

Impact of postoperative pituitary tumor adrenal insufficiency and hormone replacement therapy (HRT) on tumor recurrence

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Abstract. – OBJECTIVE: The present study was aimed to investigate the impact of postoperative pituitary tumor adrenal insufficiency and hormone replacement therapy (HRT) on tumor recurrence.

PATIENTS AND METHODS: The prospective study included 143 pituitary tumor patients as study subjects. Within 6 months after the operation, the study was planned to explore differences (if any) between the tumor recurrence rate of patients treated with hormone replacement therapy and the patients without hormone replacement therapy. Also, the relation of tumor reoccurrence was studied with pituitary tumor adrenal insufficiency.

RESULTS: The age, gender of patients as well as the size of the tumor had no significant correlation with postoperative pituitary tumor adrenal insufficiency. Further, the short-term follow-up lasting for 0.5 to 2.5 years after the operation, the hormone replacement therapy of hydrogenation had no significant impact on tumor recurrence rate.

CONCLUSIONS: The age, patient gender and the size of the tumor were not independent risk factors leading to postoperative pituitary tumor adrenal insufficiency. However, the occurrence rate of adrenal insufficiency of patients in high age group was higher than that of patients in low age group. Also, the occurrence rate of adrenal insufficiency of patients (whose one or several hormones dramatically decreased before the operation) was significantly higher than that of patients (whose hormone level did not decrease before the operation). So, the patients in high age group and whose one or several hormones dramatically decreased before the operation should be paid more attention to the condition of adrenal insufficiency and should be ready for hormone replacement.

Key Words:

Postoperative pituitary tumor, Adrenal insufficiency, Hormone replacement.

Introduction

The pituitary tumor surgery is the first factor responsible for adrenal insufficiency, and about 44% to 52% of pituitary tumor patients suffered adrenal insufficiency of variable degrees¹. Some patients had temporary adrenal insufficiency, but some patients had long adrenal insufficiency. The adrenal insufficiency impact could be noticed in the symptoms including aggregation of poor health, laziness, fatigue, lassitude, appetite decrease, nausea, loss of weight, dizziness, etc. So, the treatment of the above patients with hormone replacement therapy is essential².

Insulin Tolerance Test (ITT) is a gold standard test used for the detection of adrenal insufficiency, but is associated with various risks. Moreover, the above test is also considered as a taboo for the patients with ischaemic heart disease, arrhythmia, and epilepsy³. Further, earlier studies have confirmed that old pituitary tumor patients often suffered adrenal insufficiency after the operation. Also, adrenal insufficiency has been observed to be common in the patients with a dramatic decrease in hormones concentration before the operation. So, in the present work, we performed statistical correlation analyses between the age and gender of patients, size of the tumor, preoperative hormone levels, and postoperative adrenal insufficiency. We also studied corresponding statistics of hormone replacement therapy impact on tumor recurrence at the same time.

Patients and Methods

Among a total 143 patients undergoing the surgery for pituitary tumor from 2013 to 2015, there

Table I. Age Characteristics Description between Adrenal Sufficiency Group and Adrenal Insufficiency Group.

Adrenal function	Cases	Mean	Standard deviation	Minimum value	Maximum value
Insufficiency	72	52.69	11.89	24	80
Sufficiency	71	52.35	12.34	23	83

$t = 0.009$, $p = 0.923$ showed that the age had not statistical different between the two groups and was comparable.

were 69 cases of men and 74 cases of women. The age range was 23 to 83 years, and the average age was 52.52 years old. 129 patients were treated with trans-sphenoidal surgery, and 14 patients were treated with neurosurgery of intracranial tumor. The follow-up time lasted for 0.5 to 2.5 years old. No matter whether the patients were a lack of hormone or not, the patients were given about one week of hormone therapy of dexamethasone or hydrocortisone after the operation. The hormone therapy was stopped before the patients' discharge from the hospital. The patients were then undergone clinical reexamination after half month, 3 months, 6 months and 1 year of operation. Further, cerebral MR reinforcement examination was performed within 3 days and at about 6 months after the operation. The conventional preoperative and postoperative hormone monitoring included: ACTH, cortisol, growth hormone, prolactin, luteinizing hormone, thyroid-stimulating hormone and FT3, FT4. Insulin Tolerance Test (ITT) conducted the judgment of postoperative adrenal insufficiency^{4,5}. All clinical tests and hormone replacement methods were approved by the Ethics Committee of the hospital, and the hospital also signed an informed consent agreement with the patients.

Statistical Analysis

T-test, *chi-square*-test, and *rank-sum*-test were adopted for statistical analysis. $p < 0.05$ was considered statistically significant.

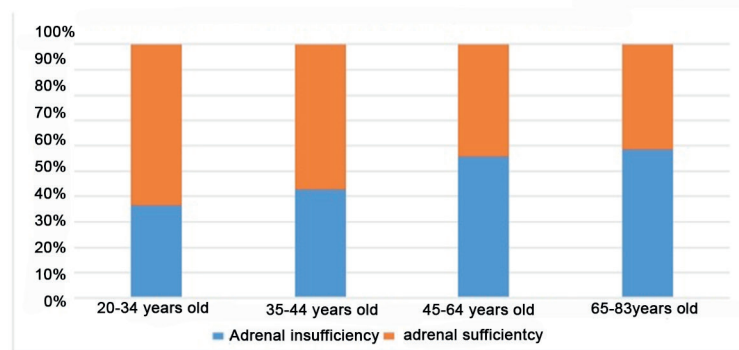
Results

Among 129 patients, 40 patients having their PRL increased obviously, 12 patients having their GH increased, 13 patients having their ACTH increased, 3 patients having TSH, T3 and T4 increased or decreased, 1 patient having ACTH and GH increased, 1 patient having TSH and PRL increased, 1 patient having PRL and GH increased. On the other hand, 73 patients showed no hormone level abnormality. Further, there were 16 patients having one or two or more hormones abnormali-

ties, including FSH, LH, cortisol, T3, T4, TSH, etc. There were 32 patients who were confirmed to suffer adrenal insufficiency through insulin-glucose tolerance test after the operation, and there were 40 patients showing symptoms of adrenal insufficiency upon the monitoring of plasma cortisol, so there was a total of 72 patients with adrenal insufficiencies. The older patients were likely to suffer adrenal insufficiency after the operation, but the difference was not significant statistically (Table I, Figure 1). Further, the gender of patients also had no correlation with adrenal insufficiency (Table II). The tumor size of postoperative adrenal insufficiency patients was not statistically different from the patients without postoperative adrenal insufficiency (Table III). The patients, whose one or several hormones markedly decreased before the operation, showed postoperative adrenal insufficiency (Table IV, Figure 2). The imageological examination was carried out within 0.5 to 2.5 years after the operation to understand the tumor recurrence rate, and there were no significant differences between the patients undergoing hydrocortisone replacement therapy and patients without hydrocortisone replacement therapy.

Discussion

The pituitary tumor is a common disease, which accounts for 10% to 15% of primary intracranial tumors⁶. Although the pharmacological and radiological therapy of pituitary tumor remains improved, the surgery is still the first treatment of choice for the above disease. Further, the recurrence rate of the pituitary tumor slightly decreased but the living standards of the affected patients were not good as reflected in the postoperative dyscrinism. The occurrence rate of permanent pituitary failure after the operation was below 3%. However, the temporary or lasting decrease of pituitary function was common after the operation. No matter what kinds of methods were adopted for surgical treatment, the secretory function of pituitary was influenced. Also, the hormone se-



$\chi^2=3.342, P=0.342$; at the same time, the statistic value was concluded to be 3.319 through rank-sum test. $P>0.05$ was showed by two test methods, so it could not conclude that the occurrence rate of adrenal insufficiency among four age groups was statistically different.

Figure 1. Comparison of occurrence rate of adrenal insufficiency among four age groups.

Table II. Patients' gender and adrenal insufficiency.

Gender	Adrenal function		Total	Insufficiency rate (%)
	Insufficiency	Sufficiency		
Men	35	34	69	50.72
Women	37	37	74	50.00
Total	72	71	143	50.35

$\chi^2 p > 0.05$

Conclusion: the gender between adrenal sufficiency group and adrenal insufficiency group showed no difference, namely, the probability of adrenal insufficiency in men and women was the same.

Table III. Tumor Diameter and Adrenal Insufficiency.

Adrenal function	Cases	Tumor diameter	<i>t</i> value	<i>p</i> value
Insufficiency	72	2.50±0.73	1.22	0.27
Sufficiency	71	2.67±0.67		

The tumor diameter between adrenal sufficiency group and adrenal insufficiency group showed no statistical difference.



Figure 2.

Table IV. Comparison of preoperative hormone decrease and occurrence rate of adrenal insufficiency in patients of two groups.

Groups	Occurrence cases	Non-occurrence cases	Total	Occurrence rate of adrenal insufficiency (%)
Patients undergoing preoperative hormone decrease	14	2	16	87.50
Patients not undergoing preoperative hormone decrease	72	71	143	50.34
Total	86	73	159	54.09

$\chi^2 = 6.572$, $p = 0.01 < 0.05$, it could be concluded that the occurrence rate of adrenal insufficiency between two groups was statistically different, and the occurrence rate of adrenal insufficiency in patients whose one or several hormones decreased before the operation was higher than that in patients whose hormones did not decrease before the operation.

Table V. Comparison of Hormone Replacement and Non-hormone Replacement in Adrenal Insufficiency Patients and Tumor Recurrence Rate in Two Groups

Groups	Recurrence cases	Non-recurrence cases	Total	Occurrence rate (%)
Hormone replacement group	11	61	72	15.28
Non-hormone replacement group	8	63	71	11.27
Total	19	124	143	13.29

$\chi^2 = 0.499$, $p = 0.480 > 0.05$, and it could be concluded that the hormone replacement and non-hormone replacement in adrenal insufficiency patients and tumor recurrence rate in two groups showed no statistical difference.

cretion of the pituitary showed a decrease, so surgical interference was one of important reasons for hypopituitarism^{7,8}.

The adrenal insufficiencies observed in earlier studies showed 85% insufficiency in growth hormone, 75% insufficiency in gonads, 38 % in adrenotropic hormone and 32% insufficiency in thyroid-stimulating hormone⁹⁻¹². The factors leading to above postoperative pituitary tumor adrenal insufficiency could be a lack of one or several hormones before the pituitary tumor surgery. Further, implementation of hormone replacement after the operation has been observed as an independent risk factors leading to adrenal insufficiency. On the other hand, age factor of the older patients tended to suffer adrenal insufficiency but the difference of each age showed no statistical significance. However, tumor size correlated significantly with adrenal insufficiency. So, the collective inference from all these observations could be that the extent of pituitary function damage might be related to comprehensive factors, such as the hardness of the pituitary tumor, the impact of pituitary tumor on pituitary blood circulation and the size of the pituitary tumor.

The decrease of preoperative hormone reflected the degree of pituitary function damage brought out by tumor from different angles. Some people put

forward that the base measuring value of perioperative hormone might be correlated with postoperative adrenal insufficiency¹³. When the function of pituitary function was damaged, the clinical manifestations showed the lack of 1 to 2 hormones¹⁴ or lack of all hormones. In the present study, the occurrence rate of postoperative adrenal insufficiency in patients who lacked one or several hormones before the operation significantly increased and the statistical analysis showed an obvious difference. So, the evaluation of pituitary patients' preoperative hormone had important guiding significance in postoperative hormone replacement and monitoring.

The replacement of growth hormone, testosterone and glucocorticoid did not influence and the observations were in sync with earlier studies^{2,15}. Even though the hormone replacement did not have significant impact on tumor recurrence, the hormone levels were monitored regularly where possible, and the replaced hormone were stopped as soon as possible to reduce other side effects.

Conclusions

The occurrence of adrenal insufficiency is very common after pituitary tumor surgery so that appropriate hormone replacement could improve

the life quality of the patients. The age and gender of patients, as well as the size of the tumor, was not significantly correlated with postoperative adrenal insufficiency, but the decrease and damage of preoperative pituitary function, as well as the disturbance of the pituitary in the process of pituitary tumor surgery, might lead to the pituitary hypofunction, thereby leading to adrenal insufficiency. The replacement of glucocorticoid could not increase the recurrence rate of the tumor, so short-term replacement is safe. Further, preoperative hormone evaluation and postoperative hormone monitoring has important guiding significance during hormone replacement therapy and should be explored in future studies.

Conflict of interest

The authors declare no conflicts of interest.

References

- KARACA Z, TANRIVERDI F, ATMACA H, GOKCE C, ELBUKEN G, SELCUKLU A, UNLUHIZARCI K, KELESTIMUR F. Can basal cortisol measurement be an alternative to the insulin tolerance test in the assessment of the hypothalamic-pituitary-adrenal axis before and after pituitary surgery? *Eur J Endocrinol* 2010; 163: 377-382.
- RAGNARSSON O, MATTSSON AF, MONSON JP, FILIPSSON NYSTRÖM H, ÅKERBLAD AC, KOŁTOWSKA-HÄGGSTRÖM M, JOHANSSON G. The relationship between glucocorticoid replacement and quality of life in 2737 hypopituitary patients. *Eur J Endocrinol* 2014; 171: 571-579.
- FISH HR, CHERNOW B, O'BRIAN JT. Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: a review. *Metabolism* 1986; 35: 763-780.
- COURTNEY CH, McALLISTER AS, McCANCE DR, BELL PM, HADDEN DR, LESLIE H, SHERIDAN B, ATKINSON AB. Comparison of one week 0900h serum cortisol, low and standard dose synacthen tests with a 4 to 6 week insulin hypoglycaemia test after pituitary surgery in assessing HPA axis. *Clin Endocrinol* 2000; 53: 431-436.
- INDER WJ, HUNT PJ. Glucocorticoid replacement in pituitary surgery: guidelines for perioperative assessment and management. *J Clin Endocrinol Metab* 2002; 87: 2745-2750.
- KOVACS, K, SCHEITHAUER BW, HORVATH E, LLOYD RV. The World Health Organization classification of adenohypophysial neoplasms. A proposed five-tier scheme. *Cancer* 1996; 78: 502-510.
- YANG Y, REN ZY, SU CB, WANG RZ, MA WB. Diagnosis and treatment of sellar germinoma. *Zhongguo YiXueKeXueYuan Xue Bao* 2003; 25: 350-353.
- BERG C, MEINEL T, LAHNER H, MANN K, PETERSENN S. Recovery of pituitary function in the late-postoperative phase after pituitary surgery: results of dynamic testing in patients with pituitary disease by insulin tolerance test 3 and 12 months after surgery. *Eur J Endocrinol* 2010; 162: 853-859.
- MARAZUELA, M, ASTIGARRAGA B, VICENTE A, ESTRADA J, CUERDA C, GARCÍA-URÍA J, LUCAS T. Recovery of visual and endocrine function following transsphenoidal surgery of large nonfunctioning pituitary adenomas. *J Endocrinol Invest* 1994; 17: 703-707.
- ARAFAH BM, KAILANI SH, NEKL KE, GOLD RS, SELMAN WR. Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas. *J Clin Endocrinol Metab* 1994; 79: 348-354.
- DEKKERS OM, PEREIRA AM, ROELFSEMA F, VOORMOLEN JH, NEELIS KJ, SCHROUJEN MA, SMIT JW, ROMIJN JA. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab* 2006; 91: 1796-1801.
- WICHES RM, HOVEN S, KRISTOF RA, BLIESENER N, STOFFEL WB. Non-functioning pituitary adenomas: endocrinological and clinical outcome after transsphenoidal and transcranial surgery. *Exp Clin Endocrinol Diabetes* 2004; 112: 323-327.
- CARINA V, KRULJAC I, RADOSEVIC JM, KIRIGIN LS, STIPIC D, PECINA HI, VRKLJAN M. Diagnostic accuracy of perioperative measurement of basal anterior pituitary and target gland hormones in predicting adrenal insufficiency after pituitary surgery. *Medicine* 2016; 95: e2898.
- LEE CC, CHEN CM, LEE ST, WEI KC2 PAI PC, TOH CH, CHUANG CC. Prediction of long-term post-operative testosterone replacement requirement based on the pre-operative tumor volume and testosterone level in pituitary macroadenoma. *Sci Rep* 2015; 5: 16194.
- FISH HR, CHERNOW B, O'BRIAN JT. Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: a review. *Metabolism* 1986; 35: 763-780.