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Presenting symptoms and endocrine dysfunction in Rathke cleft cysts — a two-centre experience

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Abstract

Introduction: Rathke cleft cysts (RCC) arise as developmental abnormalities of the pituitary gland and are usually diagnosed incidentally. However, they may present with headaches, visual impairment, or pituitary dysfunction. Rathke cleft cysts are poorly described in the Polish literature. We aimed to characterize presenting symptoms, associated endocrine dysfunction, and concomitant disorders in the Polish population of patients with RCC.

Material and methods: We performed a retrospective analysis of medical records of 102 patients diagnosed with RCC between 2006 and 2021 at Heliodor Swiecicki Clinical Hospital in Poznan and Independent Public Clinical Hospital No. 4 in Lublin.

Results: The cohort was 72% female, with a mean age of 43 years. The median maximal cyst diameter was 7 mm. The majority of subjects were overweight or obese and presented lipid profile or glucose disturbances. Common presenting symptoms included headache, vertigo, and visual impairment. Less frequently we observed sexual dysfunction, irregular menses, galactorrhoea, or fatigue. Hormonal abnormalities were identified in 30% of patients, with hyperprolactinaemia being the commonest endocrinopathy (23%). Pituitary function in patients with RCC did not correlate with cyst size. Both concomitant pituitary adenomas and pineal cysts were diagnosed in 3% of patients. A considerable proportion of subjects were diagnosed with Hashimoto's thyroiditis and multinodular goitre.

Conclusions: RCCs occur mostly in females and may result in a variety of symptoms and hormonal dysfunction. Patients require a full clinical and endocrine evaluation regardless of the cyst diameter. We report a substantial co-occurrence of RCC and metabolic disorders and primary thyroid diseases, which requires further investigation. **(Endokrynol Pol 2021; 72 (5): 505–511)**

Key words: *cleft cysts; Rathke; pituitary incidentaloma; hyperprolactinaemia; hypopituitarism; headache*

Introduction

Rathke cleft cysts (RCC) are non-malignant cystic lesions considered to be the most common incidental finding of the sellar and suprasellar region [1, 2]. They are detected in up to 15% of surgical pituitary cases and in up to 11% of unselected autopsies [2–5]. A recent extensive Polish retrospective study of over 2300 patients operated due to intrasellar mass revealed RCC in less than 1% of cases [6]. RCCs arise as a result of improper involution of Rathke's pouch; however, the pathogenesis remains unclear [1, 7]. Experimental studies indicate that defects in *Isl1* transcription factor gene might be responsible for the development of RCC [8].

Rathke cleft cysts are most commonly diagnosed in adults, with a female predominance, and they are largely asymptomatic [1, 7]. Symptoms generally occur when the size of the cyst has grown to impinge on adjacent structures (mass-effect) or due to the inflammation and oedema that affects the pituitary [9, 10]. The most common symptom of RCC is headache, followed by visual disturbances and hypopituitarism, the most common findings of which are hypogonadism and hyperprolactinaemia [10–18]. Rare complications of RCC such as aseptic meningitis, sphenoid sinusitis, and precocious puberty may occur, but have been infrequently described in the literature [3, 10, 19–24].

Intervention is required in the case of symptomatic RCC, and the treatment of choice is surgical, usually via a transsphenoidal approach. While surgical intervention commonly leads to improvement of symptoms, complications including novel postoperative endocrinopathy such as hypopituitarism or diabetes insipidus may occur. Surgical intervention does not rule out the risk of recurrence [7, 15, 18, 25–29].

RCC is poorly described in the Polish literature, and to our best knowledge no study in the adult Polish population has been published. The aim of this paper is to present comprehensive characteristics of patients with RCC in terms of laboratory and clinical data, and

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to compare the results with current literature and highlight the dominant findings.

Material and methods

Patients

We retrospectively reviewed the medical records of 102 patients diagnosed with RCC between 2006 and 2021 at Heliodor Swiecicki Clinical Hospital in Poznan (75) and between 2007 and 2019 at Independent Public Clinical Hospital No. 4 in Lublin (27). Eligibility criteria for this study included RCC confirmed by magnetic resonance imaging and age over 18 years. Both symptomatic and incidentally diagnosed RCC cases were involved in this study. The components of patient clinical charts taken into consideration included the following: age of the diagnosis, symptoms, MRI description, laboratory test results with emphasis on endocrine dysfunction, concomitant disorders, and thyroid ultrasound. Charts were not assessed for treatment post diagnosis or follow-up.

Visual impairment

For the purpose of this study, we considered the patients' subjective complaints of visual impairment. The results of the ophthalmological examination were present in one-third of the analysed cohort and were not sufficient to verify all the symptomatic cases.

Hormonal assessment and pituitary imaging

Pituitary function was evaluated using basal serum concentrations of the pituitary hormones and those released from their subsequent target organs, as well as dynamic testing when necessary. The evaluated hormones included the following: growth hormone (GH), insulin-like growth factor-1 (IGF-1), prolactin (PRL), adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), free triiodothyronine (fT_3), free thyroxine (fT_4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and oestradiol.

Hypopituitarism was defined in accordance with the current recommendations of the Endocrine Society [30]. However, due to the limited availability of GH stimulation test results in most patients, GH deficiency was defined as IGF-1 below the normal range for age and GH below or in the lower the normal range. The pituitary abnormalities previously diagnosed and reported in patients' medical history, already treated upon the evaluation, were also included in the analyses.

We analysed magnetic resonance imaging descriptions in terms of a maximal diameter of the cyst because all 3 dimensions enabling volume calculation were available in a limited number of charts. The results were also searched for accompanying abnormalities in head imaging.

Statistical analysis

Normality was assessed with the Shapiro-Wilk test. Correlation between hormonal function, age of diagnosis, and cyst diameter was evaluated using Spearman's rank correlation coefficient. For comparisons either the Mann-Whitney-Wilcoxon test, chi-squared test, or Fisher's exact test were used. A p value $<.05$ was considered statistically significant. Statistical analysis was performed using STATISTICA 13 (TIBCO Software Inc.).

Results

Patients and clinical presentation

Overall, 102 patients were included in our analysis. Patients' characteristics, presenting symptoms, and RCC imaging are summarised in Table 1.

In our cohort, participants were predominantly female (72%). The average age of the diagnosis was 43 years. In the studied group 45 women were premenopausal (62%) and 28 were postmenopausal. Half of the participants were either overweight or obese, and a significant proportion presented glucose metabolism disturbances (27%) or abnormal lipid profile (51%). Hypertension was observed in one third of the participants, whereas anaemia was identified in 8%, with a female predominance.

The majority of patients complained of at least one symptom. Headache was the most common ailment, reported in 42% of cases. The second commonest symptom was vertigo or dizziness, which occurred in 20% of participants, followed by visual impairment noted in 15%. Sixteen per cent of premenopausal women reported irregular menses, in 2 cases RCC was accompanied by polycystic ovarian syndrome, whereas almost a fifth of men reported loss of libido or sexual dysfunction. Less frequently noted symptoms included general weakness/fatigue, galactorrhoea, nausea/vomiting, or syncope. Of note, patients' complaints did not differ between groups with maximal cyst diameter below and exceeding 10 mm.

The majority of patients received MRI for subjective complaints of headache, vertigo, or visual impairment (43%). In 6 patients the symptoms had sudden onset with accompanying nausea, vomiting, or paraesthesia, resembling pituitary apoplexy. Another important reason for diagnostics was hyperprolactinaemia (8%), in 4 cases manifested by galactorrhoea. Hypogonadism presenting as amenorrhoea/oligomenorrhoea in women and loss of libido/potency or infertility in men was the grounds for neuroimaging in 5% of patients. On the other hand, 34% of subjects received MRI in the course of either endocrine, neurologic, or otolaryngologic diagnostics (acromegaly, MEN2, TSH-oma, tinnitus/hearing impairment, orbital tumour). In 12 cases the reason for MRI was not clearly specified. Ultimately, we assume that up to 50% of patients were diagnosed incidentally.

Neuroimaging findings

The median maximal diameter of the cyst was 7 mm, ranging between 1.5 and 37 mm. In 36% of subjects the cyst dimension exceeded 10 mm. The cyst size did not differ between sexes ($p = .978$) and was not associated with age ($p = .235$). A compression of the pituitary gland was observed in 11 patients, of which in 9 the maximal diameter exceeded 10 mm, while dislocation of pituitary stalk occurred in 6 patients, among which 5 cases had a cyst larger than 10 mm. In 10 patients the imaging revealed additional abnormalities including pituitary adenoma (3 women), pineal cyst (2 men, 1 woman),

Table 1. *Descriptive characteristics of the study group and clinical presentation.*

Characteristic	Total	Women	Men
N	102	73 (72%)	29 (28%)*
Age of the diagnosis (years)	43 ± 17 (12–86)	43 ± 17 (12–86)	42 ± 18 (18–73)
Body mass			
Normal weight	46 (50%)	36 (56%)	10 (36%)
Overweight	29 (32%)	17 (27%)	12 (43%)
Obese	17 (18%)	11 (17%)	6 (21%)
Metabolic disorders			
Impaired fasting glucose	15 (15%)	8 (11%)	7 (24%)
Impaired glucose tolerance	7 (7%)	4 (5%)	3 (10%)
Diabetes mellitus	5 (5%)	2 (3%)	3 (10%)
Hypercholesterolaemia	19 (26%)	13 (26%)	6 (26%)
Hypertriglyceridaemia	5 (7%)	1 (2%)	4 (13%)*
Combined hyperlipidaemia	13 (18%)	9 (18%)	4 (13%)
Hypertension	32 (31%)	21 (29%)	11 (38%)
Anaemia	8 (8%)	7 (10%)	1 (3%)
Symptom			
Headache	42 (41%)	32 (44%)	10 (34%)
Vertigo/dizziness	18 (18%)	14 (19%)	4 (14%)
Visual impairment	15 (15%)	9 (12%)	6 (21%)
Irregular menses	7 (7%)	7 (16%**)	-
Loss of libido or sexual dysfunction	5 (5%)	0	5 (17%)
General weakness/fatigue	9 (9%)	5 (7%)	4 (14%)
Galactorrhoea	5 (5%)	5 (7%)	-
Nausea/vomiting	5 (5%)	5 (7%)	0
Syncope	4 (4%)	3 (4%)	1 (3%)
Asymptomatic	25 (25%)	18 (25%)	7 (24%)
RCC in MRI			
Maximal cyst diameter [mm]	7 (5–12)	7 (5–12)	8 (5–12)
Maximal cyst diameter ≥ 10 mm	37 (36%)	27 (36%)	10 (34%)

Data are expressed as mean ± standard deviation (range) when normally distributed and median (quartiles) when non-normally distributed or as N (% of total/women/men). *$p < .05$; **of premenopausal women; RCC — Rathke cleft cyst; MRI — magnetic resonance imaging

brain aneurysm (1 man, 1 woman), meningioma (1 woman), and haemangioma (1 woman).

Evaluation of hormonal disturbances

Pituitary dysfunction was observed in 31 patients (9 men [31%], and 22 women [30%]). An overview of hormonal abnormalities with subdivision into groups with cyst diameter below and measuring or exceeding 10 mm is presented in Table 2.

Hyperprolactinaemia was the commonest hormonal abnormality overall and was identified in 23% of participants (25% of women, and 17% of men). The second commonest dysfunction was growth hormone deficiency, observed in 8% of subjects (4% of women, and 17% of men). Hypogonadotropic hypogonadism, with confirmed dysfunction as shown by dysregulation of menses and/or decreased libido/infertility and proven in the hormonal tests, was observed in 6% of patients (7% of premenopausal women and 10% of men). Additionally, in 4 men we noted decreased concentrations of testosterone and gonadotropins, but these responding fully to stimulation with gonadotropin-releasing hormone. Furthermore, 5% of patients suffered from secondary adrenal insufficiency. Finally, the least commonly observed pituitary dysfunction was secondary hypothyroidism, which occurred in 4% of participants. One patient was previously diagnosed with acromegaly. Among patients with identified pituitary dysfunction, almost a third (29%) had a multiple axis pituitary insufficiency.

Table 2. *Patients with Rathke cleft cyst (RCC) and pituitary dysfunction by the cyst size < 10 mm and ≥ 10 mm, N (%)*

Dysfunction	Cyst size < 10 mm	Cyst size ≥ 10 mm	p value
Overall	18 (28)	13 (35)	p = .33850
Hyperprolactinaemia	15 (23)	8 (22)	p = .83393
GH deficiency	3 (5)	5 (14)	p = .13512
Hypogonadism	1 (2)	5 (14)	p = .02087
Hypoadrenalism	1 (2)	4 (11)	p = .05887
Hypothyroidism	0	4 (11)	p = .01554
Acromegaly	1 (2)	0	p = .63725

GH — growth hormone; hypothyroidism, hypoadrenalism, and hypogonadism refer to secondary forms

We found no correlation between the maximal dimension of the cyst and pituitary function — basal concentrations of pituitary hormones (TSH: p = .9502; PRL: p = .0688, FSH: p = .3773, LH: p = .1375, ACTH: p = .1758; GH: p = .2489). However, hypogonadism and hypothyroidism were significantly more frequent in patients with maximal cyst diameter of 10 mm or exceeding 10 mm. The proportion of diagnosed pituitary dysfunction did not differ between sexes with the exception of GH deficiency, which was observed significantly more often in males (p = .0399). Among subjects with concomitant pituitary adenoma, one was diagnosed with acromegaly and one presented a combination of GH deficiency and hyperprolactinaemia.

Interestingly, a considerable proportion of patients were diagnosed with concomitant thyroid disease. Primary hypothyroidism was found in 31% of subjects, in 44% as a part of autoimmune thyroiditis, which was diagnosed in 24% of all analysed patients. Thyroid nodules were a common finding on ultrasonographic examination and were present in 28% of patients overall (17% of men, 33% of women).

Discussion

The demographic features and clinical presentation of patients with MRI diagnosed RCC in this large two-centre retrospective analysis largely concur with previous series. Specifically, earlier studies report a mean age of diagnosis between 30 and 55 years [4, 5, 9–19, 25, 27, 28, 31–41] and indicate female predominance with a male-to-female ratio of up to 1:5 [3–5, 9–19, 25, 27, 28, 31–41], as observed in our cohort.

Additionally, the majority of contemporary reports highlight that headache is the most common presenting symptom, occurring in 30-88% of patients [3–5, 10–13, 15–19, 25, 27, 28, 31–36, 38–41], and is not correlated to the cyst diameter or location [36, 41]. Our results substantiate those findings. Headache was the commonest symptom, reported by 42% of our cohort. The incidence of headache did not differ between groups with cyst diameter below or exceeding 10 mm, indicating that this symptom is not related to the cyst size. The second commonest symptom, based on previous series, is visual impairment, estimated in 7-82% of patients [3–5, 9–19, 25, 27, 28, 31–33, 35, 36, 38–41]. Our findings do not support previous research in this area. We noted a higher prevalence of vertigo/dizziness, which is relatively rarely reported, ranging from 5 to 29% [19, 25, 28, 38, 39]. Visual impairment was the third commonest symptom in our analysis. Nishioka et al. underline that visual disturbances correlate with the cyst size [36]. Therefore, we assume that the lower frequency of visual impairment in our study is at least partially attributable to the lower median cyst dimension compared to other studies, which report the diameter between 10 and 20 mm [5, 10, 16, 18, 31, 32, 36, 38, 39]. In most series the percentage of cysts exceeding 10 mm is over 50% [18, 26, 28, 32] while in our cohort it accounted for 36%.

We found a slightly lower rate of rapid onset of symptoms mimicking pituitary apoplexy, with respect to previous reports indicating a prevalence of 8–24% [10, 16, 25]. In such cases, patients may demonstrate hypopituitarism, as observed in one of our participants; however, the incidence is not well established. The pathology of postoperative specimens reveals either haemorrhage or non-haemorrhagic causes of pituitary damage including hypophysitis or abscess formation. However, preoperative diagnosis, based on clinical presentation and MRI is challenging [39, 42]. Several studies reported aseptic meningitis complicating RCC due to cyst rupture into the subarachnoid space or the spread of inflammatory reaction to adjacent structures [10, 19–21]. Among our cohort, one patient was diagnosed with meningitis of unknown, non-infectious aetiology, presenting with vertigo, general malaise, fatigue, and loss of appetite and a combination of adrenal insufficiency and hypogonadism in the laboratory results.

With a few exceptions, the incidence of the remaining symptoms in our analysis is consistent with previous reports, which demonstrated syncope in up to 5% of patients [17, 19], nausea and vomiting in up to 20%

[19, 25, 33], and fatigue/loss of energy in up to 60% [17, 25, 32, 33, 38]. The rate of impaired sexual function was described between 8 and 58% [16, 17, 25, 33], while menstrual cycle irregularities were noted in 7-24% of patients [16, 17, 19, 32, 33, 41]. A relatively low incidence of those symptoms in our cohort correlates with a lower percentage of associated pituitary dysfunction.

Previously most extensive studies revealed endocrine dysfunction in approximately 20–70% of patients with RCC [11–19, 26, 27], with hyperprolactinaemia and hypogonadism being the commonest dysfunctions, noted in 5–38% and 3–60% of patients, respectively [3, 4, 11–19, 25, 26, 32, 36, 40, 41]. Furthermore, the percentage of both secondary adrenal insufficiency and hypothyroidism has been described in 4–44% of patients [3, 5, 11, 13–18, 25, 26, 33, 36, 41]. The proportion of GH deficiency remains unclear because various protocols were used for the diagnosis — estimates vary between 0 and 66% of patients [3, 4, 11, 13–15, 18, 26, 33, 41]. Our findings compare favourably with earlier results in that hyperprolactinaemia was the most frequently observed disorder. In addition, our results fall within previously reported ranges, but in a relatively low percentage compared to the literature data. Contrary to earlier series, none of our patients presented with diabetes insipidus.

Similarly to previous reports [36], we found no correlation between pituitary function and mean cyst diameter. Perhaps the small percentage of pituitary dysfunction and symptoms associated with RCC in our study is related to the clinic's profile and the conservative nature of the offered treatment. Most previous studies come from neurosurgical centres, which manage mainly patients who require surgical treatment due to the cyst size, symptoms, or hormonal disorders, while the patients referred to our departments are often asymptomatic and have smaller RCC diameter. The percentage of incidentally diagnosed RCCs was higher in our cohort compared to previous studies, which reported their incidence in up to one third of patients [18, 33]. The results from a recent study by Sala et al. seem to support this theory, in that patients administered to the conservatively treated group had significantly lower cyst dimensions and lower prevalence of symptoms and pituitary dysfunction compared to patients referred to surgical treatment [18]. The proportion of symptomatic RCCs associated with hypopituitarism might be thus overestimated.

As regards concurrent pituitary adenomas, our findings are consistent with previous series indicating their coexistence in 0.5–11% of patients [2, 16, 19, 43–45]. The commonest associated pituitary dysfunction is hyperprolactinaemia and growth hormone hypersecretion [43, 46, 47], as observed in our study. Although the association between RCC and pituitary adenomas is often referred to as occasional and purely coincidental, their common pathogenesis cannot be excluded and requires further investigation [43, 47]. Evidence on pineal cysts (PC) co-occurring with RCC barely exists. Mukherjee et al. mentions such an association in 1 of 12 analysed patients [35], but other studies lack in information on this topic. We found concomitant RCC and PC in 3% of patients, which matches the prevalence observed in the general population. Symptoms caused by PC are barely distinguishable from those associated with RCC [48]. There are no literature data to support the association between RCC and PC.

Interestingly, we found a relatively high incidence of Hashimoto's thyroiditis and thyroid nodules in our cohort compared to the prevalence reported in the general population [49, 50]. Recent studies indicate a positive correlation between prolactinomas and autoimmune thyroiditis, but their relation to thyroid nodules is unclear [51–54]. Hyperprolactinaemia due to RCC may predispose to autoimmune thyroiditis; however, the association between RCC and primary thyroid disease remains to be clarified.

Finally, our work shares all the limitations of a retrospective study. Furthermore, the diagnosis of RCC in our cohort was based solely on MRI and lacks histopathological confirmation. Nevertheless, we believe our report based on a large study group provides a considerable insight into clinical presentation and endocrine dysfunction in RCC and adds novel information on patients' characteristics, especially their metabolic profile, co-existing neuroimaging findings, and thyroid disorders.

Conclusions

Increasing availability of imaging techniques has led to a sizeable increase in detected pituitary lesions. Despite being largely an incidental finding, RCC often presents with headache, dizziness, or visual impairment. Due to the significant prevalence of related hormonal disorders, both symptomatic and asymptomatic patients require complete clinical and endocrine evaluation. Hyperprolactinaemia is the commonest associated endocrine dysfunction, followed by hypopituitarism. We report a substantial co-occurrence of RCC and metabolic disorders and primary thyroid diseases, which requires further investigation.

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