Review Article

Rathke cleft cyst apoplexy: Hormonal and clinical presentation

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INTRODUCTION

Rathke cleft cyst (RCC) is an epithelium-lined benign congenital cystic lesion found in the sellar or suprasellar area. RCC originates from the craniopharyngeal duct (Rathke's pouch). Such lesions are more common among females, with a male-to-female ratio of 1:1.5. Frequently, RCC is asymptomatic and found in 20% (out of 1000 samples) of postmortem examinations; however, it is prevalent in 2–9% of those who underwent transsphenoidal surgery due to symptomatic sellar mass. If symptomatic, they usually present in adulthood between the 2nd and 6th decades. RCC apoplexy is a rare event with scarce case reports published in the...
literature. We present a case of RCC apoplexy in a 23-year-old man; additionally, we reviewed the literature to study the common demographic profile, clinical and hormonal presentation, and outcome.

MATERIALS AND METHODS

A literature review in Medline, EMBASE, Web of Science, and Scopus was used to identify existing case reports. The search included the following terms: "Rathke's cleft cyst" AND "Apoplexy" OR "Pituitary apoplexy" OR "Hemorrhagic apoplexy" OR "Nonhemorrhagic apoplexy." We included all articles with a histological confirmation of RCC apoplexy in any age group, and we excluded non-English articles (two articles). The earliest article found was published in 1990.

The items of interest in each article were patient demographics, clinical presentation, presenting hormonal profile, hemorrhagic versus nonhemorrhagic RCC apoplexy, clinical outcome, and hormonal outcome. Improvement was recorded based on clinical signs and symptoms after management. The database was last searched in February 2020. The article published by Chaiban et al. did not have individual patient information; rather, patients’ data were combined into frequency, average, and percentage. Kleinschmidt-DeMasters et al. were excluded from the analysis due to unknown hormonal status at presentation and in the final outcome. The decreased level of consciousness was defined as a Glasgow Coma Scale ≤ 14/15. Headache, visual acuity or field deficits, and diplopia were measured subjectively based on history and physical examination. We added one patient treated at our medical center to the overall data [Figures 1-6].

RESULTS

We identified 29 patients in articles published between 1990 and 2019 [Table 1]. The average age was 36.87 (8–72), with 20 female patients (68%). Of the 29 patients, 25 had hemorrhagic RCC apoplexy (86%) [Table 2]. The most common clinical presentation was headache in 27/29 patients (93%), followed by visual deficits in 9/29 (31%), diplopia in 3/29 (10%), and altered mental status in 3/29 (10%). Of the 15/29 patients (52%) who presented with hormonal deficits, 11 had hypogonadism (73%), followed by hypocortisolism in 9 patients (60%), hypothyroidism in 7 patients (47%), high prolactin in 6 patients (40%), and low sodium in 2 patients (13%) [Figure 7].

Of the 29 patients in this series, 15 improved without hormonal replacement therapy (52%), 11 improved with continued hormonal replacement therapy (38%), 1 was stable without hormonal replacement therapy (3%), and 2 were stable with continued hormonal replacement therapy (7%)
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Table 3. Of the 13 patients who are dependent on hormonal replacement therapy, 11 had hemorrhagic RCC apoplexy (85%). The most common type of hormonal replacement therapy postmanagement was thyroid hormone in 7/13 (54%), followed by gonadal hormone replacement such as testosterone in 5/13 (38%), desmopressin due to diabetes insipidus in 3/13 (23%), and corticosterone replacement in 2/13 (15%) [Figure 8].

DISCUSSION

RCC

RCC is an uncommon cystic lesion that is commonly asymptomatic. The prevalence of RCC among sellar lesions can range from 2% to as high as 7%.[8,14] Patients who manifest clinical symptoms complain of headache (44–100%) and visual acuity and field deficits or diplopia (11–56%).[5,9,14,16,22] Hormonal status abnormalities are present in 19–81% of newly diagnosed patients; the most commonly affected hypothalamic-pituitary axis is hyperprolactinemia, followed by hypogonadism, hypocortisolism, hypothyroidism, and diabetes insipidus.[8,11,12,18,22] The most common location is combined sellar and suprasellar (87%), followed by sellar (13%), with a diameter between 1–2 cm (55%), 2–3 cm (35%), and >3 cm (10%).[23]

Its appearance in MRI can be difficult to differentiate from other sellar lesions. Around 70% are hyperintense on T2 with little to no cystic wall enhancement on gadolinium administration.[11,22] Cystic content can be discerned based on MRI signal intensity, however, such as water-like content with hypointensity on T1 and hyperintensity on T2, mucoid-like content appearing hyperintense on T1 and isointense on T2, or cystic hemorrhage appearing hyperintense on T1 and T2.[41] A case series by Aho et al.[2] showed that 31% of patients had progression of cyst size with resultant visual or endocrinologic deterioration if left untreated. Conversely, Amhaz et al.[10] concluded that 31% of cysts spontaneously resolve without surgical management. Therefore, natural history may lean toward a benign course. Recurrence after surgical resection can be predicted if the histopathology shows epithelial squamous metaplasia (9–39% recurrence), contrary to the common columnar or cuboidal epithelial appearance.[2,22] As many as, 24% of patients required long-term hormonal replacement postsurgery.[9]
Table 1: Summary of cases from the literature.

| Reference          | Age/sex        | Hemorrhage | Hormonal deficits                       | Clinical presentation                                                                 | Management                  | Outcome                                                                 |
|--------------------|----------------|------------|-----------------------------------------|----------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------|
| Current case       | 23 years/male  | Yes        | Low gonadotropin and thyroid hormones   | Headache, visual acuity deficits, decreased libido, erectile dysfunction               | Trans-sphenoidal surgery   | Improved headache and vision, dependent on hormonal replacement (thyroid and testosterone) |
| Schooner et al.   | 38 years/male  | Yes        | Low gonadotropin                       | Headache and visual field deficits                                                    | Trans-sphenoidal surgery   | Improved                                                               |
| (2019)[12]        | 33 years/female| Yes        | Low gonadotropin, thyroid, and corticosteroids | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| Schooner et al.   | 36 years/female| Yes        | Low gonadotropin and corticosteroids    | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| (2019)[12]        | 37 years/female| Yes        | Low gonadotropin and thyroid            | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| Schooner et al.   | 72 years/male  | Yes        | Panhypopituitarism                      | Headache, visual field deficits                                                        | Trans-sphenoidal surgery   | Improved                                                               |
| (2019)[12]        | 49 years/male  | Yes        | Panhypopituitarism and low sodium       | Headache                                                                                       | Trans-sphenoidal surgery   | Stable, except for hormonal replacement (thyroid, corticosteroids, and testosterone) |
| Kim et al.        | 62 years/female| Yes        | High prolactin, low thyroid and corticosteroid hormones, and low sodium | Headache                                                                                       | Trans-sphenoidal surgery   | Improved, except for hormonal replacement (thyroid)                  |
| (2012)[24]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 20 years/male  | No         | Low gonadotropin hormone                | Headache, nausea, vomiting, and diplopia                                                 | Trans-sphenoidal surgery   | Improved, except for hormonal replacement (testosterone)             |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 23 years/female| No         | High prolactin                         | Headache, visual acuity deficit                                                          | Trans-sphenoidal surgery   | Improved                                                               |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 49 years/male  | No         | None                                    | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 21 years/female| No         | Low thyroid hormone                     | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 24 years/female| Yes        | None                                    | Headache                                                                                       | Trans-sphenoidal surgery   | Improved                                                               |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Binning et al.    | 54 years/female| Yes        | None                                    | Headache, visual acuity deficits, and meningism                                          | Trans-sphenoidal surgery   | Improved                                                               |
| (2008)[10]        |                |            |                                         |                                                                                             |                            |                                                                         |
| Rosales et al.    | 34 years/male  | Yes        | High prolactin and low thyroid hormone  | Headache and diplopia                                                              | Trans-sphenoidal surgery   | Improved, except for hormonal replacement (thyroid)                  |
| (2004)[25]        |                |            |                                         |                                                                                             |                            |                                                                         |

(Contd...)
RCC apoplexy demographics and pathogenesis

RCC apoplexy is extremely rare, and only a few case reports have been published in the literature. The term RCC apoplexy was coined by Chaiban et al.\cite{7} who identified 20% occurrence of RCC apoplexy among all RCC patients. Pituitary adenoma apoplexy, commonly associated with null cell type, is more prevalent in males (65.5%), whereas RCC apoplexy, much like RCC, is more prevalent in females (64%).\cite{4,19} The mean age of presentation in pituitary adenoma apoplexy is 50.9 years (15–91), while RCC apoplexy is 36.87 years (8–72), indicating a younger mean age of presentation in RCC apoplexy.\cite{19} The pathogenesis of

| Reference          | Age/sex          | Hemorrhage | Hormonal deficits | Clinical presentation          | Management                     | Outcome          |
|-------------------|------------------|------------|-------------------|-------------------------------|-------------------------------|------------------|
| Pawar et al. (2002)\cite{26} | 19 years/male | Yes        | None              | Headache, blurred vision      | Trans-sphenoidal surgery      | Improved         |
| Kurisaka et al. (1998)\cite{27} | 8 years/ female | Yes        | None              | Headache                      | Trans-sphenoidal surgery      | Improved         |
| Kleinschmidt-DeMasters et al. (1995)\cite{8} | 51 years/ female | Yes        | NA\(^b\)          | Visual acuity deficits        | Trans-sphenoidal surgery      | NA\(^b\)         |
| Onesti et al. (1990)\cite{28} | 25 years/ female | Yes        | None              | Headache                      | Trans-sphenoidal surgery      | Improved         |
| Nishioka et al. (1990)\cite{29} | 46 years/ female | Yes        | None              | Headache, visual acuity deficits | Trans-sphenoidal surgery      | Improved         |

\(^{a}\)Chaiban et al.\cite{7} didn't list the details of each patient, and thus, patients were not added in the table

\(^{b}\)The information was not mentioned in the article

| Table 2: Descriptive statistics of Preoperative findings. |
|----------------------------------------------------------|
| Age (range)\(^a\)        | 36.87 years (8-72) | |
| Males, n (%)                  | 11 (36%)       | |
| Females, n (%)                | 20 (64%)       | |
| Male to Female ratio          | 1:1.8          | |
| Hemorrhagic apoplexy, n (%)   | 25/29 (86%)    | |
| Non-hemorrhagic apoplexy, n (%)| 4/29 (14%)   | |
| Hemorrhagic to Non-hemorrhagic apoplexy ratio | 6.5:1          |
| Headache, n (%)               | 27/29 (93%)    | |
| Visual deficits\(^c\), n (%) | 9/29 (31%)     | |
| Diplopia, n (%)               | 3/29 (10%)     | |
| Decreased level of consciousness\(^d\), n (%) | 3/29 (10%)     | |
| Hormonal deficits, n (%)      | 15/29 (52%)    | |
| Low gonadotropin, n (%)       | 11/15 (73%)    | |
| Low corticosteroid, n (%)     | 9/15 (60%)     | |
| High prolactin, n (%)         | 6/15 (40%)     | |
| Low thyroid, n (%)            | 7/15 (47%)     | |
| Low sodium, n (%)             | 2/15 (13%)     | |

\(^{a}\)The standard deviation wasn’t calculated due to missing individual patients' age in Chaiban et al.\cite{7}

\(^{b}\)Kleinschmidt-DeMasters et al.\cite{8} was not added in the analysis due to missing hormonal profile and outcome post-surgery

\(^{c}\)Visual deficits include acuity and field deficits

\(^{d}\)GCS of ≤ 14/15

| Table 3: Descriptive statistics of Postoperative findings. |
|----------------------------------------------------------|
| Improved, n (%)                                          | 15/29 (52%)  |
| Improved with hormonal replacement therapy, n (%)         | 11/30 (38%)  |
| Stable, n (%)                                            | 1/30 (3%)    |
| Stable with hormonal replacement therapy, n (%)           | 2/30 (7%)    |
| Hemorrhagic apoplexy with hormonal deficits, n (%)       | 11/30 (85%)  |
| Non-hemorrhagic apoplexy with hormonal deficits, n (%)   | 2/13 (15%)   |
| Thyroid replacement post-operation, n (%)                | 7/13 (54%)   |
| Gonadal hormone replacement post-operation, n (%)       | 5/13 (38%)   |
| Corticosteroid replacement post-operation, n (%)         | 2/13 (15%)   |
| Desmopressin due to diabetes insipidus, n (%)            | 3/13 (23%)   |

\(^{a}\)At last follow up

Figure 7: Presenting hormonal status.
RCC apoplexy is still unknown; however, it can be attributed to the fragile epithelial wall vascular supply and the development of immature vascular endothelium from cystic wall granulation tissue.[8,13] Nonhemorrhagic RCC apoplexy is hypothesized to cause neurological and hormonal deficits by the expanding infarcted tissue.[9]

RCC clinical and hormonal presentation

The most common clinical presentation in RCC apoplexy is headache (93%), followed by visual acuity and field deficits (31%), diplopia (10%), and altered level of consciousness (10%). Pituitary adenoma apoplexy has a similar frequency of clinical presentation to RCC apoplexy, with headache being the most common (84–100%), followed by visual field deficits (34–70%), visual acuity deficits (56%), diplopia (45–57%), and decreased level of consciousness (13–30%).[4,17]

From the literature review analysis, 52% of RCC apoplexy patients had hormonal abnormalities on presentation, compared to 70–80% of pituitary adenoma apoplexy patients.[4] Therefore, patients with pituitary adenoma apoplexy have worse endocrinologic abnormalities than those with RCC apoplexy.[8] Hypogonadism is the most common deficient hormone, occurring in 73% of patients, mainly translated in low testosterone level; low cortisol level is the second most common deficiency (60%), followed by low thyroid hormone (47%), hyperprolactinemia (40%), and hyponatremia (13%). Low cortisol level is the most common hormonal deficiency in pituitary adenoma apoplexy, occurring in 73% of patients, followed by low thyroid hormone (55%), low gonadotropin (40%), hyperprolactinemia (11%), and hyponatremia (< 5%).[4,17] It is difficult to distinguish RCC apoplexy from pituitary adenoma apoplexy. Intraoperative diagnosis using histopathology is the gold standard method, showing hemosiderin, cholesterol crystals, and histiocytes, among others.[16]

RCC clinical and hormonal outcome

The neurological outcome posttranssphenoidal surgery has improvement in 90% of cases, with 10% having stable neurological deficits. Approximately 45% of patients required long-term hormonal replacement, with 38% improving neurologically. The neurological improvement rate posttranssphenoidal surgery in pituitary adenoma apoplexy is 53–89%; however, 58–83% of patients required long-term hormonal replacement – higher than for RCC apoplexy.[4]

The most common long-term hormonal replacement in RCC apoplexy is thyroid hormone (54%), followed by testosterone replacement (38%), desmopressin for hyponatremia (23%), and cortisol replacement (15%). This is in contrast to pituitary adenoma apoplexy, with testosterone as the most common long-term hormonal replacement (63.6%), followed by thyroid replacement (62.7%), cortisol replacement (60%), and desmopressin (10%). In our case, the patient required long-term thyroid and testosterone replacement. The prevalence of hemorrhagic type RCC apoplexy is 86%, with 85% requiring long-term hormonal replacement.

Treatment guideline

No treatment protocol is designed for RCC apoplexy; however, we can apply the current management plan for pituitary adenoma apoplexy to RCC apoplexy. A review of management guidelines and outcomes of pituitary adenoma apoplexy recommended urgent transsphenoidal microscopic or endoscopic decompression of the RCC lesion for patients presenting with acute or progressive deterioration of their visual field or visual acuity; whereas, other clinical presentations, such as headache, mild decreased level of consciousness, or endocrine abnormalities, were not statistically significant in prompting urgent surgical intervention as compared to conservative management and a wait-and-see approach.[1,7]

CONCLUSION

RCC apoplexy is a rare entity that is difficult to diagnose using standard radiological imaging. It has a higher female preponderance and commonly presents in a younger age group in comparison to pituitary adenoma apoplexy. Compared to pituitary adenoma apoplexy, the clinical and hormonal presentation is relatively less severe with a benign postoperative course. Although diabetes insipidus is comparatively more prominent in RCC apoplexy, it is recommended to apply pituitary adenoma apoplexy management guidelines to RCC apoplexy.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.
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Conflicts of interest
There are no conflicts of interest.

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