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Specificity of systemic inflammatory response syndrome during the peri-operative period in patients with GH-secreting adenoma

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ABSTRACT

Objective: To analyze the differences in systemic inflammatory responses (SIRS) during the peri-operative period following pituitary surgery, patients with pituitary adenomas were studied. *Methods:* There were three patient groups: group A consisted of 30 patients with GH-secreting adenoma, group B consisted of 20 age-matched patients with Cushing's disease, and group C consisted of 30 patients with other kinds of pituitary adenoma. Levels of white blood cells, C-reactive protein (CRP) and IL-6 in peripheral blood, as well as vital signs, were measured before and after operation. *Results:* Leucocytosis in peri-operative period was significantly milder in group A patients compared with either group B or C patients. The CRP level was significantly higher in both group B and group C patients than in group A patients. SIRS was observed in 17% of the cases in group A; by contrast, it was found in 55%, and 33% of the cases in group B, and in group C, respectively. *Conclusion:* The inflammatory reaction to surgical trauma is milder in patients with GH-secreting adenomas than in patients with other kinds of pituitary adenoma.

1. Introduction

Cross-talk between the neuroendocrine and immune systems has now been well demonstrated. During the peri-operative period following pituitary surgery, immune-neuroendocrine interactions are disturbed, since surgical trauma induces the synthesis of cytokines and systemic inflammatory response syndrome (SIRS) [1] to maintain homeostasis in humans. The duration of SIRS is reported to have a close relationship to the development of post-operative complications. Therefore, it is important to analyze the factors related to SIRS during the peri-operative period following pituitary surgery, in order to have a full knowledge of the cross-talk between the neuroendocrine and immune systems and to be able to treat post-operative patients without fatal complications.

Recent evidence supports a role for growth hormone (GH) as a peptide regulating the immune system under conditions of stress [2]. The immunostimulatory effect of GH can be seen in both cell-mediated and humoral reactions. In addition, to a protective effect of GH on the immune system when under stress, it is also possible that overexpression of GH affects the regulation of the immune system. Patients with acromegaly are good candidates for analysis of the effects of overexpression of GH in humans.

The present study was undertaken to analyze the differences in systemic inflammatory responses following pituitary surgery in patients with various kinds of pituitary adenoma, with special attention being paid to those with GH-secreting adenomas.

2. Materials and methods

Serum GH, ACTH, PRL, TSH, LH, FSH, IGF-1, cortisol, free-T3 and free-T4 levels were measured to determine the hormone secretion ability in patients with pituitary adenomas. White blood cells (WBC) levels were measured before the operation and on days 1, 3, 6 and 8 after the operation. Vital signs, such as temperature, heart rate and respiratory rate, were measured after the operation until post-operative day 10. Likewise, the levels of C-reactive protein (CRP) [3], a marker of inflammation, were measured sequentially (post-operative days 1, 3, 6 and *8*) after the operation. IL-6 levels were also measured before the operation and on post-operative day 1. CRP and IL-6 measurements were performed by SRL Co., Ltd. (Tokyo, Japan).

SIRS was defined according to SIRS diagnostic criteria [1]. When more than two out of four criteria, namely, abnormal temperature (>38 °C or <36 °C), leucocytosis (>12,000 cells/mm^3), tachycardia (>90 beats/min) or tachypnea (>20 breaths/min), were fulfilled after surgery, the patient was diagnosed as having SIRS. To measure the magnitude of surgical trauma, operation length and the volume of blood loss during surgery were employed.

Transsphenoidal surgery was performed by only one skilled pituitary neurosurgeon (H.I). Peri-operative therapy and manage-

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ment was carried out according to clinical passing made in our hospital (Table 1). There was no case of variance in this study.

The statistical significance of differences between the groups was calculated using the Student's *t*-test and the Mann–Whitney *U* test. A *p* value of less than 0.05 was considered significant.

3. Patients

A retrospective case-controlled study of patients who had undergone transsphenoidal surgery for pituitary adenoma at Ohara Medical Center Hospital between 2006 and 2007 was performed. From among 190 surgical cases, three patient groups were defined: group A consisted of 30 patients with GH-secreting adenoma, group B consisted of 20 age-and sex-matched patients with ACTH-secreting adenoma, and group C consisted of 30 age- and sex-mached patients with other kinds of pituitary adenoma. Group C included 22 cases of non-secreting adenoma, 5 cases of Rathke's cleft cyst, and 3 cases of prolactin-secreting adenoma. The mean age in all groups was 51 years. The male to female ratio was 3:2 in each groups.

The procedures were conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. Informed consent was obtained from the studied patients.

4. Results

The mean ± SD GH and IGF-1 levels were 29.1 ± 50.3 ng/ml and 687.7 ± 298 ng/ml, respectively, in group A patients, 0.812 ± 1.36 ng/ml and 170.6 ± 68.3 ng/ml, respectively, in group B patients, and 0.34 ± 0.41 ng/ml and 138.6 ± 71.0 ng/ml, respectively, in group C patients (Table 2). There were significant differences in serum GH levels between group A and B patients ($p = 0.001$), and between group A and C patients ($p = 0.001$). There were also significant differences in serum IGF-1 levels between group A and B patients ($p = 0.0001$), and between group A and C patients ($p = 0.0001$). The mean ± SD cortisol levels were 11.2 ± 3.9 in group A patients, 22.0 ± 9.2 in group B patients, and 13.6 ± 7.3 in group C patients. There were significant differences in serum cortisol levels between group A and B patients ($p = 0.0001$), and between group B and C patients ($p = 0.0009$). The mean ± SD free-T3 and free-T4 levels were 2.78 ± 0.63 ng/ml and 1.09 ± 0.19 ng/ml, respectively; in group A patients, 2.26 ± 0.62 ng/ml and 1.12 ± 0.22 ng/ml, respectively, in group B patients, and 2.67 ± 0.45 ng/ml and 0.98 ± 0.25 ng/ml, respectively, in group C patients. There were no significant differences in serum free-T3 and free-T4 levels among these three groups.

The changes in WBC counts in peripheral blood are shown in Fig. 1. Leucocytosis throughout post-operative days 1, 3, 6 and 8 was significantly milder in group A patients than in group B and C patients ($p < 0.001$). In addition, leucocytosis on post-operative days 1, 6 and 8 was significantly milder in patients with Cushing disease than in control group C patients ($p < 0.001$). The CRP levels in peripheral blood, before and after the operation, are shown in Fig. 2. These were significantly higher in group B and C patients than in group A patients ($p < 0.001$). Although there was a significant difference in WBC counts on post-operative days 1, 6 and 8 between groups B and C, there were no significant differences in CRP levels in peripheral blood at the same time points between groups B and C. During the post-operative period, abnormally high CRP levels were found in 13 cases (43%) out of 30 in group A, whereas 19 cases (95%) out of 20 in group B, and all patients (100%) in group C showed abnormally high CRP levels. The CRP levels of all of the acromegaly patients returned to normal by 6 days after surgical trauma; however, 35% of the patients in group B and 40% of the patients in group C showed prolonged high CRP levels, even 8 days after surgical trauma.

SIRS was observed in five cases out of 30 (17%) in group A; by contrast, it was found in 9 out of 20 cases (55%) in group B, and 10 out of 30 cases (33%)s in group C. Thus, the inflammatory reaction to surgical trauma is milder in group A patients than in group B and group C patients.

There were no significant differences in post-operative IL-6 values between groups A and B ($p = 0.1671$), groups B and C ($p = 0.6233$), and groups A and C ($p = 0.1823$). There was a significant correlation between operation time and Il-6 value on post-operative day 1 in group A ($p = 0.0001$), and a significant correlation between operation time and IL-6 value on post-operative day 1 in groups B ($p = 0.0001$) and C ($p = 0.002$). There was a significant correlation between the volume of blood loss and IL-6 value in groups A ($p = 0.0001$), B ($p = 0.0001$) and C ($p = 0.0002$). Therefore, IL-6 levels seemed to change in association with operation time and blood loss in patients who underwent transsphenoidal surgery. Besides, there was a significant relationship between CRP levels and IL-6 levels on postoperative day 1 in groups A ($p = 0.0001$), B (0.0001) and C (0.0280). Therefore, it was regarded that CRP on post-operative day 1 represented the magnitude of surgical stress, such as operation time and blood loss.

5. Discussion

The clinical sequelae of the massive inflammatory reaction resulting from systemic cytokine release have been termed "systemic inflammatory response syndrome" (SIRS) [4]. Inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8, are released in local

Table 1
Procedure for patients' care and management before and after pituitary surgery in our hospital.

Intravenous drip injection
Operation day: Hydrocortone 300 mg, H2-blocker 20 mg, antibiotics 2 g
Post-op day1: Hydrocortone 160 mg, H2-blocker 20 mg, antibiotics 2 g
Post-op day2: Hydrocortone 120 mg, antibiotics 2 g
Post-op day3: Hydrocortone 80 mg, antibiotics 2 g
Post-op day4: Hydrocortone 60 mg, antibiotics 2 g
Post-op day5: Hydrocortone 40 mg, antibiotics 2 g
Post-op day6: Hydrocortone 40 mg
Post-op day7: Hydrocortone 30 mg
Post-op day8: Hydrocortone 30 mg
Post-op day9: Dexamethasone 0.5 mg (oral administration)
Post-op day10: Dexamethasone 0.5 mg (oral administration)
Post-op day11: Dexamethasone 0.5 mg (oral administration)
Post-op day12: discharge

Table 2
Clinical and hormonal data in A, B, and C group. (mean ± S.D.)

Group	N	Mean age	M:F ratio	GH level	IGF-1level	Cortisol level	fT 3 level	fT 4 level
A	30	51	3/2	29.1 ± 50.3*	687 ± 298*	11.2 ± 3.9	2.78 ± 0.63	1.09 ± 0.19
B	20	51	3/7	0.812 ± 1.36	170 ± 68.3	22.0 ± 9.2*	2.26 ± 0.62	1.12 ± 0.22
C	30	51	2/1	0.34 ± 0.41	138 ± 71.0	13.6 ± 7.3	2.67 ± 0.45	0.98 ± 0.25

* $P < 0.001$.