomas to be indicative of intermediate lobe origin and its absence to be indicative of anterior lobe origin. They also proposed that patients with type II adenomas show suppressibility of cortisol levels with bromocriptine, lower sensitivity to dexamethasone, and hyperprolactinemia.

This hypothesis has not been analyzed in a large number of patients, although a few reports with
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several cases have been presented. In this report, 125 cases of Cushing's disease with microadenoma were studied to evaluate the applicability of the hypothesis. First, the anatomical location of the microadenoma was determined; the typical intermediate lobe-type adenoma was described as situated at the border between the anterior and posterior lobe. Second, the microadenomas were analyzed for a-MSH immunoreactivity; positive staining was considered to be characteristic of the intermediate lobe-type tumor. The endocrine findings in patients were correlated with the adenoma location and a-MSH immunoreactivity.

Clinical Material and Methods

A total of 165 patients with Cushing's disease underwent transphenoidal surgery at the Department of Neurosurgery, Nagoya University School of Medicine, between 1977 and 1987. In 151 cases, the presence of ACTH-secreting pituitary adenomas was shown: 125 (83%) of these tumors were microadenomas and 26 (17%) were macroadenomas. Only microadenomas were evaluated in this study.

The location of the microadenoma was determined as follows. At transphenoidal surgery, the sphenoid bone and dura mater at the sellar floor were opened enough to ensure a clear view of the margin of the pituitary gland bilaterally. Adenomas situated adjacent to the posterior lobe were classified as being in the intermediate zone group, as shown in the dotted portion of Fig. 1. The anterior lobe group included the adenomas in other locations, which were further divided into three parts: right, center, and left. There were 13 tumors in the intermediate zone group and 112 in the anterior lobe group (Fig. 1).

The endocrine findings and recurrence rates were compared between the two groups. The levels of anterior pituitary hormones and cortisol in plasma or serum were determined by the use of commercial assay kits. The bromocriptine test (CB-154 test) was performed to measure the serum cortisol level every hour for 5 hours after oral administration of 2.5 mg bromocriptine. A dexamethasone suppression test was performed according to Liddle's method. 

Results

Endocrinological Evaluation in Relation to Adenoma Location

As shown in Table 1, there were no significant differences in basal hormone levels between the anterior lobe and the intermediate zone groups. Hyperprolactinemia was detected in 16 (18%) of 91 cases in the anterior lobe group and two (18%) of 11 cases in the intermediate zone group. Thus, hyperprolactinemia was not characteristic of the intermediate zone group only.

The bromocriptine test was performed in 22 patients (Fig. 2). The percentage of cortisol suppression by the administration of bromocriptine was 83% in the anterior lobe group and 64% in the intermediate zone group. There were no significant differences between the two groups.

In the dexamethasone suppression test (Table 2), 50% suppression of urinary 17-OHCS by 2 mg dexamethasone administration was found in 25 (36%) of 70 cases in the anterior lobe group and in two (20%) of 10 cases in the intermediate zone group. Fifty percent suppression by 8 mg dexamethasone occurred in 54 (75%) of 72 cases in the anterior lobe group and five (63%) of eight cases in the intermediate zone group. Thus, there were no apparent differences in suppressibility between the two groups.

The remission rate of the adenomas in the anterior lobe group was 87 (90%) of 97 cases, while all 13 patients in the intermediate zone group had remission. The adenoma recurrence rate in the anterior lobe group was
6% (five of 87 cases) while that for the intermediate zone group was 15% (two of 13 cases). Again, there was no significant difference (Table 3).

These results indicate that the adenomas localized just adjacent to the posterior lobe do not necessarily exhibit the characteristic features of an intermediate lobe-type tumor as proposed by Lamberts, et al. 7

**Endocrinological Evaluation in Relation to α-MSH Immunoreactivity**

Immunohistochemical testing for α-MSH revealed that eight (38%) of the 21 tumors analyzed were positive and the other 13 cases (62%) were negative. The location of microadenomas that were positive for α-MSH is shown in Fig. 3. Immunoreactivities for α-MSH were detected in four of 10 tumors in the intermediate zone and in four of 11 in the lateral part of the anterior lobe. This suggests that α-MSH-positive microadenomas are not always situated in the intermediate zone.

When the endocrine findings were compared between groups positive or negative for α-MSH, there were no significant differences in basal prolactin levels, cortisol suppressibility by bromocriptine, or 17-OHCS suppressibility by dexamethasone (Table 4). Thus, positive α-MSH staining was not associated with the characteristic features of an intermediate lobe-type tumor.

**Discussion**

In 1932, Cushing 4 first reported the characteristics of patients with central obesity, moon facies, hypertension, and hypertrichosis. He suggested that these symptoms were caused by a pituitary basophilic adenoma. Subsequently, it was demonstrated that Cushing’s disease is characterized by the hypersecretion of ACTH from the adenoma tissue.

The pathogenesis of Cushing’s disease has been controversial. It has been discussed whether this disorder is a result of corticotroph stimulation by hypothalamic
corticotropin-releasing factor (CRF) or a spontaneous ACTH-secreting adenoma in the anterior pituitary. Saeger and McKeever, et al., noted the presence of nodular hyperplasia in the absence of pituitary adenoma, and suggested that the cause was of hypothalamic origin. However, ACTH-secreting pituitary adenomas were found in about 90% of cases following operations. When recurrence of Cushing's adenoma is observed, the adenoma usually grows at the same site where the tumor was previously resected. This may suggest that the recurrence is not due to hypothalamic CRF stimuli, but to the regrowth of adenoma cells left behind during the first operation. Moreover, CRF concentrations in the plasma and cerebrospinal fluid of patients with Cushing's disease were considerably lower than those in normal subjects. These findings strongly support the idea of pituitary adenoma is the cause of Cushing's disease. Rarely, an ectopic CRF-secreting tumor has been reported.

The hypothesis proposed by Lamberts, et al., for the etiology of pituitary adenomas had an important impact for neurosurgeons because it suggested that differences in preoperative endocrine findings predicted tumor location and recurrence rates. In this study, the hypothesis was evaluated by analyzing the location of microadenomas in 125 patients with Cushing's disease and by correlating the endocrine and immunohistochemical findings to the locations. No significant differences in basal hormone levels, in sensitivity to bromocriptine or dexamethasone, or in the remission or recurrence rate were detected. Thus, the classification of ACTH-secreting pituitary adenoma into "anterior lobe type" and "intermediate lobe type" is not possible by preoperative endocrinological evaluation as proposed by Lamberts, et al.

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References


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