Assessment of pre- and postoperative endocrine function in 94 patients with Rathke’s cleft cyst

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Abstract. We reviewed 94 patients with Rathke’s cleft cyst (RCC) who were surgically treated at Nippon Medical School Hospital between December 1995 and July 2009 to clarify the effect of surgery on their endocrine function. In our statistical analysis we considered their age and sex, the cyst volume, and preoperative MRI findings. Using simple linear- and multiple regression analysis we evaluated the association between these factors and their preoperative hormone baseline levels. To assess pre- and postoperative anterior pituitary function we subjected the results of various hormone loading tests to the Wilcoxon rank sum test. Surgery improved headache and visual impairment in most patients and elevated PRL levels were significantly normalized after surgery (p = 0.004). However, pre- and postoperative anterior pituitary hormone loading tests revealed that the levels of GH, TSH, LH, and FSH were not improved significantly by surgery. Although the ACTH loading test showed postoperative improvement, the change was not statistically significant. We suggest that RCC patients with headache or visual impairment are good candidates for surgery. We also recommend that patients with hyperprolactinemia and those with ACTH deficiency whose MRI findings reveal low-intensity on T1WI and high-intensity on T2WI are likely to benefit from surgery. In contrast, RCC patients with other hormone dysfunctions do not appear to benefit from surgical intervention.

Key words: Rathke’s cleft cysts, Endocrine function, Hyperprolactinemia

RATHKE’S CLEFT CYST (RCC) is a benign cystic lesion resulting from the persistence of the fetal Rathke pouch. Microscopic evidence for RCC is found in 2-26% of autopsies and the spread of magnetic resonance imaging (MRI) has led to the incidental identification of many asymptomatic individuals [1-3]. In RCC patients with symptoms, surgery tends to improve chronic headache and visual impairment [4-12]. However, as there is currently no consensus on surgical indications from the perspective of their endocrine function, we retrospectively evaluated the pre- and postoperative status of the endocrine function and clinical manifestations in RCC patients.

Patients and Methods

Patient population

We reviewed 94 RCC patients who were surgically treated at Nippon Medical School Hospital between December 1995 and July 2009. Their diagnosis was confirmed by both operative and pathological findings. They were 27 men and 67 women, their average age was 46.4 ± 18.4 years. The mean follow-up period was 72 months (range 2-190 months).

Statistical analysis

In our statistical analysis we considered the patient age and sex, the cyst volume, the color of the cyst content and preoperative MRI findings. The cyst volume was calculated with the formula: cyst height × width × depth (mm). We evaluated the association between these factors and the preoperative hormone baseline including the level of prolactin (PRL), thyroid stimulating hormone (TSH), free thyronine (fT3), free thyroxine (fT4), adrenocorticotropic hormone (ACTH), cortisol, insulin-like growth factor 1 (IGF-1), and testosterone by using simple linear- and multiple regression analysis. We excluded growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol from the hormone baseline analysis because these hormones fluctuate under the influence...
of factors such as stress and the menstrual cycle. To assess pre- and postoperative anterior pituitary function we applied the Wilcoxon rank sum test to the results of various hormone loading tests. We used the $1 \times m$ contingency table test to evaluate the association between changes in the PRL level and the patient age (0-19-, 20-39-, 40-59-, and $\geq$ 60 years) and sex, the maximum cyst diameter (< 10-, 10-15-, 16-20-, 21-25-, and $>26$ mm), and the MRI signal intensity of the cyst (high-, iso-, or low-intensity on T1- and T2 weighted images (T1WI, T2WI)).

**Surgical technique**

Of the 94 patients, 91 (96.8%) underwent transsphenoidal surgery (TSS). Of these procedures, 31 (34.1%) were microscopic sublabial TSS, and 60 (65.9%) were endoscopic endonasal TSS. Three patients (3.2%) underwent transcranial surgery. To preserve the normal pituitary gland we usually only drained the cyst content and partially resected the cyst wall for pathological diagnosis.

**MRI findings and cyst color**

In 84 patients MRI scans were available for review (Table 1a). On 22 scans (26%) the cyst fluid was low-intense on T1- and high-intense on T2WI, on 17 scans (20%) it was high-intense on T1- and low-intense on T2WI, on 15 scans (18%) it was iso-intense on T1- and high-intense on T2WI, and in another 15 cases (18%), it was high-intense on both T1- and T2WI.

In 76 of these 84 patients the color of the cyst content was recorded in the operative notes. We analyzed the correlation between the color of the cyst content, i.e. clear, yellow, and white, and imaging findings on both T1- (b) and T2-weighted MRI scans (c). The cyst content was white in most of the 76 patients (n=39, 51.3%) followed by yellow (n=20, 26.3%) and clear (n=17, of factors such as stress and the menstrual cycle. To assess pre- and postoperative anterior pituitary function we applied the Wilcoxon rank sum test to the results of various hormone loading tests. We used the $1 \times m$ contingency table test to evaluate the association between changes in the PRL level and the patient age (0-19-, 20-39-, 40-59-, and $\geq$ 60 years) and sex, the maximum cyst diameter (< 10-, 10-15-, 16-20-, 21-25-, and $>26$ mm), and the MRI signal intensity of the cyst (high-, iso-, or low-intensity on T1- and T2 weighted images (T1WI, T2WI)).

**Endocrine function tests**

The GH level was determined with the GH-releasing hormone (GRH) test or, in patients treated after 2007, the GH-releasing peptide-2 (GHRP-2) test. In the GRH test, peak values of 3 ng/mL were recorded as a low, anomalous response; peak values greater than 3 ng/mL were considered to represent a normal response. In the GHRP-2 test, peak values below 9 ng/mL were defined as severe deficiency, of 9-15 ng/mL as moderate deficiency, and values above 15 ng/mL as a normal response. The level of both FSH and LH was assayed with the LH-releasing hormone test. We considered a level less than twice the preloading basal hormone level to represent a low response. ACTH levels were evaluated with the corticotrophin-releasing hormone test; a value less than twice the preloading basal hormone level was recorded as a low, anomalous response.

We analyzed PRL secretion by using only the serum PRL level; no loading tests were performed. We determined the presence of hyperprolactinemia, defined as a PRL level greater than 24 ng/mL in women and 17 ng/mL in men. None of the patients with hyperprolactinemia took medications that can induce hyperprolactinemia.

**Results**

**Presenting symptoms**

Headache was reported by 36 of the 94 patients (38%) and visual impairment by 32 (34%); 26 patients (28%) manifested some endocrine dysfunction. Visual impairment was defined as failing corrected visual acuity or visual field loss by the Goldmann visual field test. Some patients presented with more than one symptom. In 10 patients (11%) RCC was found incidentally on MRI scans and they were offered elective surgery.

**Table 1** MRI findings and cyst colors

<table>
<thead>
<tr>
<th></th>
<th>T1WI</th>
<th>T2WI</th>
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<tbody>
<tr>
<td><strong>a.</strong></td>
<td>Low</td>
<td>Iso</td>
</tr>
<tr>
<td>T1WI</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Iso</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>High</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

| **b.** | Clear | Yellow | White |
|---|---|---|
| T1WI | 13 | 2 | 7 |
| Iso | 2 | 4 | 15 |
| High | 2 | 14 | 17 |

| **c.** | Clear | Yellow | White |
|---|---|---|
| T1WI | 2 | 8 | 8 |
| Iso | 2 | 5 | 3 |
| High | 13 | 7 | 28 |

a. In 84 patients MRI scans were available for review. On both T1- and T2 weighted images we observed different levels of intensity.
b. In 76 patients the color of the cyst content was recorded in operative notes. We analyzed the correlation between the color of the cyst content and findings on both T1- (b) and T2-weighted MRI scans (c).
identify factors that affected the baseline level of each hormone (Table 2). We found that there was an inverse correlation between the IGF-1 level and the cyst volume. The PRL baseline level decreased with advancing age (-0.31/year); it was higher in women and in patients whose cysts contained non-clear fluid. The ACTH baseline level decreased as the cyst volume increased; it was also low in patients with white cyst fluid.

Pre- and postoperative anterior pituitary hormone loading tests revealed that the levels of GH, TSH, LH, and FSH were not improved significantly by surgical treatment ($p = 0.638$, $p = 0.807$, $p = 0.208$, $p = 0.82$, respectively; Wilcoxon rank sum test) (Fig. 4). Although the ACTH loading test tended to show postoperative improvement, the change was not statistically significant ($p = 0.135$).

As the elevated PRL level was significantly improved after surgery ($p = 0.004$) we assessed contributing factors. We found that none of the factors included in our analysis (sex: $p = 0.444$, age: $p = 0.643$, maximum cyst diameter: $p = 0.229$, and MRI T1WI: $p = 0.821$, T2WI: $p = 0.916$) exhibited a significant correlation with the improvements seen in the PRL level.

Of the 94 patients included in this study, 7 had diabetes insipidus (DI) before the operation; these patients

**Endocrinological findings**

Using simple linear regression analysis we assessed the association between the preoperative anterior pituitary hormone baseline and factors such as the patient age and sex, the cyst volume, and the color of the cyst content (Figs. 1-3). In younger patients, the PRL and IGF-1 level tended to be high while in elderly patients the level of TSH tended to be high. Also, the level of IGF-1 and testosterone was low in patients whose cyst content was clear. There was no strong association between other hormone levels and the color of the cyst content (Fig. 3).

We next performed multiple regression analysis to
Fig. 2 Analysis of the correlation between the cyst volume and the preoperative hormone baselines. Red and black dots indicate females and males, respectively.

Fig. 3 Analysis of the correlation between the color of the cyst content and the preoperative hormone baselines. C: clear, Y: yellow, W: white
did not benefit from surgery and required postoperative hormone replacement therapy. One patient developed DI after the operation.

**Discussion**

RCCs exhibit different intensity on MRI scans [13-15]. We analyzed the correlation between MRI findings and the color of the cyst content. Like Sumida et al. [15] we found that cysts that were high-intense on T1WI tended to contain yellow or white fluid. According to Hayashi et al. [14] cystic fluids that exhibited increased protein concentrations in vitro were high-intense on T1- and low-intense on T2WI, indicating that the signal intensity reflects their protein density. Our findings coincide with those reported by others [13, 14] that the color of cyst content with low intensity on T1- and high intensity on T2WI tended to be clear.

Our study of the correlation between the color of the cyst content and the preoperative hormone baseline levels revealed that in patients with clear cyst con-
tent the baseline level of IGF-1 and testosterone was low. We also noted that patients with clear cyst content tended to manifest visual impairment, suggesting that their cysts compressed the optic chiasm as well as the hypothalamic-pituitary axis, resulting in decreasing both the IGF-1- and testosterone levels. Others [10, 13, 15] reported that cyst with clear content tended to be low-intense on T1- and high-intense on T2WI; they attributed the visual impairment experienced by patients with these cysts to compression of the hypothalamic-pituitary axis. According to Hayashi et al. [14], a high-intensity signal on T1- and an iso- or low-intensity signal on T2WI relative to the white matter reflects the protein concentration of the cystic fluid, and chronic inflammation around these cysts may explain the headache and pituitary dysfunction exhibited by these patients. Indeed, in 32 of our 33 patients (93.9%) with a high-intensity signal on T1WI the cyst content was mucinous white or yellow and there were some cases with histological evidence of lymphocytic infiltration into the cyst wall, indicating inflammatory reaction in surrounding structures.

Like others [4–6, 8, 10–12], we found that surgical intervention improved the symptoms of headache and visual impairment in most patients with RCC. Consequently, these patients may be good candidates for surgical intervention. Nishioka et al. [16] who analyzed the headache associated with RCC reported that frontal episodic headache is common and characteristic and may indicate intermittent inflammatory reaction around the cyst resulting in irreversible endocrine dysfunction and that these patients should undergo surgical treatment to prevent possible irreversible endocrine dysfunction. Our results, as those of others [5, 6, 10, 17], indicate that surgery rarely improved preoperative endocrine dysfunction and we agree that it may be primarily indicated in RCC patients with episodic headache.

From the perspective of endocrine function, our RCC patients with hyperprolactinemia, as those of others [6, 10, 17], experienced statistically significant postoperative improvement.

Although our patients with ACTH hyposecretion showed postoperative improvement, the changes in our study population were not statistically significant ($p = 0.135$) because in most of our patients the preoperative serum ACTH level was normal. In 3 of 4 patients whose ACTH secretion recovered after surgery the cyst fluid was low-intense on T1WI and high-intense on T2WI; perioperative findings revealed it to be a CSF-like liquid. Thus, the symptoms elicited in RCC patients with low-intensity on T1WI and high-intensity on T2WI may be attributable to simple compression of surrounding structures without inflammation and cyst decompression by surgery can improve the secretion of ACTH.

Like el-Mahdy and Powell [6], we did not observe a statistically significant difference in the pre- and postoperative levels of GH, cortisol, and gonadotropin, indicating that surgical intervention may not correct hyposecretion of those hormones. Wichers-Rother et al. [18] showed that in patients with non-functioning adenomas, surgery did not significantly improve anterior pituitary function. They attributed this finding to long-term compression of the hypothalamic-pituitary axis by macroadenomas. Similarly, in patients with RCC, long-term compression by cysts may result in irreversible hyposecretion of some hormones and inflammation induced by the cyst content may additionally perpetuate endocrine impairment.

Our multiple regression analysis showed an inverse correlation between the cyst volume and the IGF-1 level. We posit that the compression exerted by larger cysts is an etiologic factor in the development of hypothalamic disorders, resulting in decreased GH and IGF-1 secretion.

Surgery did not improve the symptoms in our 7 patients with pre-existing DI. This finding coincides with other reports [5, 17]. One patient whose cyst contained white, viscous fluid developed DI postoperatively. As we aspirated the cyst content without surgically addressing the posterior pituitary, we posit that inflammatory reaction in surrounding structures might played a role in the development of DI by this patient.

In summary, from the perspective of endocrine function, we suggest that RCC patients with hyperprolactinemia and those with ACTH dysfunction who harbor cysts exhibiting low intensity on T1WI and high intensity on T2WI are good candidates for surgical intervention. In contrast, RCC patients with other pituitary hormone dysfunctions including DI do not appear to benefit from surgery and the advisability of surgery should be carefully considered in such patients.

Conclusions

We analyzed the endocrine function and clinical manifestations in 94 RCC patients before and after surgery to identify surgical indications. Ours is the first
study reviewing the results of pre- and postoperative hormone loading tests in RCC patients to clarify the effect of surgical intervention on their endocrine functions. Since TSS is minimally invasive from the perspective of addressing endocrine function, we suggest that RCC patients suffering from headache or visual impairment are good candidates for surgery. Patients with hyperprolactinemia and those with ACTH deficiency whose MRI findings reveal low-intensity on T1WI and high-intensity on T2WI are also good candidates for surgical treatment. However, RCC patients with dysfunctions in other pituitary hormones may not benefit significantly from surgical intervention.

References