Recent management of pituitary adenomas

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Introduction

Pituitary adenomas can be classified into several types according to their endocrinological functions; ie,

* non-functioning adenoma
* functioning adenoma
  * prolactin secreting adenoma (prolactinoma)
  * GH secreting adenoma (acromegaly and/or gigantism)
  * ACTH secreting adenoma (Cushing’s disease, Nelson’s syndrome)
  * TSH secreting adenoma
  * gonadotropin secreting adenoma

Each type of adenoma is treated by different strategies which include surgery, medicine and irradiation. Therapeutic principles are not uniform among neurosurgeons, endocrinologists, gynecologists and radiologists. Here I would like to describe our present management of pituitary adenomas especially from the viewpoints of pituitary neurosurgeons.

Non-functioning adenoma

At present, effective pharmacotherapy is not available for non-functioning adenomas, though some tumors may show a minimal response to bromocriptine because of the presence of some dopamine receptors. Therefore, in most patients the first choice of treatment is surgery. We prefer the transsphenoidal approach regardless of the size and shape of the tumor, because this surgery is very safe and less invasive. We have experienced a lot of problems with transcranial surgery, especially for large pituitary adenomas. When huge adenomas are resected extensively by the transcranial route, the operative results are generally very poor.

If a small amount of tumor is left after transsphenoidal surgery, we treat the patient with conventional irradiation (usually 45 Gray/5 weeks). When the volume of residual suprasellar tumor is large, we plan the second transsphenoidal surgery before the adhesion of nasal mucosa is completed (within one month). Since some irregularly shaped tumors or large fibrous adenomas cannot be totally removed by repeated transsphenoidal surgery, we
sometimes adopt transcranial surgery for the residual tumor. As a rule, radiation therapy is carried out after surgery except for cases of complete tumor removal.

**Prolactin secreting adenoma**

The number of surgical cases has been decreasing, because bromocriptine is very effective for prolactinomas. In most patients bromocriptine significantly decreases not only serum PRL levels but also tumor volume, although sensitivity to this drug differs from case to case\(^2\). In very sensitive cases, a small dose of bromocriptine can induce the normalization of serum PRL and a marked reduction in tumor size. However, in about 10\% of prolactinomas this medication can hardly normalize serum PRL levels (relatively resistant cases)\(^3\). Several authors have reported extremely resistant cases which showed the exacerbation or metastases of the tumor in spite of the continuous administration of bromocriptine\(^2\). Recently we have also experienced a case of bromocriptine resistant prolactinoma. In this patient the tumor grew gradually on serial MRIs, whereas serum PRL levels fell abruptly from 1,500 ng/ml to less than 1 ng/ml.

In most patients bromocriptine can control hyperprolactinemia and tumor size, but it cannot cure the disease completely. Usually, serum PRL levels raised again quickly if administration of bromocriptine is stopped. Serum PRL levels increased again to about 50\% of the pre-treatment values one month after withdrawal of bromocriptine, which could sufficiently suppress hyperprolactinemia for at least one year. Therefore the patients must take this medicine for an indefinite period.

Given this background, our present policy for the treatment of prolactinomas is as follows: if hyperprolactinemia is present but a microadenoma is not detected by imaging diagnoses, we treated the patient with a small dose of bromocriptine or simply observe without any treatment. When MRI shows an enclosed microadenoma, we recommend transsphenoidal surgery because the success rate for cure is approximately 90\%. For invasive micro- or small adenomas we use bromocriptine, because we cannot estimate a high remission rate by surgery alone. If a patient gets pregnant by this pharmacotherapy, the degree of exacerbation is controllable in these small adenomas. For large prolactinomas with suprasellar extension, we adopt transsphenoidal surgery in order to reduce the tumor bulk. The purpose of surgery is not the normalization of hyperprolactinemia but the decompression of the optic pathway and the sealing of the sellar floor. Patients with CSF rhinorrhea and/or pneumocephalus have been reported during bromocriptine treatment for large invasive prolactinomas. After surgery bromocriptine (7.5~22.5 mg/day) is administered. We do not use radiation therapy for patients with prolactinoma except in cases of bromocriptine resistant tumors.

**GH secreting adenoma**

Although several kinds of treatment for acromegaly are available, surgery must be the first choice in most patients. The post-operative cure rate correlates with pre-operative serum GH levels, size of tumor and invasiveness. If serum GH levels are less than 50 ng/ml,
about 90% of the patients show remission after surgery. Since GH levels do not always correlate with tumor size, some large adenomas are not accompanied by high GH levels. In such cases we can hardly normalize GH values in spite of the extensive removal of the tumor.

In the 1980s most investigators adopted “GH level of less than 5 ng/ml” as the criteria for cure in acromegalic patients. Recently it has become much stricter, and a GH level of less than 2−3 ng/ml in glucose tolerance test1) is required. Our present definition for post-operative cure is the normalization of serum GH level (<5 ng/ml) and IGF-1 value (variable according to age).

Therefore, if the criteria for cure are not satisfied after surgery, the patients should undergo additional treatment. Since about two thirds of acromegalic patients are sensitive to bromocriptine, we usually give this drug to patients with unsuccessful surgical results. Although serum GH levels decrease significantly, size reduction of the tumor occurs in fewer cases. The daily dose for acromegalic patients is usually 7.5−22.5 mg.

For non-responders to bromocriptine we use conventional irradiation with Co60. The actual effect of irradiation appears one or two years later. Serum GH levels decrease gradually year by year. However, since hypopituitarism may be accompanied as the adverse effect, we do not recommend the radiation therapy for young patients.

Somatosatin analogue (octreotide or Sandostatin®) is effective in reducing serum GH levels in almost all patients and in decreasing tumor volume in 20−30% of them. However, octreotide must be injected subcutaneously three times a day or given with a microinfusion pump. Therefore, it can be used to control GH hypersecretion for a short period, such as pre-operative adjuvant therapy. In most cases, a reduction of tumor size occurs within one or two weeks4,5). Like bromocriptine, somatostatin can only control the disease. Thus, serum GH values and tumor volume return to the original level after withdrawal of this medication.

**ACTH secreting adenoma**

ACTH hypersecretion from the pituitary gland under hypercortisolism is called Cushing’s disease. It is sometimes difficult to distinguish Cushing’s disease from an ectopic ACTH secreting tumor not only by endocrinological examinations but also by imaging diagnoses. Previously, bilateral adrenal glands were resected in patients with an indefinite cause of hypercortisolism (Nelson's syndrome).

As a rule high dose dexamethasone (8 mg) suppresses cortisol hypersecretion in Cushing’s disease, while there are many exceptions. CRH (corticotropin releasing hormone) stimulates ACTH secretion in most patients with Cushing’s disease. However, the same responses can be seen in some ectopic ACTH secreting tumors.

High resolution CT scan can detect a microadenoma in at most 50% of patients with a pituitary lesion. Smaller microadenomas (3−4 mm in diameter) can be diagnosed by MRI, especially by dynamic study. Thus, diagnostic accuracy has increased to about 70−80% of all pituitary lesions. However, tiny microadenomas with diameter of less than 3 mm cannot be found by imaging diagnoses at present. Moreover, even if an abnormal finding is obtained,
it is not always the lesion responsible for hypersecretion of ACTH. many kinds of incidental lesions, such as adenomas, Rathke's cysts, hematomas are contained in the pituitary glands of routine autopsy cases.

In order to confirm ACTH hypersecretion from the pituitary gland, selective venous sampling has been used. Traditionally, venous samples were taken from bilateral inferior petrosal sinuses (IPS). However, some false negative cases (usually, 10~20%) were inevitable because of the dilution of pituitary venous blood by extra-pituitary blood. Therefore, we developed the direct cavernous sinus sampling method using the superselective catheterization technique. It provides a sufficient c/p ratio of ACTH values for differential diagnosis without false negative results.

The choice of treatment for Cushing's disease should be transsphenoidal surgery. Patients with high operative risks, such as severe diabetes, cardiac failure and infectious diseases are treated with irradiation and/or pharmacotherapy. During the operation, microadenomas can be detected in about 90% of the patients, in whom hypercortisolism can be corrected after surgery. If a definite microadenoma cannot be found, we resect the half of the anterior pituitary gland, in which the intercavernous ACTH gradient is higher. Those patients who cannot resume the normal ACTH-cortisol rhythm are treated with irradiation and/or medicine. The γ-knife irradiation may be good indication for such patients or for recurrent cases.

References


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