

Significant Improvement in Chronic Persistent Headaches Caused by Small Rathke Cleft Cysts After Transsphenoidal Surgery

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Abstract: Purpose: Rathke cleft cysts (RCC) are usually asymptomatic and can be observed using conservative methods. However, some patients with RCCs have severe headaches even if they are small enough to be confined to the sella, and these small RCCs have seldom been discussed. This study presents an investigation into clinical characteristics of small RCCs associated with severe headaches, demonstrating efficacy and safety of endoscopic transsphenoidal surgery (ETSS) to relieve headaches.

Methods: In this study, 13 patients with small RCCs (maximum diameter < 10mm) who presented with headaches and were treated at our institute from 2009 to 2014 were recruited. Headache impact test (HIT)-6 score was calculated both pre- and postoperatively to evaluate headache severity.

Results: All patients complained of severe headaches, which disturbed their daily life. Most headaches were non-pulsating and localized in the frontal area. Characteristically, 6 patients (46%) experienced severe headaches with sudden onset while continued chronically. Headache impact test (HIT) -6 score was 64 on average, meaning headaches affected daily life severrely. After surgical decompression of the cyst, headache in all of the patients improved dramatically and HIT-6 score decreased significantly to 37, suggesting that headaches were diminished. No newly developed deficiencies of the anterior pituitary lobe function were detected. Postoperative occurrence of diabetes insipidus was found in 2 patients, both of which were transient. No recurring cysts were found.

Conclusion: Severe headaches can develop from small RCCs. In the present study, ETSS was performed on such patients effectively and safely to relieve their headaches.

Cover Letter

September 16, 2016

Editor-in-Chief of "World Neurosurgery"

We would like to submit the enclosed manuscript entitled, "**Significant improvement in chronic persistent headaches caused by small Rathke cleft cysts after transsphenoidal surgery**", for publication in "World Neurosurgery"

I think that this paper may contribute to clarification of small rathke cleft cysts causing headache, and the efficacy and safety of endoscopic transsphenoidal surgery.

The content of this manuscript has not been published elsewhere in any form.

The authors declare that the article content was composed in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Thank you for your consideration of our paper. We are looking forward to hearing from you with kind regards.

Sincerely,

Issei Fukui, Yasuhiko Hayashi, Daisuke Kita, Yasuo Sasagawa, Masahiro Oishi,
Osamu Tachibana, Mitsutoshi Nakada

[Conflict of interest]

The authors declare that they have no conflicts of interest with regard to this study.

【List of Abbreviations】

CT: computed tomography

DI: diabetes insipidus

ETSS: endoscopic transsphenoidal surgery

HIT: headache impact test

MR: magnetic resonance

RCC: Rathke cleft cyst

WI: weighted image

【Highlights】

- Severe headaches disrupting daily life can develop from small RCCs.
- Severe headaches could be caused by even small RCCs and be improved by ETSS safely and dramatically.
- ETSS should be performed for small RCCs associated with severe headaches.

**Significant improvement in chronic persistent headaches caused by small Rathke cleft
cysts after transsphenoidal surgery**

regular article

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Running head: Headache caused by small Rathke cleft cyst

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anterior pituitary lobe function were detected. Postoperative occurrence of diabetes insipidus was found in 2 patients, both of which were transient. No recurring cysts were found.

Conclusion. Severe headaches can develop from small RCCs. In the present study, ETSS was performed on such patients effectively and safely to relieve their headaches.

Key words: Rathke cleft cyst, headache, transsphenoidal surgery, endoscope

【Introduction】

Rathke cleft cyst (RCC) is a benign cystic lesion appearing between the anterior and posterior lobes of the pituitary gland that originates from a remnant of the Rathke pouch (1). Autopsy studies show that RCCs are detected in 3.7-22% of cases (2, 3). Although RCCs are usually asymptomatic, some become symptomatic with symptom such as headaches, endocrine dysfunction, and visual function disturbances (1, 4, 5). Among them, headaches are the most common symptom of RCC (4, 6, 7), and can greatly impact normal daily life (8).

In the case of symptomatic RCCs, surgical aspiration of cyst content is considered to be necessary to remove mass and reduce its effects on surroundings, and the inflammation due to cyst content (6, 9, 10). Because generally most asymptomatic RCCs are considered to be small, it remains unclear whether small RCCs can result in severe headaches. In order to determine surgical indication for small RCCs, we investigated the clinical characteristics of small RCCs causing headaches, and the efficacy and safety of endoscopic transsphenoidal surgery (ETSS) in this study.

【Methods】

This retrospective study was approved by the Kanazawa University Institutional Review Board. In our institute, 27 patients harboring RCC were treated surgically between April 2009 and November 2015. Among them, 13 patients with RCCs with maximum diameters smaller than 1 cm on magnetic resonance (MR) image sagittal sections, and with the chief complaint of severe headaches, were enrolled in this study. We compiled the following items from their clinical charts: age, sex, headache characteristics, endocrinological functions, radiological findings of MR images, operative findings, pathology, and recurrence.

Headache evaluation

Severity of headache was assessed both pre- and postoperatively (3 months after TSS) with a headache impact test (HIT) -6, which is a tool to assess the impact on patients' daily lives and has been used in several studies (8, 11, 12). The HIT-6 score is calculated from the simple summation of six items ranging between 36 and 78. The higher scores suggest more severe headaches. If the score is 60 or more, the headaches have a very severe impact on their daily lives. If the score is 49 or less, the headaches have little impact.

Radiological evaluation

We used a 3.0-tesla MR imaging (GE Health care Japan Corp., Tokyo) to obtain sagittal images before ETSS. Radiological evaluation was undertaken as follows: signal intensities of cyst contents in both T1 and T2-weighted images (WI). Enhancement of cyst wall was in T1-WI with gadolinium administration.

Endocrinological evaluation

Endocrinological status was examined both pre and postoperatively, and included determining levels of plasma growth hormone, prolactin, adrenocorticotrophic hormone, cortisol, thyroid-stimulating hormone, luteinizing hormone, and follicle stimulating hormone. Urine volume and gravity were evaluated to diagnose diabetes insipidus (DI). After ETSS, corticotropin-releasing hormone, thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone loading tests were carried out for reserve capacity evaluation of each hormone tested preoperatively.

Surgical procedures

ETSS for RCCs was indicated when headaches were uncontrollable with painkillers

and disturbed patients' daily lives. The inferior aspects of RCCs were usually covered with the thinnest part of the anterior lobe, which could be observed accurately in a sagittal section of MR T1-WI with contrast enhancement. After incision of the cyst wall, the cyst content was drained out sufficiently and the cyst wall was resected partially for pathological diagnosis. Sellar floor reconstruction was not done unless a cerebrospinal fluid leakage was present.

Statistical analysis

Statistical analysis was performed using commercially available software (Ekuseru-Toukei 2010, Social Survey Research Information Co). Paired Student's t test was used for comparison between pre and post HIT-6 scores. A *p*-value of <0.05 was considered statistically significant.

【Results】

Patient characteristics

The details of the 13 patients in this study are summarized in Table 1. There were 3 males and 10 females, and their mean age was 42.2 (25–72) years. All patients complained of uncontrollable headaches. The mean HIT-6 score was 63.9 (60–72), which means that their headaches had a significant influence on their daily lives, with a mean period since onset of headaches being 41.8 (2–240) months. The headaches were localized frontally in 8 patients (62%) and in the entire head in 5 patients (38%). The headaches were characterized as chronically persistent in 11 patients (85%), of which 6 patients (46%) experienced sudden headaches, and 2 patients (15%) had severe sudden onset headaches without chronic headaches. Most of the patients complained that their headaches were a non-pulsating compression. After ETSS, headaches were dramatically improved in all patients and the postoperative mean HIT-6 score was 37.2 (36–40), which was significantly lower than preoperative score ($P < 0.01$).

Endocrinological findings

None of the patients had endocrinological insufficiencies except one, who had pituitary dysfunction, and required hormone replacement therapy for hypothyroidism

and hypocortisolism. Sudden onset DI was present in 2 patients (15%), which was persistent postoperatively, and their MR images demonstrated obviously swollen pituitary glands, indicating hypophysitis. These two patients also manifested sudden onset headaches supposedly derived from rupture of RCC. After surgery, no additional functional insufficiencies of the anterior pituitary lobe were detected, but transient DI was found in 2 (15%) (Table 2).

Radiological findings

The mean size of cysts presented in our study was 7.0 ± 1.8 mm (mean \pm S.D., 4.3–9.9 mm). Signal intensities of the cyst contents in T1-WI were as follows: hyper-intense in 9 patients (69%), iso-intense in 3 patients (23%) and hypo-intense in 1 patient (8%). Signal intensities in T2-WI were as follows: hyper-intense in 6 patients (46%), iso-intense in 1 patient (8%), and hypo-intense in 6 patients (46%). Intracystic nodules, which were seen as very hypo-intense in T2-WI, were recognized in 7 patients (54%) (Table 2).

Operative and histopathological findings

Intraoperative macroscopic findings revealed cyst contents were a mucinous yellow

fluid in 12 patients (92%) and cerebrospinal-fluid-like in 1 patient (8%). Upon histopathological examination, accumulation of lymphocytic cells and massive fibrosis in cyst walls was found in 5 patients (38%) and there was no evidence of squamous metaplasia were. Postoperatively, patients were followed for 36.0 (5-87) months on average and no recurrence of RCC were encountered (Table 3). Representative cases are shown in Figure 1.

【Discussion】

Although it is well known that headaches are the most common symptom in patients with RCC (4, 6, 7), it has not yet been determined if small RCCs, like microadenoma, could lead to severe headaches affecting daily life. The results of our study indicate that severe headaches could be caused by even small RCCs and be improved by ETSS safely and dramatically.

Previous reports demonstrated that the headaches were improved by surgical aspiration of the cyst content at a high rate (5, 5, 13, 14). In our study, severe headaches disappeared dramatically in all patients and HIT score decreased significantly with the use of ETSS. Protein rich cyst content, hyper-intensities in T1-WI, and pathological chronic inflammation of the cyst wall, were recognized in patients manifesting headaches (5, 7, 15). Nishioka et al. described the features of these headaches as frontal, episodic, and non-pulsating (7). These headache characteristics are similar that found in our study, suggesting that small RCCs could induce severe headaches that could be improved almost completely by surgery. Regarding the etiology of headaches caused by RCCs, many authors report the importance of inflammation spreading to surrounding structures including the dura of the sella turcica, the pituitary, and the internal carotid artery (1, 16). This is considered to be applicable to small RCCs. In our study, MR

images revealed that most of the cyst contents had hyper-intensities in T1-WI and had intracystic nodules with very hypo-intensities in T2-WI. Moreover, pathological inflammation, such as lymphocyte infiltration and massive fibrosis, was recognized at the cyst wall. Therefore, presumably in small RCCs, cyst content caused enough inflammation to surrounding structures to lead to severe headaches that effect daily life.

No additional endocrinological insufficiencies were found except for 2 transient DI after ETSS. Preservation of endocrinological function was accomplished by puncturing the thinnest cyst wall at the lower aspect of the sella. Aho et al. revealed that aggressive resection of cyst could cause postoperative endocrinological insufficiencies (9). In our study, cysts could be drained completely with minimum wall resection with the use of an angled endoscope; no recurrence of RCCs has been reported so far. It should be noted that ETSS with an angled endoscope could contribute to not only reliably improving headache and preventing their recurrence, but also preserving endocrinological function.

Sanno et al. reported that 15.9% of untreated RCCs decrease in size and 76.5% remain unchanged (17). In addition, spontaneous involution of RCCs has been reported (18). Therefore, the question remains whether all symptomatic RCCs need to be

surgically treated, given the risks of an operation. In our study, it became clear that small RCCs could lead to severe headaches that impact daily life, and headaches improve dramatically or disappear after surgery. These results indicate that small RCCs causing severe headaches should be treated surgically. However, the timing of surgery remains controversial. Some studies have claimed that it is difficult to recover from multiple preoperative endocrinological insufficiencies, and a minor rupture of the cyst gradually leads to irreversible pituitary dysfunction, with some subsequent chemical responses (4, 19, 20). In addition, repeated minor ruptures have been thought to result in squamous metaplasia of the cyst walls, which is a risk factor of recurrent of RCC (14). In our study, more than half of our patients had surgery performed 3 months after headache onset and their postoperative courses were excellent. It can be concluded that small RCCs associated with severe headaches are an operative indication of TSS, and should be operated on before endocrinological function is irreversibly altered.

There are some limitations to our study. Our sample size was not large enough to draw significant conclusions on small RCCs. HIT is a subjective assessment of patients. Although HIT has been used in several studies (8, 11, 12), objective assessment for headaches would be a better alternative to evaluate headache severity.

【Conclusion】

Severe headache disrupting daily life can develop from small RCCs. In the present study, ETSS was performed effectively and safely to relieve these patient' headaches.

We conclude that ETSS should be performed for small RCCs associated with severe headaches.

【Compliance with ethical standards】

Informed consent

Informed consent was obtained from all individual participants included in the study

Conflict of interest

The authors declare that they have no conflicts of interest with regard to this study.

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【Figure legend】

Fig. 1

Sagittal view of preoperative magnetic resonance (MR) images (a: T1-weighted image (WI), b: T2-WI, c: T1 gadolinium enhancement image), as obtained in a 30-year-old woman with severe headaches (case 11). Cyst is hyper-intense in T1-WI and intracystic nodule is seen as very hypo-intense in T2-WI, which suggests protein rich cyst content. Postoperative MR image (d: T1-WI) showing that the cyst has disappeared. A histopathological examination (e, f: hematoxylin and eosin stain, $\times 200$) showing RCC with accumulation of lymphocytic cells in cyst walls.

【Table legends】

Table 1

Characters of headache presented by thirteen patients with small Rathke cleft cyst

Table 2

Characters of endocrinological dysfunction and radiological findings presented by thirteen patients with small Rathke cleft cyst

Table 3

Characters of operative and histopathological findings presented by thirteen patients with small Rathke cleft cyst

Table(s)

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Table 1 Characters of headache presented by thirteen patients with small rathk

| Case | Sex/Age | headache | | | HIT score | |
|------|---------|----------|-----------------|----------------------|-----------|---------|
| | | location | type | suffered period (mo) | preope | postope |
| 1 | M/57 | frontal | chronic, sudden | 84 | 63 | 38 |
| 2 | F/25 | frontal | chronic, sudden | 60 | 63 | 38 |
| 3 | F/38 | whole | chronic, sudden | 240 | 60 | 36 |
| 4 | M/55 | frontal | sudden | 2 | 60 | 38 |
| 5 | F/68 | frontal | chronic | 2 | 64 | 38 |
| 6 | F/32 | frontal | chronic, sudden | 2 | 68 | 36 |
| 7 | F/30 | whole | chronic | 2 | 62 | 36 |
| 8 | F/30 | whole | chronic, sudden | 30 | 72 | 40 |
| 9 | F/29 | frontal | chronic | 3 | 66 | 38 |
| 10 | M/43 | whole | chronic | 2 | 65 | 36 |
| 11 | F/30 | frontal | sudden | 2 | 63 | 38 |
| 12 | F/72 | frontal | chronic | 6 | 60 | 36 |
| 13 | F/39 | whole | chronic, sudden | 108 | 65 | 36 |

Table 2 Characters of endocrinological dysfunction and radiological findings presented by thirteen patients with small Rathke cleft cyst

| Case | endocrinological dysfunction | | radiological findings | | | | |
|------|----------------------------------|----------------|-----------------------|-------|-------|-----------------------|--------------------|
| | preope | postope | size (mm) | T1-WI | T2-WI | cyst wall enhancement | intracystic nodule |
| 1 | — | — | 6.8 | hyper | hypo | — | — |
| 2 | — | — | 7.3 | hyper | hypo | — | — |
| 3 | — | — | 7.7 | hyper | hypo | — | + |
| 4 | DI | DI (permanent) | 5.7 | iso | hyper | — | — |
| 5 | DI | DI (permanent) | 4.3 | iso | hyper | — | — |
| 6 | — | — | 8.6 | hyper | hypo | + | + |
| 7 | — | — | 8 | hyper | hyper | — | + |
| 8 | — | — | 5.1 | hypo | hyper | — | + |
| 9 | — | DI (transient) | 9.9 | hyper | iso | — | — |
| 10 | hyperthyroidism, hypocortisolism | — | 9.3 | iso | hyper | — | + |
| 11 | — | — | 4.9 | hyper | hypo | — | + |
| 12 | — | — | 5.6 | hyper | hypo | — | — |
| 13 | — | DI (transient) | 8.2 | hyper | hyper | — | + |

Table 3 Characters of operative and histopathological findings presented by th

| Case | operative findings | histopathological findings | | recurrence | follow-up (mo) |
|------|--------------------|----------------------------|--------------|------------|----------------|
| | cyst content | squamous metaplasia | inflammation | | |
| 1 | mucinous | — | — | — | 87 |
| 2 | mucinous | — | — | — | 58 |
| 3 | mucinous | — | — | — | 50 |
| 4 | mucinous | — | — | — | 44 |
| 5 | mucinous | — | + | — | 68 |
| 6 | mucinous | — | + | — | 35 |
| 7 | mucinous | — | — | — | 33 |
| 8 | CSF like | — | + | — | 33 |
| 9 | mucinous | — | — | — | 21 |
| 10 | mucinous | — | + | — | 15 |
| 11 | mucinous | — | — | — | 11 |
| 12 | mucinous | — | — | — | 8 |
| 13 | mucinous | — | + | — | 5 |

Figure 1

