0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 84, No. 11
Printed in U.S.A.

Cystic Lesions of the Pituitary: Clinicopathological Features Distinguishing Craniopharyngioma, Rathke's Cleft Cyst, and Arachnoid Cyst

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ABSTRACT

The distinction among craniopharyngioma (CR), Rathke's cleft cyst (RCC), and intrasellar arachnoid cyst (AC) remains a difficult preoperative problem. Accurate diagnosis of these rare pituitary lesions is important to determine the type of treatment and predict prognostic outcome. The majority of the literature describes the clinical manifestations and management of only one of CR, RCC, or AC, rendering comparisons difficult. We conducted a study to 1) investigate distinguishing preoperative clinical, biochemical, and radiographic features of patients with CR, RCC, and AC; and 2) identify clinicopathological features that independently predict recurrence in CR and RCC in adults. Fifty-two adult patients included 21 patients with CR (mean age at initial surgery, 35 ± 14 yr), 26 patients with RCC (mean age, 37 ± 14 yr), and 5 patients with AC (mean age, 53 ± 12 yr). Mean follow-up duration was 70 ± 13 months.

Patients with CR presented with hypopituitarism in 95% of cases and hyperprolactinemia in 38%. These patients also had more preoperative neurological deficits (67%), ophthalmological complaints (67%), and significantly higher psychiatric manifestations (33%; $P = 0.003$) than those with RCC or AC. Patients with AC presented with headaches (60%), visual field deficits (60%), or impotence (50%) in the absence of other specific endocrine dysfunction symptoms. Using biochemical criteria, the percentage of patients with two or more pituitary hormonal axes impaired preoperatively was 67% for CR and 62% for RCC, significantly greater ($P = 0.03$) than that for the AC patients who had pituitary dysfunction of only one axis.

The composition of CR lesions was cystic (38%), solid (10%), or mixed solid and cystic (43%). Patients with RCC or AC groups had a significantly greater proportion ($P = 0.006$) of purely cystic lesions (88% and 100%, respectively). Calcification detectable on computed tomographic scanning was present in 87% of patients with CR, a significantly greater proportion ($P < 0.001$) compared to those with RCC (13%) or AC (0%). No significant differences were found between the groups based on computed tomography density, the presence of postcontrast enhancement, or magnetic resonance imaging. Recurrence rate was 62% for CR, 19% for RCC, and 20% for AC. Surgical intervention statistically improved most neurological, ophthalmological, and psychiatric manifestations; in contrast, galactorrhea, menstrual dysfunction, and diabetes insipidus (52% CR; 31% RCC) did not improve or became worse postoperatively. A significantly higher percentage of patients with CR required postoperative hormone replacement. Similarly, there was a biochemical trend suggesting that a smaller proportion of patients with CR improved in at least one pituitary axis after surgery ($P = 0.08$) compared to those with RCC or AC. There was a positive correlation between cyst size and recurrence rate ($r = 0.689$; $P < 0.01$) and between cyst size and time to recurrence ($r = 0.582$; $P = 0.037$) for all three groups.

We describe the largest clinical, biochemical, radiographic, and histological series of adult patients with cystic disease of the sella turcica. Patients with AC tended to be older at initial diagnosis than CR or RCC patients. Mass effects, such as visual problems and headaches, are common symptoms of all three cystic lesions, but psychiatric deficits favor a diagnosis of CR. Calcification or solid components on neuroimaging characterize CR. Endocrinological deficits, especially diabetes insipidus, had the worst prognosis after surgery. Low recurrence rates can be expected for RCC and AC. These data have direct implications for the management and monitoring of patients with cystic lesions of the sella turcica. (*J Clin Endocrinol Metab* **84:** 3972–3982, 1999)

THE SELLAR region can be affected by a variety of cystic lesions, including neoplastic craniopharyngioma (CR), nonneoplastic Rathke's cleft cyst (RCC), and arachnoid cyst (AC). The distinction among CR, RCC, and intrasellar AC remains a difficult preoperative problem, because the symptoms, signs, and biochemical and radiographic features of these lesions can mimic each other. In the presence of hyperprolactinemia, they may also mimic pituitary adenomas, leading to inappropriate medical therapy. Although it has been suggested that these lesions represent a continuum of epithelium-lined cysts (1), much effort is directed at identifying factors that distinguish them preoperatively. This has implications for the type and aggressiveness of treatment, the recurrence rate, and the prognosis. Descriptions of RCC and intrasellar AC have been primarily reports of one to five cases each (2–4). Larger series of CR have been reported because they constitute the most common pediatric brain tumor of nonglial origin, representing 3% of all brain tumors (5–8), and they occur at a rate of 1.3/million person yr (9). With advances in magnetic resonance imaging (MRI), the incidence of RCC diagnosis is increasing. This is reflected in recent reports of up to 28 pathologically confirmed RCC (10, 11). Almost all reports describe the clinical manifestations and management of only one of CR, RCC, or AC (6, 11–18), rendering comparisons difficult. This retrospective study of 52 adult patients (21 CR, 26 RCC, and 5 AC) represents one of the largest combined series to date.

We undertook the present study to 1) investigate distin-

Received June 7, 1999. Revision received July 13, 1999. Accepted July 22, 1999.

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guishing preoperative clinical, biochemical, and radiographic features of patients with CR, RCC, and AC; and 2) identify clinicopathological features that independently predict recurrence in CR and RCC in adults.

Subjects and Methods

Patients

We reviewed the clinical, radiographic, and operative findings; pathological features; and biochemical tests of 56 patients operated on by one of the authors (H.S.S.) at an acute care University of Toronto teaching hospital over a 24-yr period (1974–1998). Patients were selected based on histological diagnosis by biopsy of pituitary surgical or autopsy material. Four cases could not be histologically confirmed, but a presumptive diagnosis of CR (2 cases), and RCC (2 cases) was made based on preoperative radiographic and intraoperative findings. These cases are not included in the analyses. We have previously reported 10 of the 26 patients with RCC (19).

All patients underwent a complete history, general physical, and neurological examination. Visual fields were tested pre- and postoperatively using Goldmann perimetry. Pre- and postoperative biochemical pituitary functions were evaluated using standardized basal and dynamic stimulation tests and were evaluated based on currently accepted criteria. Specifically, hypothyroidism was based on a low T_4determination, GH deficiency on the basis of a value of 3 μg/L or less during an insulin tolerance test, and hypogonadism on the basis of inappropriately low gonadotropin levels in the setting of a diminished testosterone concentration in males or amenorrhea in females. A water deprivation test was performed when diabetes insipidus was suspected clinically.

Neuroimaging reports included computed tomography (CT) and MRI scans. All films between 1978–1998 were also reviewed by one of us (H.S.S.). Fifteen (71%) CR, 16 (62%) RCC, and all of the AC were examined by CT; 12 (57%) CR, 15 (58%) RCC, and 2 (40%) AC patients were also imaged by MRI.

Management

A total of 36 surgeries for the 21 patients with CR, 29 surgeries for 26 patients with RCC, and 5 surgeries for 5 patients with AC were performed. Radiotherapy after initial surgery was performed for 6 CR patients, but was not part of the treatment for any RCC or AC patient.

Postoperative evaluation

All patients were reviewed within 6 weeks of their discharge from the hospital for clinical and biochemical assessment. Follow-up included assessment of the presenting complaints and their outcome, neurological examination, visual field testing, biochemical measurement of pituitary function, and a CT or MRI examination.

Pathological methods

The surgical material was fixed in 10% buffered formalin, embedded in paraffin, and sectioned. For light microscopy, the tissues were stained with hematoxylin-eosin and the periodic acid-Schiff (PAS) technique. The individual who performed all histological analyses was blinded to any clinical information. Immunostains for keratin and electron microscopy were also performed in several cases.

Statistical analysis

Sigmastat (Jandel Scientific, San Rafael, CA) and Statistical Analysis Systems (SAS Institute, Inc.) were used. Descriptive statistics included the mean ± SE. One-way ANOVA was used to examine differences among the three groups (CR, RCC, and AC) for continuous variables. *Post-hoc* comparisons were made using Student-Newman-Keuls test. Correlations were examined using Pearson's product-moment correlation coefficient. Categorical data were compared across the three groups using χ^2 testing and between two groups (CR *vs.* RCC) using Fisher's exact testing. Multiple regression analysis was used to determine whether independent predictors of recurrence rate and outcome could be identified. Differences were deemed significant at $P < 0.05$.

Comparison of the cumulative rate of recurrence-free survival between group 1 (craniopharyngiomas) and group 2 (Rathke's cleft cysts) were made using the Kaplan-Meier survival analysis. The recurrence time (months) of 13 cases of CR were compared to those of 5 cases of RCC and 1 case of AC.

Results

Clinical findings

The mean age at initial surgery was significantly older (53 ± 12 yr) for AC compared to both CR (35 ± 14 yr) and RCC (37 ± 14 yr; $P = 0.0038$). The 21 CR patients included 11 males and 10 females. Of 26 RCC patients, there were twice as many females (n = 17) as males (n = 9). In the AC group there were 2 males and 3 females. There was no significant difference in the duration of preoperative symptoms at presentation among CR (mean ± SEM, 20 ± 7 months), RCC (24 ± 5 months), and AC patients (5 ± 1 months).

Patients with CR or RCC frequently presented with pituitary hormone insufficiency and neurological and/or ophthalmological deficits. Preoperative endocrine dysfunction (see below) was found in 95% of CR, 81% of RCC, and 40% of AC patients; preoperative neurological dysfunction was found in 67% of CR, 65% of RCC, and 60% of AC patients, and preoperative ophthalmological complaints were found in 67% of CR, 38% of RCC, and 60% of AC patients. A distinguishing feature of CR is the significantly higher proportion of patients who had preoperative psychiatric deficits, characterized by loss of short term memory and personality changes (33%; $P = 0.003$) compared to RCC or AC (0% of patients). Patients with AC were more likely to present with neurological and ophthalmological deficits rather than endocrine dysfunction.

Patients with CR commonly presented with amenorrhea (64%), impotence or diminished libido (45%), hyperprolactinemia (38%), and reduced short term memory (33%; Table 1). The most prevalent symptoms in RCC patients were impotence or diminished libido (67%), hyperprolactinemia (46%), galactorrhea (35%), and amenorrhea (24%). The mean preoperative PRL was 38 ± 11 μg/L (mean ± SEM) for CR patients, 37 ± 7 μg/L for RCC patients, and 14 ± 3 μg/L for AC patients. Interestingly, one patient in the RCC group had a coexistent PRL cell adenoma contributing to hyperprolactinemia (PRL, 144 μg/L). A significantly higher proportion of patients in the CR group presented with amenorrhea ($P = 0.05$) and reduced short term memory ($P = 0.003$), which favored a diagnosis of CR over RCC or AC. The incidence of diabetes insipidus at the time of presentation was not significantly different between those with CR and those with RCC (Table 1). The majority of patients with AC presented with headache (60%), visual field deficits (66%), or impotence

TABLE 1. Preoperative presentation of 52 patients

Preoperative sign/symptom	No. of CR cases (n = 21)	No. of RCC cases (n = 26)	No. of AC cases (n = 5)
Endocrine			
Amenorrhea	64	24	0
Lethargy	62	62	20
Impotence/decreased libido	45	67	50
High PRL (>20 μg/L)	38	46	20
Reduced 2° sex features	29	23	0
Somnolence	24	12	0
Gynecomastia	18	11	0
Galactorrhea	18	35	0
Diabetes insipidus	10	4	0
Oligomenorrhea	9	24	0
Neurologic			
Headache	62	65	60
Dizziness	10	8	20
Seizures	2	0	0
Ophthalmologic			
Visual field defects	67	38	60
Psychiatric			
Reduced short term memory	33	0	0
Depression	0	0	0

Values given are percentages.

(50%) in the absence of other symptoms of endocrine dysfunction.

Headaches were usually bifrontal or frontotemporal, throbbing, progressive, and associated with retroorbital pain in patients with visual deficiencies. Headaches without a coexisting endocrine disturbance were uncommon in association with CR (7%) or RCC (17%), in contrast to AC patients, whose headaches often occurred in the absence of endocrine dysfunction symptoms. Similarly, the psychiatric symptoms of CR patients were never present in isolation of a neurological deficit such as headaches, dizziness, or seizures. Alterations in psychiatric function included reduced short term memory, personality changes, dementia, and depression.

A biochemical analysis of the number of pituitary axes impaired revealed that 22% of CR, 13% of RCC, and 50% of AC patients had no impairment of pituitary axes; 11% of CR, 17% of RCC, and 50% of AC patients had impairment of one pituitary axis; 28% of CR, 17% of RCC, and 0% of AC patients had two or more pituitary axes impaired; and 39% of CR, 52% of RCC, and 0% of AC patients had three more pituitary axes impaired. Comparison of the proportions of patients with one or no pituitary axes impaired *vs.* those with two or more axes impaired using χ^2 testing revealed that the CR and the RCC groups had a significantly higher proportion ($P = 0.03$) of patients with two or more pituitary axes impaired (67% of CR and 62% of RCC) compared to the AC group (0% with two or fewer axes impaired) who had pituitary dysfunction in only one axis, if any. Table 2 illustrates the number of patients requiring preoperative hormone replacement therapy, and Table 3 illustrates the number of patients who had that particular axis impaired upon preoperative biochemical testing. The most common dysfunctions were gonadotropin, cortisol, and GH deficiencies for CR, RCC, and AC.

TABLE 2. Preoperative hormonal medical therapy

Replacement hormone	No. of CR cases (n = 21)	No. of RCC cases (n = 26)	No. of AC cases (n = 5)
Thyroid	33	23	0
Glucocorticoids	24	8	0
Testosterone/estrogen	10	19	0
Antidiuretic hormone	0	8	0

Values given are percentages.

Radiographic findings

Cyst size was defined as the largest preoperative cyst diameter recorded. The mean cyst size (±SEM) was 36.2 ± 4.7 mm for CR and 16.3 ± 1.2 mm for RCC lesions. Only two of the five AC patients had measurements of cyst size that could be verified, so a mean was not calculated. Twenty percent of CR patients and 82% of RCC patients had lesions between 10–20 mm in diameter. In contrast, 80% of CR patients and 18% of RCC patients had lesions greater than 20 mm in diameter. Fisher's exact testing was used to compare the proportion of patients with cysts 10–20 mm in diameter to those with cysts greater than 20 mm diameter in the CR and RCC groups. Results revealed that the proportion of patients with lesions greater than 20 mm in diameter was significantly greater ($P = 0.003$) in the CR group (80%) than in the RCC group (20%). There was no correlation between cyst size and degree of hyperprolactinemia or number of impaired pituitary hormonal axes.

The primary location of the lesion is a distinguishing feature between the CR and RCC groups. The CR lesions were divided among suprasellar (67%) and intrasellar (29%) locations, whereas all RCC and AC lesions were intrasellar. Ten percent of CR lesions were purely suprasellar, and 12% of RCC and 40% of AC lesions were purely intrasellar. Secondary extension of CR was primarily to the third ventricle (52%) and suprasellar region (19%), although some masses expanded into the sella (10%) or laterally (5%), and one extracranial CR case expanded to the nasopharynx. In contrast, most RCC (81%) and AC (60%) expanded into the suprasellar space.

Together with the clinical presentation, some preoperative radiographic features were useful in the differential diagnosis of CR, RCC, and AC. The composition of CR lesions was cystic (38%), solid (10%), or mixed cystic and solid (43%). The RCC and AC groups had a significantly greater proportion of patients ($P = 0.006$) with cystic lesions (88% and 100%, respectively), rather than solid lesions (0%). One pattern on CT scans that illustrated the likelihood of a CR lesion over a RCC or AC lesion was the presence of calcified regions (87% of CR *vs.* 13% of RCC and 0% of AC; $P < 0.001$). CT was also used to determine whether the lesion was hypodense (55% of CR, 79% of RCC, and 80% of AC), isodense (45% of CR, 21% of RCC, and 20% of AC), or hyperdense (none of the patients). No significant differences among the groups were found based on CT density (Table 4). None of the AC patients who underwent CT scanning showed enhancement of the lesion after contrast administration. Moreover, the presence of postcontrast enhancement was not useful in distinguishing CR (60% enhanced) from RCC (56%). MR im-

TABLE 3. Pre- and postoperative anterior and posterior pituitary function

	No. of preoperative cases (n = 18)	*Postoperative onset (n = 18)	*No. change postoperatively	*Normalized postoperatively
CR				
Hypothyroid	7 (39)	7 (39)	6 (86)	1 (14)
Hyperprolactinemic	6 (33)	1 (6)	3 (50)	3 (50)
Hypogonadal	10 (56)	3 (17)	9 (90)	1 (10)
GH deficiency	7 (39)	3 (17)	1 (14)	6 (86)
Hypocortisolism	9 (50)	7 (39)	7 (78)	2 (22)
Diabetes insipidus	1 (6)	9 (50)	1 (100)	0
RCC	(n = 23)	(n = 23)		
Hypothyroid	8 (35)	5 (22)	5 (63)	3 (37)
Hyperprolactinemic	9 (39)	2 (9)	3 (33)	6 (67)
Hypogonadal	10 (43)	4 (17)	6 (60)	4 (40)
GH deficiency	8 (35)	3 (13)	3 (37)	5 (63)
GH excess	3 (13)	0	2 (67)	1 (33)
Hypocortisolism	13 (57)	4 (17)	7 (54)	6 (46)
Diabetes insipidus	2 (9)	7 (30)	2 (100)	0
AC	(n = 5)	(n = 5)		
Hypothyroid	0	0	N/A	N/A
Hyperprolactinemic	0	0	N/A	N/A
Hypogonadal	1 (20)	0	0	1 (20)
GH deficiency	1 (20)	0	0	1 (20)
Hypocortisolism	3 (60)	0	0	3 (60)
Diabetes insipidus	0	0	N/A	N/A

Values in *parentheses* are percentages.

TABLE 4. CT and MRI features of CR and RCC

	% CR	% RCC
CT imaging	(n = 15)	(n = 16)
Calcification	87	13
Enhancement	60	56
Precontrast density		
Hypodense	55	79
Isodense	45	21
Hyperdense	0	0
MR imaging	(n = 12)	(n = 15)
T1-weighted images		
Hypodense	33	50
Isodense	50	7
Hyperdense	17	42
T2-weighted images		
Hypodense	92	50
Isodense	0	29
Hyperdense	8	21

Values given are percentages.
[a] Numbers for AC cases are included in the text.

aging was not helpful in detecting significant differences between the CR and RCC patients (Table 4).

Operative findings

There were significant differences among the CR, RCC, and AC groups regarding the route of surgical intervention ($P < 0.001$). A total of 36 resections were performed on the 21 CR patients (69% transcranial and 31% transsphenoidal). Neurosurgical options at first surgery for CR included subtotal resection (STR) with radiotherapy (29%), STR alone (57%), and gross total resection (GTR) alone (14%). If a lesion was intrasellar in location, it was usually approached transsphenoidally. All STR with radiotherapy were performed before 1977. A total of 29 surgeries (93% transsphenoidal and 7% transcranial) and no radiotherapy was performed on the 26 RCC patients. Each AC patient underwent 1 neurosurgical treatment, all of which were approached transsphenoidally. GTR/STR classification was not performed for RCC or AC because there was no available information regarding postoperative scans, so we could not classify the extent of resection. The texture, rather than the color, of the cyst content was helpful in distinguishing CR from RCC and from AC. All AC cysts were colorless and resembled cerebrospinal fluid. RCC cysts tended to be mucoid (70%), and a few were yellow and grumous (15%); CR cysts also exhibited these features, but 10% were mucoid, and 24% were grumous. None of the RCC exhibited the "machine oil" (14% of CR), turbid (19% of CR), semifluid (29% CR), or waxy (5% CR) texture observed in CR.

Complications

Three patients with CR died, and their histology was confirmed at the time of autopsy. One patient died as a result of neurosurgical intervention; CT scanning showed a massive hemorrhage 24 h after a ventriculoperitoneal shunt procedure to relieve obstructive hydrocephalus. Two patients died of causes unrelated to the disease or surgical procedure. The mortality rate was 4% for CR and 0% for RCC and AC.

Pathological findings

The summaries of the pathological findings are reported in Table 5. Of the five AC cases, two were diagnosed by the presence of arachnoid cells lining the cyst cavity. For the remaining three AC cases, the diagnosis was made surgically by aspirating clear cerebrospinal fluid from the cyst, instilling metrizamide solution into the cyst cavity, and showing that it did not communicate in a reverse manner with the subarachnoid space intracranially. The CR and RCC patients were diagnosed histologically by the epithelium lining the lesion and the stromal components. Statistical comparison was restricted to the CR and RCC groups due to the small sample size of the AC group. The following is a list of the

TABLE 5. Histopathological features of cystic lesions

Histological feature	No. of CR cases (n = 21)	No. of RCC cases (n = 26)
Epithelial lining		
Stratified squamous	16 (76)	3 (12)[a]
Interlacing bands of squamous epithelium	4 (19)	0[a]
Simple columnar	1 (5)	7 (27)[b]
Pseudostratified columnar	0	6 (23)[b]
Simple cuboidal	0	7 (27)[b]
Transitional	0	1 (4)
Ciliated	1 (5)	18 (69)[b]
Cholesterol clefts	9 (43)	6 (23)
Calcification	9 (43)	0[a]
Necrotic debris and fibrosis	8 (38)	4 (15)
Keratin nodules	7 (33)	1 (4)[a]
Chronic inflammation	4 (19)	0[a]
Foreign body giant cells	3 (13)	3 (12)
Hemosiderin	5 (24)	1 (4)
Goblet cells	0	(4)

Values in *parentheses* are percentages.
[a] Favors a diagnosis of CR over RCC ($P < 0.01$).
[b] Favors a diagnosis of RCC over CR ($P < 0.001$).

pathological features that were significantly different between the CR and RCC groups (Fisher's exact testing); CR were more likely to contain stratified squamous epithelium ($P < 0.001$), calcification ($P < 0.001$), keratin nodules ($P = 0.015$), and chronic inflammation ($P = 0.034$); RCC were more likely to have cuboidal or columnar epithelium ($P < 0.001$) and ciliated epithelium ($P < 0.001$). It is interesting to note that 12% of RCC displayed stratified squamous epithelium, a characteristic commonly associated with CR. The proportion of patients with cholesterol clefts, necrotic debris and fibrosis, foreign body giant cells, hemosiderin, or goblet cells was not significantly different between the CR and RCC groups.

Outcome

Due to the higher incidence of recurrence and persistence of symptoms, CR patients had the longest follow-up duration of 105 ± 24 months (*vs.* 35 ± 8 months for RCC and 33 ± 17 months for AC; mean ± SEM). CR had a worse prognosis than RCC or AC. χ^2 testing revealed that a significantly higher percentage of patients in the CR group required postoperative replacement hormones such as T_4($P = 0.037$), cortisone ($P = 0.04$), testosterone or estrogen ($P = 0.004$), or antidiuretic hormone ($P = 0.001$) compared to the RCC or AC groups. Seventy-six percent of CR, 42% RCC, and 20% AC were taking T_4after their last treatment; 67% of CR and 35% of RCC were taking cortisone, 67% of CR and 23% of RCC were taking testosterone or estrogen, and 43% of CR and 23% of RCC were taking antidiuretic hormone for diabetes insipidus. GH replacement was not undertaken in any of these patients. None of the AC patients was taking cortisone, sex steroids, or antidiuretic hormone after their last treatment.

Similarly, there was a trend toward a smaller proportion of patients in the CR group improving in at least one pituitary axis after surgery ($P = 0.08$) compared to the RCC or AC groups. Fifty percent of CR and 39% of RCC patients had no improvement in any of the six pituitary axes, whereas 39% of CR and 48% of RCC patients showed improvement in at least one of the six pituitary axes. In general, patients with AC had excellent outlook (100%) for normalization of pituitary function postoperatively. Table 3 details biochemical changes in pituitary function. There was no significant difference in postoperative change in individual pituitary axes among the three different groups. This could also be attributed to the small sample sizes (n = 1–13) that resulted from dividing each lesion type into the six hormonal axes. Figure 1 describes the prognostic outcome of preoperative endocrine, neurological, ophthalmological, and psychiatric symptoms after surgery. In the CR group, approximately 35%, 50%, and 50% of patients normalized with respect to endocrine, neurological, and ophthalmological dysfunction, respectively. Eighty-six percent of CR patients with psychiatric deficits improved, and the other14% remained unresolved. The RCC groups demonstrated the most improvement in neurological function (71%), followed by ophthalmological function (70%). This trend was reversed in the AC group, where 67% had improved visual function, but only 33% improved neurologically. Interestingly, endocrine function for RCC and AC showed poor improvement (19% and 0%, respectively).

The endocrine symptoms least likely to improve after surgery for CR were amenorrhea (three of seven had no change) and galactorrhea (two of two had no change). In contrast, greater than 65% of RCC patients had improvement of amenorrhea, galactorrhea, and oligomenorrhea. The prognosis for preoperative diabetes insipidus was poor. None of the patients with preoperative diabetes insipidus improved (n = 2 CR; n = 1 RCC), and the postoperative onset of permanent diabetes insipidus was also common after treatment (n = 9 CR; n = 7 RCC).

Headaches resolved in 54% of CR, 82% of CR, and 33% of AC; remained the same in 15% of CR, 12% of RCC, and 33% of AC; and became worse with a postoperative onset of headaches in 31% of CR, 6% of CR, and 33% of AC. Visual field defects resolved in 50% of CR, 70% of RCC, and 67% of AC; did not change in 43% of CR, 30% of RCC, and 33% of AC; and became worse in 7% of CR and in none of the RCC and AC patients.

Tumor recurrence

Recurrence rate was 62% (13 of 21) for CR, 19% (5 of 26) for RCC, and 20% (1 of 5) for AC. Recurrence was defined as those patients in whom definite lesion was detected by neuroimaging after surgery. Mean time to recurrences was 62 ± 24 months for CR (mean ± SEM), 25 ± 19 months for RCC, and 99 months for the single AC patient who suffered a recurrence. Within the CR group, none of the patients who had gross total resection had a recurrence, in contrast to the 67% (12 of18) who had STR. There was a positive correlation between cyst size and recurrence for all groups combined ($r = 0.689$; $P < 0.01$). Moreover, there was also a positive correlation between cyst size and time to recurrence ($r = 0.582$; $P = 0.037$).

Independent predictors of recurrence

The following factors were considered for possible association with tumor recurrence: age, gender, tumor size,

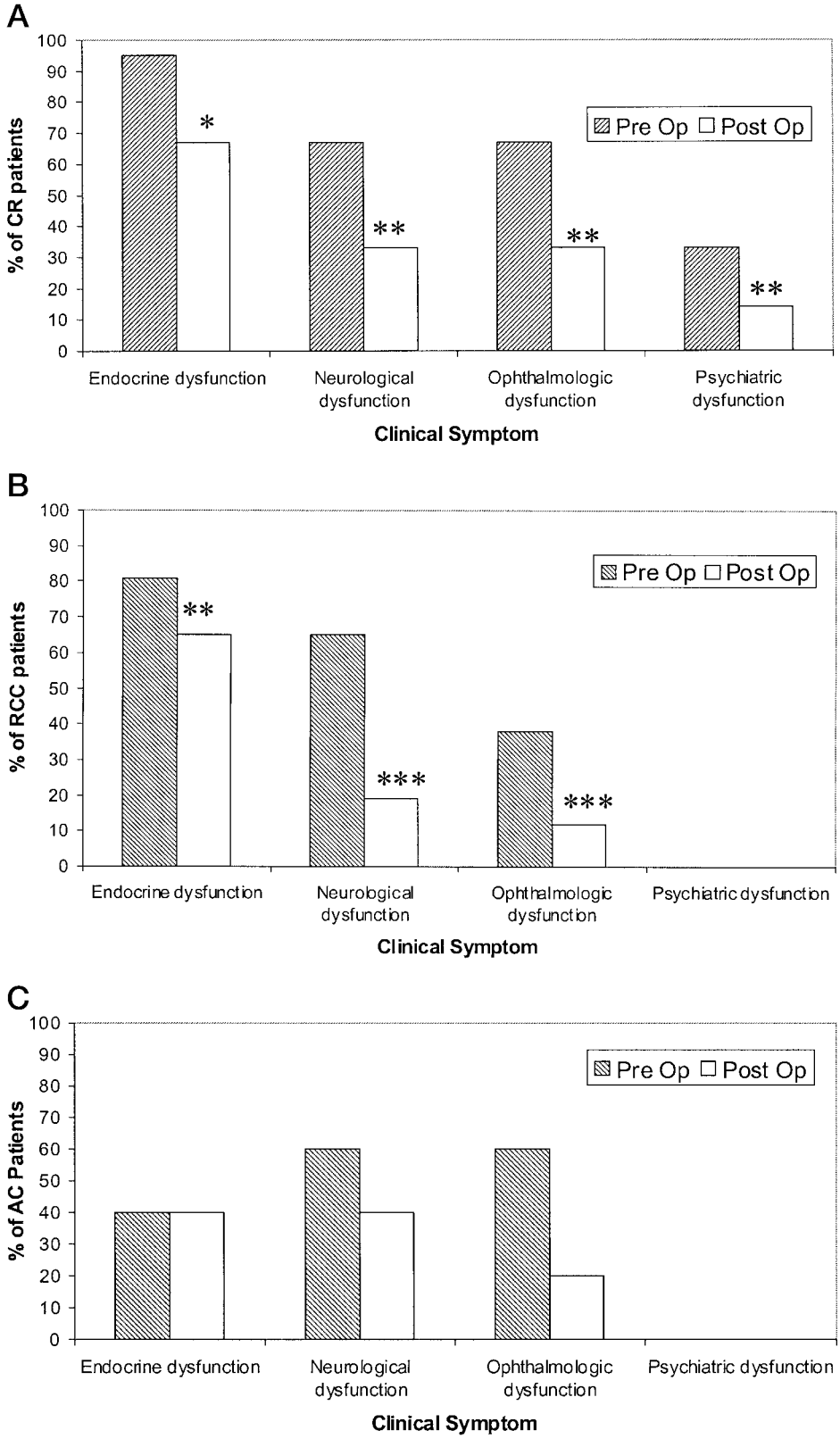

FIG. 1. a, Prognostic outcome of clinical symptoms in CR patients (n = 26). The mean follow-up duration (±SEM) is 105 ± 24 months. Significant differences are indicated: *, $P < 0.05$; and **, $P < 0.01$. b, Prognostic outcome of clinical symptoms in RCC patients (n = 26). The mean follow-up duration (±SEM) is 35 ± 8 months. Significant differences are indicated: **, $P < 0.01$; and ***, $P < 0.001$. c, Prognostic outcome of clinical symptoms in AC patients (n = 5). The mean follow-up duration (±SEM) is 33 ± 17 months. Differences were not significant due to small sample size.

calcification on radiography, and histopathological features. The relatively small sample size for CR and RCC patients who experienced recurrences (n = 13 CR; n = 5 RCC) precluded the detection of any significant predictors of recurrence using the above clinicopathological characteristics.

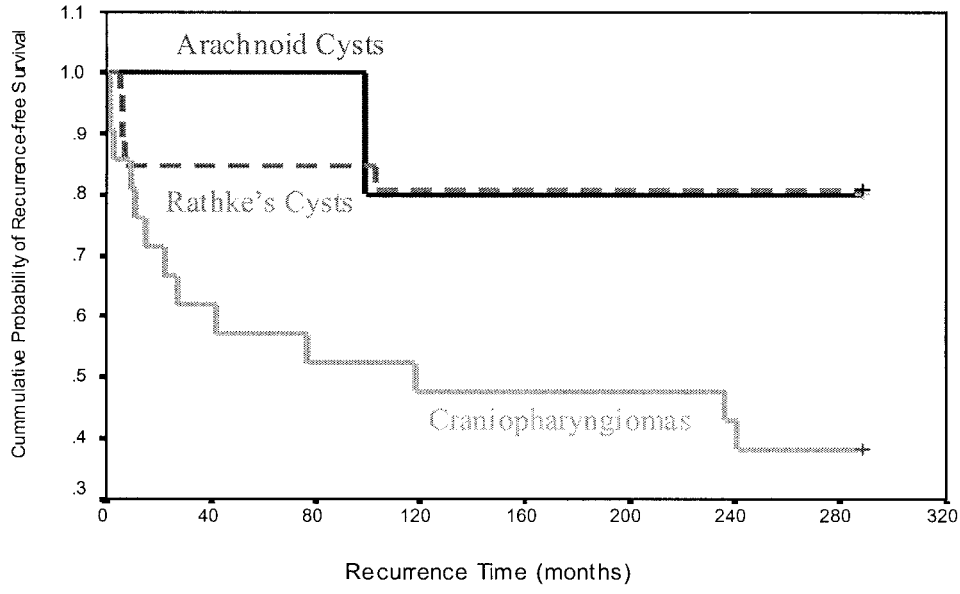

FIG. 2. The cumulative rate of recurrence-free survival was 57.1% after 5 yr, 47.6% after 10 yr for the CR group, 84.6% after 5 yr and 80.8% after 10 yr for the RCC group, and 100% after 5 yr and 80% after 10 yr for the AC group.

Survival analysis

The cumulative rates of recurrence-free survival were 57% at 5 yr, 48% at 10 yr, and 43% at 20 yr for CR patients; 85% at 5 yr, 81% at 10 yr, and remained at 81% at 20 yr for RCC patients; 100% at 5 yr, 80% at 10 yr, and remained at 80% at 20 yr for AC patients (Kaplan-Meier estimate). Figure 2 is a graphic depiction of recurrence-free survival times in patients with CR, RCC, or AC.

Discussion

This study represents the largest combined series to date comparing craniopharyngiomas, Rathke's cleft cysts, and intrasellar arachnoid cysts in adult patients. These cystic lesions surrounding and within the sella turcica can mimic each other clinically, radiographically, biochemically, and even histologically (5, 10, 20). In addition to presenting our experience with these lesions, we undertook a systematic statistical analysis to clarify the differential diagnosis of craniopharyngiomas, Rathke's cleft cysts, and arachnoid cysts. Among the adult population, CR and RCC do not differ significantly from each other with respect to the age of onset, the mean age being the latter half of the third decade in our series. On the other hand, the AC group was significantly older, presenting in the fifth decade of life. The small sample size of five AC may skew the result, but Meyer *et al.*, also found that intrasellar AC patients present at an average age of 46 yr (n = 13) (21). In accordance with the literature, our RCC series showed a preponderance of female cases in the ratio of 2:1 (10, 22, 23), but at least one review did not note any significant differences in gender (24). Several hypotheses may account for this gender bias. The monthly female check of one part of the endocrine system may alert women earlier to any abnormalities, especially when preoperative endocrine dysfunction was found in 95%, 81%, and 40% of CR, RCC, and AC patients, respectively. No gender bias was found for CR or AC.

Clinical features

The signs and symptoms of CR, RCC, and AC are dominated by mass effects of the lesion on the optic apparatus and pituitary gland, resulting in headaches, visual loss, and pituitary dysfunction. The most common endocrine abnormality in males was impotence or low libido in all three groups of lesions. In females, the most common endocrine dysfunction was amenorrhea for CR, hyperprolactinemia for RCC, and low libido for AC. The high incidence of preoperative symptoms in our patient cohort is attributable to formal inquiry and testing, a more thorough approach than patients' complaints at initial presentation. However, in comparison to a large study comprised primarily of adults (n = 96 of 143) (25), formal ophthalmological testing showed visual compromise in 75% of patients, *vs.* 67% in our adult population (16, 25).

The presence of psychiatric deficits, such as reduced short term memory and personality changes, are significant to distinguish CR from RCC and AC. In our series, 33% of 21 CR patients presented with changes in mentation, compared with 22% of 48 CR patients in the study by Crotty *et al.* (13) and over 50% of 93 CR patients in the study by Adamson *et al.* (6). Neuropsychological deficits after treatment were addressed primarily in children in the CR literature (7); they indicate postoperative impairment of memory in 57% of children. Most studies that include an adult population do not mention the postoperative outcome of neuropsychological deficits (6, 13, 67). One recent prospective study of neuropsychological function in adults before and after CR surgery (26) noted that immediate recall, delayed recall, and recognition memory were not impaired in 12 of 13 patients after surgery. However, preoperative memory function was normal in all 13 patients in that study. Our experience revealed that 86% of the CR patients who presented with neuropsychological deficits before treatment normalized in this respect after treatment.

Atypical presentations for RCC include abscess formation

within the cyst (27), aseptic meningitis (4), entirely suprasellar RCC (28), and associated pituitary adenomas (3, 29). Two of our patients with RCC also presented with coexisting pituitary adenomas. One patient with RCC had an associated PRL-secreting adenoma.

Preoperative biochemical features

Patients with CR or RCC have a high incidence of preoperative impairment of two or more pituitary axes. This is significantly different from patients with AC who have impairment in one axis, if any. Our detailed presentation of the endocrine deficits for the adult CR, RCC, and intrasellar AC population addresses a gap in the literature. The few endocrine reports on CR primarily focus on children (18, 30, 31). Seven reports were used to compare our data to the literature with respect to biochemical pituitary function in CR (32–38). Our data closely approximated the results found by other investigators; GH deficiency was found in 43% of our CR patients compared to 39% (74 of 170) in the literature, gonadotropin deficiency in 56% of CR patients in our series *vs.* 59% (51 of 86) in the literature, and hyperprolactinemia in 33% in our series *vs.* 32% (23 of 73) in the literature. Differences between our data and published reports were revealed by hypothyroidism in 39% of CR patients in our series *vs.* 25% (50 of 199), hypocortisolism in 50% of our series compared to 32% (59 of 183), and diabetes insipidus in 6% of our series *vs.* 19% (34 of 175) in the literature. A more recent endocrinological study in 143 CR patients (2 of 3 adults; 1 of 3 children) revealed 75% GH deficiency, 41% hyperprolactinemia, 25% hypothyroidism, 78% hypogonadism, 32% adrenal failure, and 16% preoperative diabetes insipidus (25). These differences could be due in part to our focus on an adult population as well as a smaller sample size of our experience compared to the results of the seven combined reports.

A review of the RCC literature performed by Voelker *et al.* (23). reported that hypopituitarism was found in 39% (60 of 155) of patients with RCC. More recently, Eguchi *et al.* (14) suggested that the incidence of pituitary dysfunction in patients with RCC was much higher than suspected; 100% (19 of 19) in their series. Our data support their hypothesis with 88% of our patients showing dysfunction in at least 1 pituitary axis. The only other report that evaluated the endocrinological axes in detail is that by Eguchi *et al.* (14). In general, the incidence of pituitary dysfunction in our RCC patients is lower than those by Eguchi *et al.*, but the trends were similar. The most common abnormalities were hypogonadism, followed by hypocortisolism. One difference between our study and that by Eguchi *et al.* was the high incidence of GH deficiency in their series (79%) compared to our series (35%). This difference may represent our adoption of the more current stricter criteria for the diagnosis of GH deficiency.

Neuroimaging features

It is difficult to confirm the diagnosis of CR, RCC, or AC radiographically due to the variability found on CT and MR (10, 12, 15, 17, 23, 39–51). However, any features that would favor a preoperative diagnosis of AC or RCC from CR is important because RCC and AC require less aggressive treatment. Partial excision and biopsy of the cyst wall with drainage of the contents via the transsphenoidal route is effective (19, 21). We attempted to find statistically significant features that would aid in the differential diagnosis of the three cystic lesions. The presence of solid components favors a diagnosis of CR over RCC and AC. Only 10% of the CR were purely solid, comparable to the 15% reported by Scheithauer and 11% by Fahlbusch (16, 52). Secondly, CR were predominantly located in the suprasellar area, in contrast to RCC and AC, which were all intrasellar. However, suprasellar RCC and AC have been reported (28, 53–55). Due to the cystic nature of RCC, it can easily extend into the suprasellar area through the cleft of the diaphragma sellae (48). We found a much higher percentage of RCC that had suprasellar extension (81%) than the one third previously reported by Rout *et al.* (56). Thirdly, the presence of calcifications (87% of CR *vs.* 13% of RCC or 0% of AC) significantly favored the likelihood of CR over RCC or AC. Fourthly, CR tended to be greater than 20 ± 5 mm in greatest diameter (mean $\pm$ SEM), in contrast to RCC, which were all between 10–20 mm in maximal diameter. This is similar to the data from a study of 148 CR in a mixed adult and pediatric population in whom 70% of CR tumors were greater than 20 mm in diameter (16).

Features that could not distinguish the lesions with statistical significance were intensity on CT or MR and postcontrast enhancement pattern. On CT imaging, CR were divided between hypointense signals (55%) and isointensity (45%). On MR imaging, CR cases could be hyperintense, iso-intense, or hypointense on T1, and 92% were hyperintense on T2. This degree of variability was also reported in others (39, 42, 43, 49). Detailed biochemical analysis has shown that a high signal intensity of cystic fluid on T1 is caused by protein concentrations greater than 90 g/L and/or the presence of free methemoglobin. Hemorrhagic CR that have both of the above features are hyperintense on T1 imaging. Cholesterol and triglycerides do not affect the signal intensity on T1-weighted imaging (39).

RCC were typically hypointense on CT. However, this feature is also found in CR, arachnoid cysts, epidermoid cysts, abscesses, and pituitary microadenomas (10). AC are hypointense because they possess density and signal characteristics similar to those of cerebrospinal fluid. To make the task of a preoperative radiographic diagnosis more difficult, other less common features, such as hyperdensity, mixed lesions, and postcontrast enhancement, have been reported in RCC (10, 44, 47). Calcification is characteristically not seen on CT imaging of RCC, but 13% of our RCC cases (same as in Ref. 11) and in other isolated cases possessed calcification (47, 57). MR patterns are equally nonspecific. The hyperintensity seen on 50% of the RCC T1-weighted images is suggested to be due to mucinous fluid (45), mucopolysaccharides in the cyst fluid (3, 47), or hemosiderin pigment (58).

A combination of clinical, biochemical, and radiographic data must be used together to favor a diagnosis of CR, RCC, or AC before surgery.

Operative features

The selection of surgical approach depends on the location where the tumors arise. CR that have enlarged the sella and are predominantly outside of the arachnoid membrane can

be excised transsphenoidally (33, 59–61). In our study, 96% of intrasellar lesions were excised using the transsphenoidal approach. Transsphenoidal surgery is favored whenever possible to avoid leakage of cyst contents into the subarachnoid space and other associated complications (2, 4, 19, 23, 62). In addition, attempted radical excision can cause additional unnecessary pituitary damage. However, the mortality using the transcranial approach and that using the transsphenoidal approach were not significantly different (20). Our mortality rate of 4% for CR was comparable to the 5.4% postoperative mortality found by Weiner *et al.* (63).

The extent of resection and the role of radiotherapy in the treatment of CR are a controversial issue (7, 33, 64, 65). Many studies compare subtotal resection (STR) plus radiotherapy to the merits and detriment of gross total resection (GTR). Morbidity and mortality rates tend to be greater in patients with GTR (46). One measure of good clinical outcome in these studies is the recurrence rate. We observed an unexpectedly high number of recurrences in STR plus radiotherapy (83%) *vs.* STR alone (58%). Upon closer examination of the STR plus radiotherapy patient data with respect to the rest of the CR patients, several trends were identified that may account for the skewed recurrence rate when radiotherapy was added to STR. Patients with recurrences in this cohort tended to be younger (24 ± 8 yr) at first surgery. Three of the initial surgeries were performed by another neurosurgeon, and all surgeries were performed before 1977. The time to recurrence was also long (164 ± 82 months), and the patients remained relatively asymptomatic between the time of surgical and radiation intervention to the time of recurrence.

Pathogenesis and histological features

The pathogenesis of CR is controversial and is based on two opposing hypotheses (66). According to the first hypothesis, CR arise from ectopic embryonic remnants of the craniopharyngeal duct. These cells initially connect Rathke's pouch with the stomodeum. According to the second hypothesis, CR arise from metaplastic squamous epithelial cells in the adenohypophysis (50, 66). Recently, two clinicopathologically separate types of CR have been postulated: the adamantinomatous CR and squamous papillary CR (6, 13, 63, 67). The adamantinomatous type predominantly found in children and one quarter of adults is mainly cystic and is characterized by calcification, keratin nodules, cholesterol clefts, suprasellar location, and high recurrence rate. The squamous-papillary type predominantly found in adults is mainly solid and is characterized by a much lower incidence of calcification, keratin, recurrence, and brain invasion compared to the adamantinomatous type (6, 13, 50, 63, 67, 68). Other investigators argue for a continuum of CR (15, 63), and although there may be histological differences, they have no known prognostic significance.

The pathogenesis of RCC is also debated. There are three theories of origin. RCC are postulated to be derived from 1) remnants of Rathke's pouch (69, 70), 2) neuroepithelium (71, 72), and 3) metaplasia of anterior pituitary cells (66, 70, 73).

AC can be congenital or acquired cystic lesions. They are attributed to herniation of the arachnoid membrane through an incompetent diaphragma (21).

Histological features that distinguish CR, RCC, and intrasellar AC are stratified squamous epithelium and chronic inflammation for CR, cuboidal or ciliated columnar epithelium for RCC, and arachnoid cells lining the cyst cavity for AC. However, CR and RCC can also be considered a continuum of endodermal derivatives with some degree of overlap (1). Twelve percent of our RCC cases had stratified squamous epithelium, as did 23% (36 of 155) in a review of several reports by Voelker *et al.* (23). Squamous cells arise from metaplasia of the lining epithelium. We also observed ciliated foci of columnar epithelium in CR, as did other investigators (74, 75). This may represent a transition from RCC to papillary CR.

Prognosis

Visual and neurological deficits (*i.e.* headaches) demonstrated the most promising improvements after surgery. These symptoms tend to recover relatively soon after surgery (10, 19). Endocrine symptoms normalized in only 35% of CR, 19% of RCC, and none of the AC groups. The poor endocrine prognosis was hypothesized by Baskin to be due to the chronic pressure in the arachnoid cyst causing more damage to the anterior pituitary than the expansile pressure by CR and RCC (22). The most common postoperative onset of endocrine deficit was diabetes insipidus in both CR and RCC (9 of 18 CR patients and 7 of 23 RCC patients), implying irreversible damage to the posterior pituitary. Normalization of preoperative diabetes insipidus after treatment was also low (0% of CR and 0% of RCC resolved), similar to published reports (24, 62). Hyperprolactinemia was noted in 38% of patients with CR (38 ± 11 μg/L) and 46% of patients with RCC (37 ± 7 μg/L) cases, although the levels did not reach those usually recorded in prolactinomas. The apparent postoperative reduction in PRL levels may be due to the restoration of the dopamine inhibition from the hypothalamus or possible compromise of adenohypophysial function (20).

Recurrence

The recurrence rate was 62% (13 of 21) for CR, 19% (5 of 26) for RCC, and 20% (1 of 5) for AC. There was a positive correlation between cyst size and recurrence for all groups combined ($r = 0.689$; $P < 0.01$). Moreover, there was also a positive correlation between cyst size and time to recurrence ($r = 0.582$; $P = 0.037$). Weiner *et al.* (63) noted a trend between tumor size and extent of resection. This suggests that the larger the cyst, the greater the extent of resection, which, in turn, increases the time to recurrence.

Craniopharyngiomas are more aggressive and infiltrative compared to RCC or AC; hence, it is more difficult to excise them completely, and this can result in higher recurrence rates of 10–40% (66, 67). Within our CR group, none of the patients who had gross total resection had a recurrence, in contrast to the 67% (12 of 18) who had subtotal resection. A similar recurrence rate (69%) of CR (n = 9 of 13) with partial removal was found by Fahlbusch *et al.* (16). There is a tradeoff between the risk of higher rates of mortality and morbidity, causing further damage to the pituitary and surrounding area, *vs.* the risk of recurrence. Weiner *et al.* found that the most significant factor associated with recurrence in

CR is extent of surgical resection rather than histopathological subtype of CR (16, 63).

Recurrence rates are commonly lower for Rathke's cleft cysts. Mukherjee *et al.* found a rate of 33% (17), much higher than numbers found in our study (19%) and in the literature (in 5–10%) (23). Fager and Carter (69) suggested that Rathke's cleft cysts and craniopharyngiomas may contain overlapping histological features, more so in the case of recurrent Rathke's cleft cysts.

Conclusions

This series compared 52 adult patients with CR, RCC, or intrasellar AC to present our experience with these cystic lesions and to demonstrate the difficulty of determining a definitive diagnosis before surgery. An attempt to identify factors aiding the differential diagnosis of CR, RCC, and AC revealed several interesting results. Patients with AC tended to be older at the time of initial diagnosis than those with CR or RCC; mass effects, such as visual problems and headaches, are common symptoms of the three cystic lesions, but psychiatric deficits, such as reduced short term memory, favor a diagnosis of CR. Endocrinological deficits, including diabetes insipidus, showed the worst prognosis after surgery; calcification or solid components on neuroimaging favor a diagnosis of CR; and lower recurrence rates can be expected for RCC and AC after treatment. Only cyst size was found to be a significant predictor of recurrence rate for CR and RCC. Although our study represents the largest combined series to date looking at CR, RCC, and AC, further studies with larger sample sizes are needed to better understand the complex relationship among preoperative features that may predict prognosis and recurrence.

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