





Unraveling the Mystery of Rathke's Cleft Cyst Presenting with Hyponatremia: A Case Report with a Comprehensive Review of Literature

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Abstract

Keywords

- ▶ syndrome of inappropriate antidiuretic hormone secretion
- ▶ Rathke's cleft cyst
- ▶ hyponatremia
- ▶ hypothalamic–pituitary axis
- ▶ sellar–suprasellar lesion

Background Rathke's cleft cyst (RCC) is a benign cystic lesion that is commonly discovered incidentally and remains asymptomatic in most cases. However, its association with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion leading to hyponatremia (HN) is rare and has only been sporadically reported in the medical literature. In this article, we present a unique case of RCC manifesting with HN and discuss the diagnostic and management challenges encountered in a neurosurgical context. Additionally, we provide a comprehensive review of existing literature on RCC presenting with HN to enhance our understanding of this rare presentation.

Case Description A 56-year-old woman with acute-onset blurry vision, headaches, and low fluid intake was diagnosed with euvolemic HN secondary to SIADH. Further evaluation revealed an intrasellar cystic lesion consistent with RCC, which was successfully resected through endoscopic transnasal transsphenoidal surgery, resulting in a complete recovery without the need for hormone replacement.

Conclusion The most likely explanation for the HN due to SIADH in this case is the release of accumulated antidiuretic hormone (ADH) due to compression by the cyst and the irritating effect of inflammation at this location. Accurate evaluation and classification of HN are essential for proper diagnosis and management, considering the rarity of RCC presenting with HN. A multidisciplinary approach to treatment can lead to favorable functional outcomes; however, further research is necessary to better comprehend this unique clinical entity and optimize neurosurgical approaches.

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Introduction

Rathke's cleft cyst (RCC) is a benign cystic lesion that arises from remnants of Rathke's pouch, an embryonic structure involved in the development of the anterior pituitary gland.¹ These cysts are typically found in the sellar and suprasellar regions and are usually small in size and asymptomatic and most commonly identified as incidental findings. Larger lesions may result in symptoms by compressing the optic chiasm, pituitary stalk, and hypothalamus. The most typical symptoms in adults are vision loss, endocrine problems, and headaches, creating diagnostic challenges due to their overlapping clinical presentations with other sellar and suprasellar lesions.²

Hyponatremia (HN) is a sellar-suprasellar lesion that can be a result of various factors altering the normal physiology of the hypothalamic-pituitary-adrenal axis. RCC presenting with HN due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported only a few times in the published literature (►Table 1).³⁻⁹

SIADH is characterized by euvolemic HN, typically with low serum osmolality, increased urine osmolality, and high urine sodium concentration. Patients with SIADH often present with nonspecific symptoms, such as nausea, vomiting, headache, confusion, seizures, and muscle cramps, which can range from mild to severe depending on the degree of HN and its rate of development. In SIADH, antidiuretic hormone (ADH) is secreted despite normal physiological conditions, resulting in impaired water excretion and dilutional HN. The pathophysiology of SIADH involves various mechanisms that lead to increased ADH secretion or enhanced renal responsiveness to ADH. Commonly reported etiologies of SIADH include tumors (such as lung cancer, small cell lung carcinoma, and oat cell carcinoma), central nervous system disorders, pulmonary diseases, medications, and certain systemic conditions.¹⁰

In the context of RCC, SIADH can occur due to mechanical and/or chemical alternation of the hypothalamic-pituitary axis. Surgical resection of the cyst may be necessary in the cases where symptoms are significant or when complications like SIADH arise. Further research and understanding of the pathophysiology, diagnostic approaches, and management strategies for both RCC and SIADH are essential to optimize patient outcomes and improve clinical management in neurosurgery. This report focuses on a rare case of HN caused by SIADH in a patient with RCC, highlighting the challenges faced in treatment and management in the neurosurgical setting. We obtained written informed consent from the patient for the publication of this case report and accompanying images.

Case Report

A 56-year-old woman with no significant past medical history presented with acute-onset blurry vision with headaches, nausea, and low fluid intake for the past few days. Laboratory investigations revealed severe HN with a serum sodium level of 114 mEq/L, serum glucose level of 98 mg/dL,

serum blood urea nitrogen (BUN) of 6 mg/dL, and creatinine of 0.50 mg/dL. Other investigations revealed serum osmolality of 247 mOsm/kg, urine sodium of 53 mEq/L, and urine osmolality of 321 mOsm/kg. Her endocrine workup revealed an 8 a.m. serum cortisol level of 12.06 µg/dL, thyroid-stimulating hormone (TSH) of 3.64 µIU/mL, free-T4 (FT4) of 1.10 ng/dL, adrenocorticotropic hormone (ACTH) of 17.4 pg/mL, follicle-stimulating hormone (FSH) of 68.15 IU/L (postmenopausal), luteinizing hormone (LH) of 33.76 IU/L (postmenopausal), prolactin 10.32 ng/mL, and insulin like growth factor 1 (IGF-1) of 116 ng/mL. Her blood pressure was within normal limits, and she was not dehydrated. Based on these, she was diagnosed as euvolemic HN secondary to SIADH. She was managed with hypertonic saline and fluid restriction, without success for 1 week in the hospital.

For further evaluation, she underwent brain magnetic resonance imaging (MRI), which showed an intrasellar cystic lesion, measuring 8 × 7 × 7 mm, which was T1 hypointense and T2 hyperintense, and was nonenhancing on T1-weighted contrast imaging. Based on the findings, our working diagnosis was RCC (►Fig. 1). She then underwent endoscopic transnasal transsphenoidal resection of the cyst. She tolerated the procedure well and recovered well from anesthesia. During the postoperative period, she was treated with hydrocortisone and tolvaptan (Arginine Vasopressin-selective V2 receptor antagonist). Her HN gradually improved to 135 mEq/L in the postoperative period. Postoperative MRI revealed no residual disease with operative site changes (►Fig. 1).

A histopathological examination of the surgical specimen revealed a cyst lined by ciliated columnar cells adjacent to unremarkable adenohypophyseal tissue. Reticulin stain showed normal lobular architecture of adenohypophysis and the cells are positive for cytokeratin, FSH, LH, ACTH, prolactin, growth hormone, TSH (rare cells), T pit (few cells), SF1, Pit 1, and negative for GATA3 and Ki-67 supporting the diagnosis. The diagnosis was consistent with RCC (►Fig. 2).

At discharge, her Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 1 and her Karnofsky performance status (KPS) was 90. At the 3-month follow-up, she is asymptomatic, with ECOG PS of 0 and KPS of 100, with normal serum electrolyte levels without any requirements of hormone replacement.

Discussion

The embryological Rathke's pouch gives rise to RCCs. The primitive oropharynx develops a rostral outpouching between the third and fourth weeks of gestation, which eventually gives rise to the anterior lobe, pars intermedia, and pars tuberalis of the pituitary gland. The craniopharyngeal canal is formed by this rostral outpouching from the oropharyngeal ectoderm or Rathke's pouch. The infundibulum originates from the diencephalon around the same time as the neurohypophysis. Around the fifth week of gestation, both structures come into contact with one another to form the adenohypophysis and neurohypophysis, respectively. By the sixth week of gestation, the Rathke pouch shrinks to a tiny cleft. RCCs, which are typically found in the pars

Table 1 Comprehensive review of literature of the published cases of Rathke's cleft cysts presenting with hyponatremia

Study	Age/sex	Clinical presentation	Preoperative serum sodium level (mEq/L)	Location of lesion and management	Histopathology	Underlying mechanism	Medical management and outcome
Moroi et al ³	68/F	Drowsiness, vomiting, and diarrhea	109	Sellar and suprasellar region; transcranial resection	RCC with Carinopharyngioma component	Rapid compression of the anterior hypothalamus with intracystic hemorrhage	<ul style="list-style-type: none"> • Outcome: NA
Nakayama et al ⁴	68/M	Drowsiness, lethargy, meningitis, and weight loss	115	Sellar and suprasellar region; transsphenoidal resection	RCC	Rupture of the cyst and intracranial spillage: chemical meningitis Salt wasting due to hypothalamic-pituitary axis injury	<ul style="list-style-type: none"> • Good clinical outcome • Panhypopituitarism • On hormone replacement
Iwai et al ⁵	70/F	Drowsiness, lethargy, vomiting, diarrhea, and weight loss	100	Intrasellar region; medically managed	Radiological impression: RCC; no histopathology	SIADH (due to large cystic lesion) with secondary adrenal insufficiency (due to compression of the pituitary gland/stalk)	<ul style="list-style-type: none"> • Good clinical outcome • Water restriction during the first episode • Hydrocortisone during the second episode
Hsu et al ⁶	18/F	General weakness, nausea, vomiting, headache, and lightheadedness	125, then 152	Sellar and suprasellar region; transsphenoidal resection	RCC	ADH release by local mechanical stimulation: SIADH Further enlargement and compression causing destruction of ADH-releasing cells: CDI	<ul style="list-style-type: none"> • Asymptomatic at 1-y follow-up • Permanent CDI requiring dDAVP
Ogawa et al ⁷	73/F	Retro-orbital pain, nausea, vomiting, and bitemporal hemianopsia	129	Sellar and suprasellar region; transsphenoidal resection	RCC	Hyponatremia secondary to hypocortisolemia resulting from rupture of cyst/intracystic hemorrhage causing fibrosis and decreased reserve of pituitary gland	<ul style="list-style-type: none"> • Outcome: NA • Dexamethasone
	34/M	Motor weakness, fatigue	120	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Hydrocortisone
	73/M	Fatigue	122	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Hydrocortisone → dexamethasone

(Continued)

Table 1 (Continued)

Study	Age/sex	Clinical presentation	Preoperative serum sodium level (mEq/L)	Location of lesion and management	Histopathology	Underlying mechanism	Medical management and outcome
	51/F	Nausea, vomiting, and loss of consciousness	112	Intrasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Hydrocortisone + Na supplement
	75/M	Body weight loss and anemia	119	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Dexamethasone
	33/F	Severe headache, nausea, high fever, fatigue, and thirst	118	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Hydrocortisone + dDAVP
	70/M	Drowsiness	126	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Fludrocortisone + dexamethasone
	66/F	Loss of consciousness	126.2	Sellar and suprasellar region; transsphenoidal resection	RCC	Same	<ul style="list-style-type: none"> • Outcome: NA • Hydrocortisone
Sivakumar et al ⁸	33/M	Sudden severe headaches, visual changes, dizziness, nausea, vomiting, and a metallic taste in his mouth	121	Sellar and suprasellar region; transsphenoidal resection	RCC	Transient hypocortisolemic state resulting in hyponatremia	<ul style="list-style-type: none"> • Outcome: NA • Levofloxacin and hydrocortisone
Hinata et al ⁹	49/M	Headache, nausea, appetite loss, and fatigue; 1 mo later, thirst, polydipsia, and polyuria	112	Intrasellar region; medically managed	RCC (based on imaging)	<ul style="list-style-type: none"> • Chemical damage to the posterior pituitary caused by leaked RCC content: ADH hypersecretion (SIADH) • Axons degenerate from the posterior pituitary to the magnocellular cell bodies: CDI 	<ul style="list-style-type: none"> • Good outcome • Medical management • For SIADH: fluid • For CDI: dDAVP

Abbreviations: ADH, antidiuretic hormone; CDI, antidiuretic hormone; dDAVP, desmopressin; RCC, Rathke's cleft cyst; SIADH, syndrome of inappropriate antidiuretic hormone.

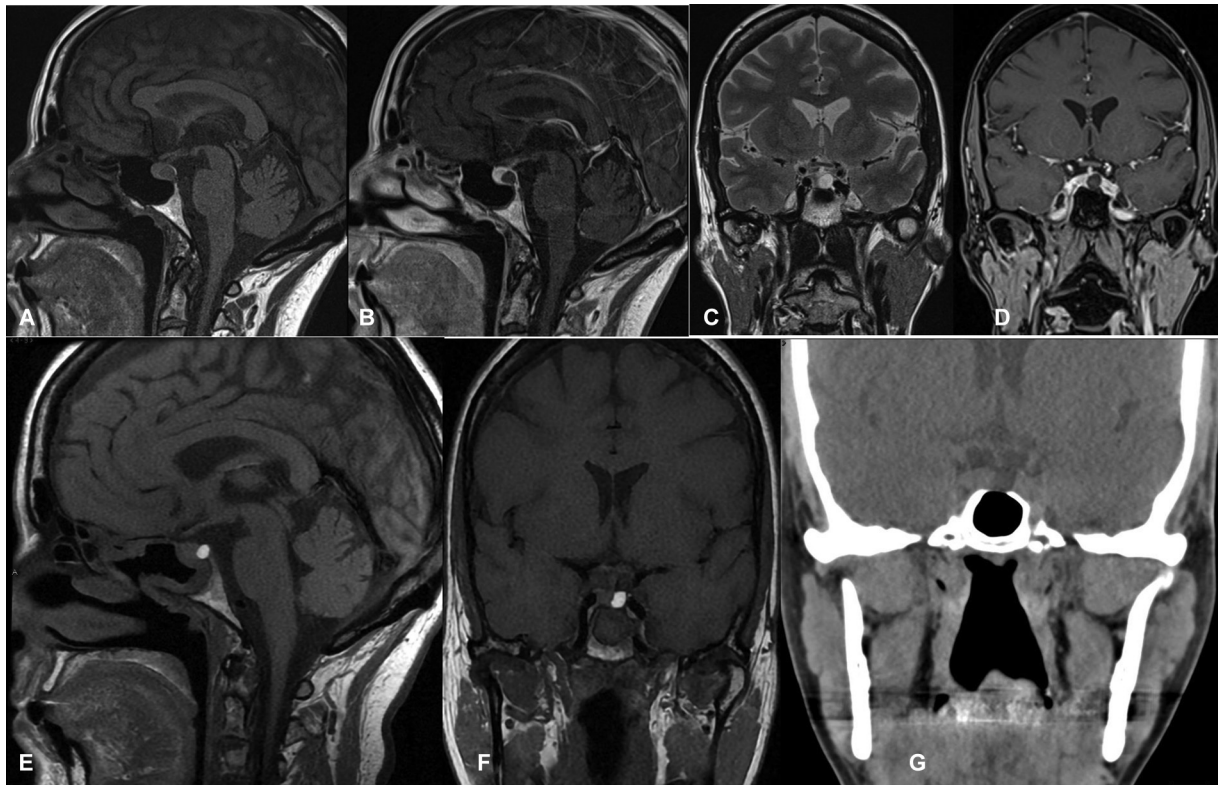


Fig. 1 (A–D) Preoperative magnetic resonance imaging (MRI) reveals $8 \times 7 \times 7$ mm round focus of T1 hypo-, T2, and fluid-attenuated inversion recovery (FLAIR) hyperintense and T1 contrast nonenhancing lesion in the intrasellar region and at the dorsal aspect of the pituitary gland, just left of the midline without any suprasellar extension. The pituitary stalk is in the midline with normal thickness (2–3 mm). (E, F) Postoperative MRI reveals a T1 hyperintense signal at the operative site and (G) postoperative computed tomography (CT) demonstrates a left-sided cystic cavity without any evidence of residual lesion.

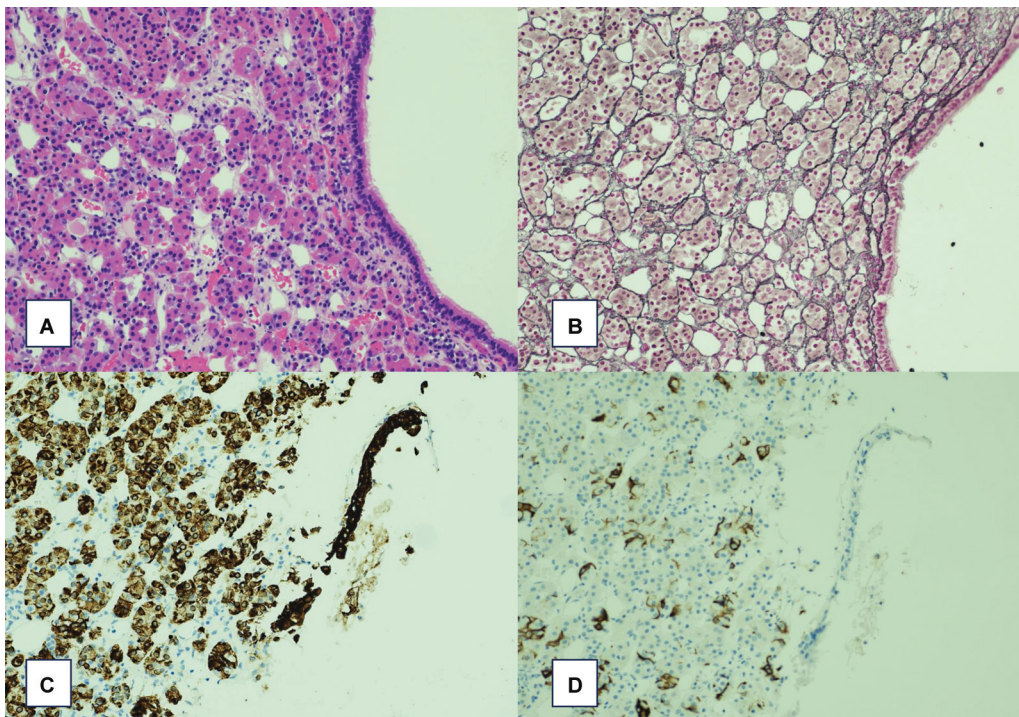


Fig. 2 (A) Histological examination reveals a portion of the cyst lined by ciliated columnar cells (hematoxylin and eosin [H&E] stain at 40X), juxtaposed to unremarkable adenohypophyseal tissue and containing detached thick eosinophilic material. (B) Reticulin staining (20X) confirms the normal lobular architecture of the adenohypophysis. (C) Cells have positive immunoreactivity for cytokeratin (20X). (D) Negative glial fibrillary acidic protein (GFAP) (20X).

intermedia, are formed as a result of the persistence and expansion of these clefts.²

Various theories have been described in the published literature to explain the HN associated with RCC (–Table 1).^{3–9}

Hypocortisolemia as a Result of Chronic Inflammation of the Pituitary Gland Causing Hyponatremia

Cortisol promotes sodium reabsorption and potassium excretion in the collecting tubules, which helps maintain plasma volume and serum sodium levels. In cases of hypocortisolemia, there can be a reduction in sodium reabsorption, leading to secondary HN. This hypothesis is further supported by the observation that patients recovered from HN with corticoid treatment alone with low baseline serum cortisol levels, without requiring additional sodium supplementation. The development of HN can be initiated by recurrent intracystic hemorrhage and cyst rupture, leading to inflammation of the cyst wall. This inflammatory process, along with histological repair, results in changes from a single cuboidal epithelium of RCC to stratified epithelia and significant interstitial fibrosis causing pituitary atrophy with reduced reserve.⁷ The deficiency in the mineral corticoid effect of cortisol can result in HN.⁷ Nevertheless, the normal preoperative serum cortisol level eliminates this possibility in our case.

Salt Wasting as a Cause of Hyponatremia

Certain intracranial organic lesions can promote sodium diuresis, known as cerebral salt wasting. This condition involves disturbances in the hypothalamic function and an increase in the concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).⁷ Considering that these patients usually present with hypovolemia and signs of dehydration (hypovolemic HN), it is highly improbable that this possibility is responsible for HN in our case.

SIADH as a Cause of Hyponatremia

ADH is produced by magnocellular neurosecretory cells located in the hypothalamic supraoptic and paraventricular nuclei. Subsequently, it travels through axons that traverse the infundibular stalk and reaches the posterior pituitary, where ADH is stored in vesicles until its controlled release into the bloodstream.⁹ One of the explanations of this plausible causation is that RCC compresses the posterior pituitary, which can lead to SIADH due to the release of accumulated ADH into the bloodstream. Additionally, as the inflammation progressed along the magnocellular axons, SIADH persisted due to the release of AVP from the degenerating axons.⁹ Considering the euvolemic status and clinical presentation, this theory (HN secondary to SIADH) appears to be the most plausible explanation for HN in our case.

To address the RCC and its potential contribution to the patient's SIADH, a transsphenoidal resection of the cyst was performed. This neurosurgical intervention aimed to alleviate the effect of the lesion on the hypothalamic–pituitary axis and the possible disruption of normal ADH regulation.

Following the resection, the patient experienced an immediate improvement in symptoms, and her HN also got corrected. And in subsequent follow-ups, she did not require any hormone replacement therapy to maintain normal electrolyte levels. The relationship between RCC and SIADH warrants further investigation to comprehensively understand the intricate pathophysiological interplay.

Conclusion

The management of SIADH in the neurosurgical setting is highly challenging, demanding a delicate balance between fluid restriction and the prevention of complications arising from HN. Collaborative efforts between neurosurgery, endocrinology, and other specialized disciplines are paramount to optimize patient outcomes and ensure appropriate management. This intriguing case report underscores the rare association between RCC and SIADH. The unusual presentation of SIADH in this context highlights the need for vigilant monitoring and meticulous management of HN in neurosurgical patients. Prompt recognition of SIADH in the setting of RCC, along with interdisciplinary collaboration and timely intervention, holds the key to achieving the best possible outcomes in these complex cases. Further research and investigations are imperative to enhance our understanding of this unique clinical entity and optimize treatment approaches in the realm of neurosurgery.

Note

The study was conducted in accordance with the Declaration of Helsinki. The requirement for approval from the institutional review board was waived for this case report.

Authors' Contributions

S.H., S.S., P.R.B., and J.A.B. contributed conception or design, data acquisition, data analysis, data interpretation, drafting the work, and critical revision for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. S.S. and J.A.B. also supervised the study. A.H., B.K.P., M.H., L.M., and M.D. contributed to data acquisition, data analysis, data interpretation, drafting the work, and critical revision for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. A.M. contributed to data acquisition, data interpretation, drafting the work, and critical revision for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Availability of Data and Material

Data will be made available to the editors of the journal for review or query upon request.

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Conflict of Interest

None declared.

References

- 1 Raper DMS, Besser M. Clinical features, management and recurrence of symptomatic Rathke's cleft cyst. *J Clin Neurosci* 2009;16(03):385–389
- 2 Gowtham MS, Sunilkumar D, Ramesh AS, Srinivas BH, Verma D, Nagarajan K. Intrasphenoidal Rathke cleft cyst: a rare case report. *J Pediatr Neurosci* 2021;16(04):350–353
- 3 Moroi J, Orita T, Tsurutani T, Nomura S. Symptomatic Rathke's cleft cyst presenting with hyponatremia: a case report. *No Shinkei Geka* 1995;23(12):1117–1120
- 4 Nakayama Y, Tanaka A, Naritomi K, Yoshinaga S. Hyponatremia-induced metabolic encephalopathy caused by Rathke's cleft cyst: a case report. *Clin Neurol Neurosurg* 1999;101(02):114–117
- 5 Iwai H, Ohno Y, Hoshiro M, et al. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and adrenal insufficiency induced by Rathke's cleft cyst: a case report. *Endocr J* 2000;47(04):393–399
- 6 Hsu YJ, Chau T, Yang SS, Tsai WS, Lin SH. Rathke's cleft cyst presenting with hyponatremia and transient central diabetes insipidus. *Acta Neurol Scand* 2003;107(05):382–385
- 7 Ogawa Y, Tominaga T, Ikeda H. Clinicopathological and endocrinological study of Rathke's cleft cyst manifesting as hyponatremia. *Neurol Med Chir (Tokyo)* 2007;47(02):58–63, discussion 63–64
- 8 Sivakumar W, Cole CD, Couldwell WT. Rathke cleft cyst presenting with hyponatremia: an unusual presentation. *Neurosurg Focus* 2011;31(01):E4
- 9 Hinata Y, Ohara N, Komatsu T, et al. Central diabetes insipidus after syndrome of inappropriate antidiuretic hormone secretion with severe hyponatremia in a patient with Rathke's cleft cyst. *Intern Med* 2022;61(02):197–203
- 10 Yasir M, Mechanic OJ. Syndrome of Inappropriate Antidiuretic Hormone Secretion. StatPearls Publishing; 2023. Accessed August 2, 2023 at: <http://www.ncbi.nlm.nih.gov/books/NBK507777/>