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Recent Management of Pituitary Adenomas

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Pituitary adenomas can be classified into several types according to their endocrinological functions.

1. Non-functioning adenoma.
2. Functioning adenoma.

2.1 Prolactin (PRL) secreting adenoma (prolactinoma).

2.2 Growth hormone (GH) secreting adenoma (acromegaly and/or gigantism).

2.3 Adrenocorticotropic hormone (AC TH) secreting adenoma (Cushing's disease, Nelson's syndrome).

2.4 Thyroid stimulating hormone (TSH) secreting adenoma.

2.5 Gonadotropin secreting adenoma.

Each type of adenoma is treated by different strategies which include surgery, medicines and irradiation. Therapeutic principles are not uniform among neurosurgeons, endocrinologists, gynecologists and radiotherapists. Here I would like to present our current management of the more commonly found pituitary adenomas from the viewpoints of pituitary neurosurgeons.

Non-functioning Adenoma

At present, effective medical treatment is not available for the non-functioning adenoma, 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 transsphenoidal approach regardless of the size and shape of the tumor, because this surgery is very safe and less invasive.[1] We had a lot of hard experiences with transcranial surgery, especially for large pituitary adenomas. When hugh adenomas are resected extensively by a transcranial route, the operative results are gen-

erally very poor.

If a small amount of tumor is left after a transsphenoidal surgery, we treat the patient with conventional irradiation (usually 45 Gray in 5 weeks). When the volume of the residual suprasellar tumor is large, we commonly plan the second transsphenoidal surgery before the adhesion of the nasal mucosa is completed (within 3 months). Since some irregular shaped tumors or large fibrous adenomas cannot be totally removed by repeated transsphenoidal surgery, then we adopt transcranial surgery. And as a rule, radiation therapy is followed after surgery except for the cases of complete tumor removal.

Prolactin Secreting Adenoma

The number of surgical cases has been decreasing because bromocriptine is very effective for prolactinoma. Although the sensitivity to this drug may differ from case to case, in most patients, bromocriptine can significantly decrease not only the serum PRL levels but also the tumor volume.[2] In very sensitive cases, a small dose of bromocriptine can induce the normalization of serum PRL and a marked reduction of tumor size. However, in about 10 per cent of prolactinoma (relatively resistant cases), this medication can hardly normalize serum PRL levels.[3] Several authors also reported the extremely resistant cases in which the tumor showed exacerbation or metastases in spite of the continuous administration of bromocriptine.[2]

In most patients, bromocriptine can control hyperprolactinemia and tumor size, but it cannot cure the disease completely. Usually, serum PRL levels will elevate again quickly when the administration of bromocriptine is stopped. Serum PRL levels may reelevate to about 50 per cent of the pre-treatment values within one month after the withdrawal of bromocriptine which can sufficiently suppress the hyperprolactinemia for at least one year. Therefore, most patients must take the medicine for an indefinite period.

From this background, our present policy for the treatment of prolactinoma is as follows: If hyperprolactinemia is present but a microadenoma is not detected by imaging diagnoses, we treat the patient with a small dose of bromocriptine or follow the patient without any treatment. When MRI shows an enclosed microadenoma, we recommend transsphenoidal surgery because the success rate for cure may be approximately 90 per cent. For invasive micro or small adenomas, we use bromocriptine because we cannot ascertain a high remission rate. And if these patients become pregnant after the medication, the degree of exacerbation may still be controllable because the tumor size is small. For large prolactinoma with suprasellar extension, we adopt transsphenoidal surgery for tumor bulk reduction. The purpose of surgery is not to normalize the hyperprolactinemia but to decompress the optic pathway and to seal the sellar floor. Cases with cerebrospinal fluid rhinorrhea and/or pneumocephalus have been reported during the bromocriptine treatment of large and invasive prolactinomas. After surgery, bromocriptine (7.5-22.5 mg/day) is administered. We do not use radiation therapy for patients with prolactinoma except for cases with bromocriptine resistant tumor.

Growth Hormone Secreting Adenoma

Although several kinds of treatments for acromegaly have been known, surgery must be considered the first choice in most patients. The postoperative cure rate correlates well with the preoperative serum GH levels, the size of the tumor and the tumor invasiveness. If the serum GH levels are less than 50 ng/ml, about 90 per cent of the patients will show remission after surgery. However, since the GH levels do not always correlate with the tumor size, some large adenomas may not accompany with high GH levels. In such cases, we can hardly normalize GH values without extensive removal of the tumor.

In 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 more strict, for instance, GH level of less than 2-3 ng/ml in glucose tolerance test.[1] Our present definition for postoperative cure is the normalization of serum GH level (to less than 5 ng/ml) and the insulin-like growth factor 1 (IGF-1) level (the normal value of which is variable with age).

Therefore, if the criteria for cure are not

achieved after surgery, the patient should undergo additional treatments. Since about two thirds of acromegalic patients are sensitive to bromo-criptine, we usually give this drug to patients with unsatisfactory surgical results. In genreal, the daily dose of bromocriptine for acromegalic patients is 7.5-22.5 mg. And although serum GH levels may decrease significantly after the medication, the reduction of tumor size occurs only in fewer cases.

For non-responders to bromocriptine, we use conventional irradiation with Co.60 The actual effect of irradiation appears one or two years later and serum GH levels will decrease gradually year by year. However, since hypopituitalism may occur as the adverse effect of irradiation, we do not recommend the radiation therapy for younger patients.

Somatostatin analogue (Sandostatin®) is effective in reducing serum GH levels in almost all acromegalic patients and may decrease tumor volume in 20-30 per cent of cases. However, Sandostatin need to be injected subcutaneously 3 times a day or administered by a microinfusion pump. Therefore, it can be used for the control of GH hypersecretion only for a short period, such as during the preoperative adjuvant therapy. Like bromocriptine, somatostatin analogue can only control the disease and the serum GH as well as the tumor volume will usually return to the original stage after the 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 the endocrinological examinations but also by imaging diagnoses. Previously, bilateral adrenal gland resection might be necessary in patients with an indefinite cause of hypercortisolism (Nelson's syndrome).

As a rule, high dose dexamethasone (8 mg) can suppress the cortisol hypersecretion in Cushing's disease. However, many exceptional cases may exist. Corticotropin releasing hormone (CRH) may stimulate ACTH secretion in most patients with Cushing's disease. However, the same response can be seen in some patients with ectopic ACTH secreting tumors as well.

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

In order to confirm that the ACTH hypersecretion originates from the pituitary gland, the selective venous sampling has been used. Traditionally, venous blood samples were taken bilaterally from the inferior petrosal sinuses (IPS).[5] However, some false negative cases are always inevitable because of the dilution of the IPS blood by the extra-pituitary sources. Thus, we developed direct cavernous sinus sampling method using superselective catheterization techniques.[6] This can provide a sufficient central to peripheral ratio of ACTH values for the differential diagnosis without false negative cases.

The first choice of treatment for Cushing's disease should be transsphenoidal surgery. Exceptional cases with high operative risks, such as severe diabetes, cardiac failure or infectious diseases are treated with irradiation and/or medication. During the operation, a microadenoma can usually be detected in about 90 per cent of the patients in whom the hypercortisolism can be corrected after the surgery. If a definite microadenoma cannot be found, we shall resect the half of the anterior pituitary gland in which the intercavernous ACTH gradient is higher. The patients who fail to resume normal ACTH-cortisol rhythm are treated with irradiation and/or medication. The Gamma knife irradiation may be indicated for such patients or for the recurrent cases.

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