



# Demonstration of high coincidence of pituitary adenoma in patients with ruptured Rathke's cleft cyst: Results of a prospective study



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## ABSTRACT

**Objective:** Repeated chronic inflammation, such as under circumstances of ruptured Rathke's cleft cyst (RCC), is known as the fundamental basis of various pathological changes including neoplastic change, therefore to examine accurate incidence of pituitary adenomas is important for the preventive medicine. **Materials and methods:** As a prospective study, patients were initially screened by the symptoms such as periodic headache and dizziness together with the abnormal findings such as seller floor bone defect on 3D-CT. Those screened patients who showed abnormal basal pituitary hormone values were additionally examined by several loading test and 3T magnetic resonance imaging (MRI) by three-dimensional reconstructions of Flair cube images. The presence of pituitary adenomas was evaluated by composite 3T MRI and <sup>11</sup>C methionine MET positron-emission tomography imaging. Immunohistochemical studies were employed for surgical biopsy specimens to demonstrate hormone production.

**Results:** 308 cases of RCC were diagnosed by both radiologic and intraoperative findings. Pathological examination confirmed 111 pituitary adenomas in 106 patients with ruptured RCC, therefore the rate of coincidence was revealed 34%. In 78 patients with abnormalities of pituitary hormone secretion, MET uptake was observed in the pituitary gland and verified pituitary adenoma pathologically. In addition, 28 adenomas were verified without MET-PET study on pathological examination only, for a total of 106 cases.

**Conclusions:** High coincidence (34%) of ruptured RCC and pituitary adenomas was demonstrated, which is a proof that ruptured RCC is contributed to a risk factor of pituitary adenoma.

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## 1. Introduction

Although Rathke's cleft cyst (RCC) is relatively common (20% out of our 2000 consecutive surgical series) in pituitary tumors, RCCs are not easily found or demonstrated by means of the different types of imaging techniques and often overlooked. For these reasons, RCC loose chance to be recognized which shows a pathological cycle of growth, rupture and regression [1,2]. Repeated chronic inflammation, such as under circumstances of ruptured Rathke's cleft cyst, is known as the fundamental basis of various pathological changes including neoplastic change. With the aid of <sup>11</sup>C-methionine positron-emission computed tomography (MET-PET), which was introduced to our institute in 2008, pituitary adenoma in early stage became possible to detect [3–5]. Unexpectedly high association of ruptured RCC and early region of pituitary adenomas was our impression during our initial experience of

MET-PET for the patients with ruptured RCC. As of 2011, when 3-D Flair cube images come into use, we prospectively tried to detect pituitary adenoma in patients with RCC who showed abnormal baseline of pituitary hormones in combination with various hormones loading tests and MET-PET scans.

This study was attempted to prove our hypothesis that “the incidence of pituitary adenoma is high in patients with ruptured RCC”, and we performed prospective study about the coincidence of RCC and pituitary adenomas.

## 2. Methods

### 2.1. Patients

We prospectively studied 308 cases of RCC rupture diagnosed by both radiological findings and intraoperative findings and undergone transsphenoidal surgery by one of the author (H.I.) between 2011 and 2014 at our Hospital. They consisted of 77 men and 231 women, aged from 11 to 81 years, with an average age of  $39.7 \pm 17.9$  years. Frequency distributions of the patient's age are shown in

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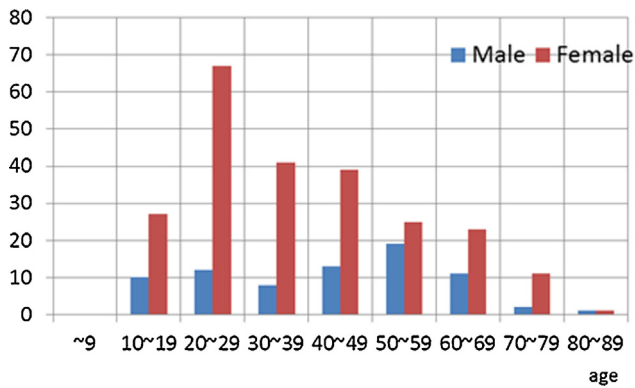


Fig. 1. Frequency distributions of the patient's age.

Fig. 1. The yearly incidences of pituitary adenoma in association with RCC were calculated between 2011 and 2014 by prospective study.

The research protocol was approved by our Institutional Review Board. All patients have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients provided written informed consent.

## 2.2. Evaluation of clinical symptoms of ruptured RCC

Fig. 2 shows our process for the examination of the suspected patients with RCC till the final diagnosis of the coincidence of RCC and pituitary adenomas.

Patients were asked about symptoms of periodic headache and dizziness, their degree, frequency, age of onset, and resistance to medical therapy. Those patients suspected of having migraine, tension headache, and cluster headache were excluded from this study. The Headache Impact test (HIT)-6 [6] was employed to evaluate headache before surgery and more than 6 months after surgery.

## 2.3. Evaluation of pituitary hormone abnormalities

Basal values of pituitary hormones, IGF-1, cortisol, and free T4 levels were measured for all patients. We compared the changes in these values between baseline and postoperative day 12 values. Those patients who showed abnormal baseline hormone values were additionally examined with a dexamethasone 0.5 mg and 8 mg overnight suppression test, a DDAVP stimulation test, and CRH stimulation test for ACTH abnormalities, a GHRP-2 stimulation test, a 75 g-oGTT suppression test, and TRH + LHRH stimulation test for GH abnormalities.

## 2.4. Neuroradiologic diagnosis of RCC

The size and extent of the tumors were determined using magnetic resonance imaging (MRI) obtained with a 3.0 T MR unit (Signa HDx; General Electric, Fairfield, CT, USA). The shape of the cyst cavity on 3-dimensional Flair cube images (GE; TR=6000, TE=116, Echo Train length=140, Matrix size=224 × 224, 1NEX, 1.4 mm thickness, ARB factor=2.84) on MRI was compared with surgical findings. Convincing MRI-based evidence of RCC rupture is provided in Fig. 3.

For the patients with abnormal ACTH and GH secretory dynamics, both FDG-PET and MET-PET studies, which have been shown to be able to detect hormonally active pituitary adenoma in the early stages [3–5] were undertaken using a PET-CT scanner (Discovery LS General Electric, Fairfield, CT, USA). In addition, FDG-PET was examined to rule out malignant tumors in the whole body which can be associated with either GH secreting adenomas or ectopic ACTH hypersecretion.

All patients fasted before the procedure and received intravenous injections of [<sup>11</sup>C] methionine 5.6 MBq × body weight (kg) (dose range, 6.1–15.1 mCi [225.7–558.3 MBq]). One hour after the MET injection, 185 MBq (5 mCi) FDG was injected intravenously. Ten minute PET scans were obtained, starting 60 min after injection. The MET-PET procedure was performed in 3D mode, which provided a set of 35 planes with a section thickness of 4.1 mm. Attenuation correction was performed by a transmission scan. The FDG-PET provided a set of 35 planes with a 4.1-mm section thickness in 3D mode. Uptake of glucose and MET during PET scanning

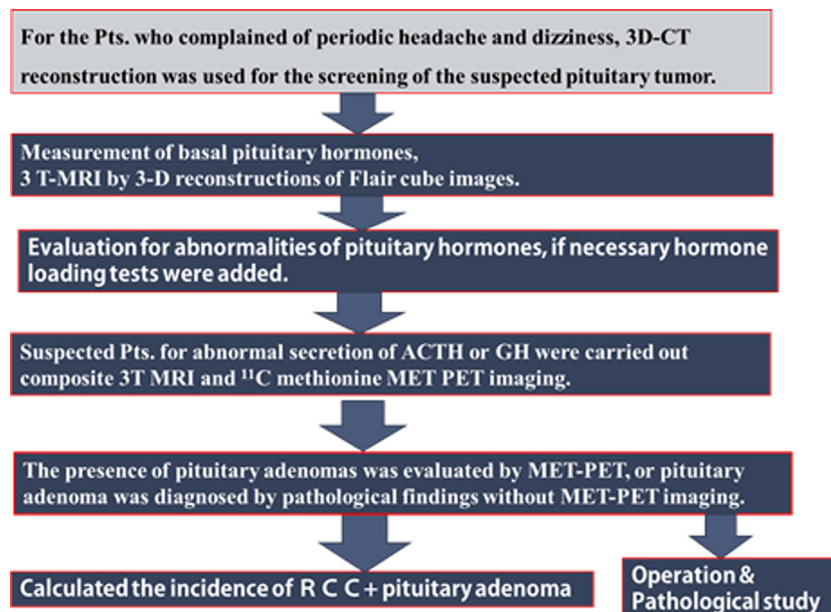


Fig. 2. Algorithm for the examination of RCC.

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