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CLINICAL CASE REPORT

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Patient With Severe Hyponatremia Caused by Adrenal Insufficiency Due to Ectopic Posterior Pituitary Lobe and Miscommunication Between Hypothalamus and Pituitary

A Case Report

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Abstract: Hyponatremia may be one of the clinical manifestations of adrenal insufficiency (AI) and during the diagnostic workup of hyponatremic patients investigation of AI should be included.

We report the case of an 82-year-old patient who was admitted to our hospital with clinical symptoms and laboratory findings of hyponatremia. Following the diagnostic algorithm of hyponatremia we reached the diagnosis of AI. Clinician's attention must focus on the underlying cause of AI which in this case was hidden in a miscommunication between hypothalamus and pituitary due to an ectopic posterior pituitary lobe and became apparent by a pituitary magnetic resonance imaging (MRI) scan. Treatment with oral hydrocortisone resulted in full clinical recovery and electrolyte balance, which was maintained after 7 months of follow-up.

Secondary AI is related with hyponatremia through increased ADH secretion. Although a hyponatremic episode may be the first presentation of AI, clinical suspicion is of high importance in order to place the right diagnosis. Disruption of communication between hypothalamus and pituitary is a rare but considerable cause of AI.

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Abbreviations: ACTH = adrenocorticotropic hormone, ADH = antidiuretic hormone, AI = adrenal insufficiency, CRH = corticotropin-releasing hormone, eGFR = estimated glomerular filtration rate, MRI = magnetic resonance imaging, SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

INTRODUCTION

Hyponatremia is a common electrolyte disturbance biochemically defined as a serum sodium concentration below 135 meq/L and is considered severe when the serum level is below 125 mEq/L.[1] These values can vary to a small degree in different clinical laboratories.[1] Hyponatremia usually presents with symptoms related to dysfunction of the central nervous system (CNS) and ranging from nausea, headache and malaise, to lethargy, decreased level of consciousness, and (if severe) seizures and coma.[2] In addition to the severity of hyponatremia, the rate of serum sodium decline determines the severity of symptoms.[3] The diagnostic approach of patients with hyponatremia may be challenging making the use of diagnostic algorithms necessary. In most patients with hyponatremia a single cause is identified but, in selected cases, multiple factors contribute to the decline in plasma sodium. A commonly used diagnostic algorithm classifies the causes of low sodium levels to hypovolemic, hypervolemic, and normovolemic states (based on plasma osmolality) in combination with urine sodium concentration[3] (Figure 1). According to this approach, adrenal insufficiency (AI) may be a cause of normovolemic, low osmolality, sometimes severe hyponatremia.[3] However, most cases refer to primary AI (i.e., Addison disease). In the following paper, we describe a case of secondary AI due to an ectopic posterior pituitary lobe and disruption of communication between hypothalamus and pituitary that remained undiagnosed before the severe hyponatremic episode.

Patient Information

An 82-year-old Caucasian man presented to the emergency department of our hospital with dysarthria, walking unsteadiness, anorexia, and nausea gradually deteriorating over the previous 10 days. He was a senior citizen, married, and has 5 kids. The patient had no recent history of vomiting, diarrhea, or diuretic abuse. He was treated with a low dose of acetylsalicylic acid and 500 mg of hydroxyurea per day for the last 30 years, because he was suffering from idiopathic thrombocytosis. He was recently diagnosed with depression and prescribed with a daily dose of 20 mg of citalopram. Prior to his admission repeated blood tests on routine examination failed to show any abnormal findings in serum electrolyte levels.

Clinical Findings

Physical examination at the time of admission revealed no signs of dehydration or edema. Patient vitals were within normal range. The temperature was 36.3 °C, the blood pressure 130/72 mm Hg, and the pulse 80 beats per minute. The abdomen was not distended, with normal bowel sounds and moderate tenderness to palpation in the epigastric, while the remainder of the clinical examination was normal. Further

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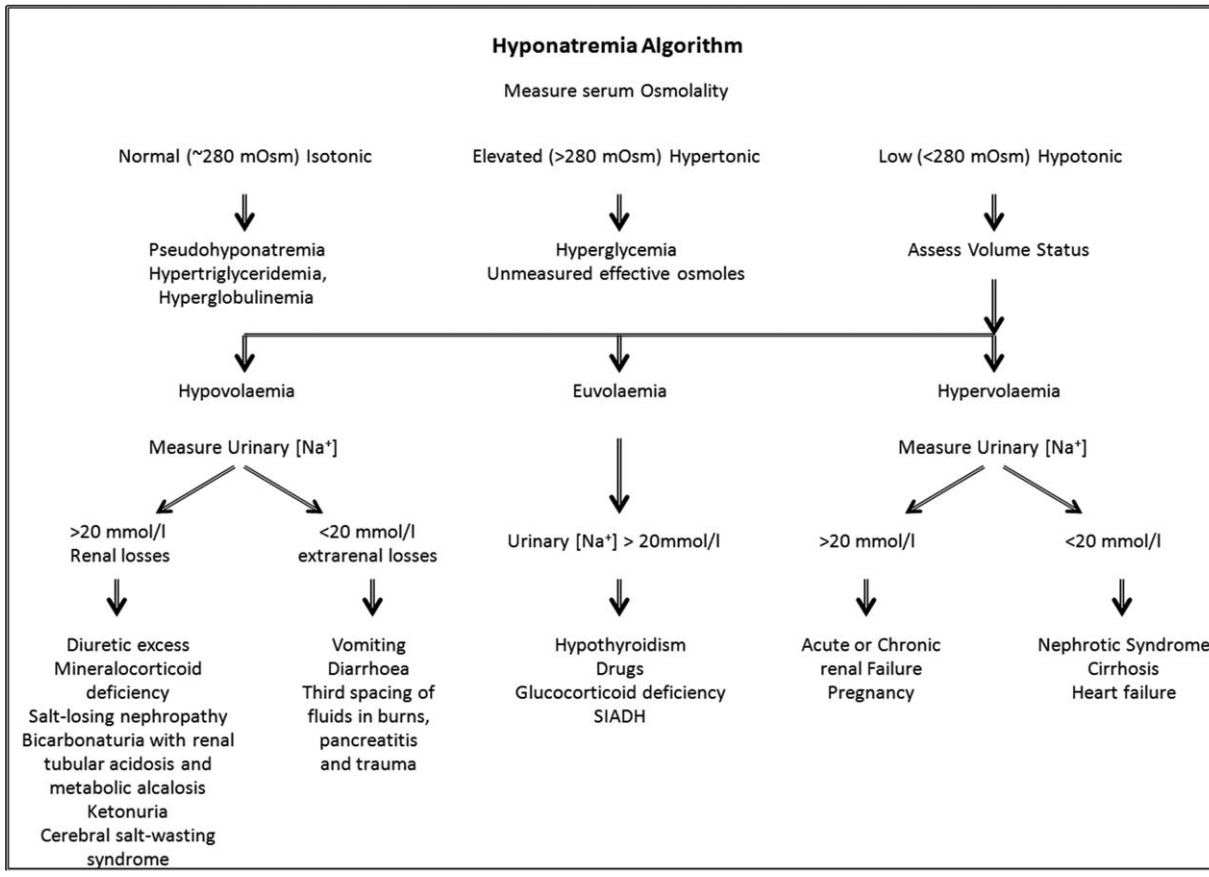

FIGURE 1. Diagnostic algorithm of hyponatremia. Modified scheme.[3]

neurological assessment by a specialist did not reveal any pathological signs.

Diagnostic Assessment

On the initial laboratory tests hematocrit, hemoglobin level and platelet count were normal while findings of serum electrolyte tests showed severe hyponatremia (sodium [Na] = 121 mEq/L) with normal potassium levels. The rest of the biochemical analysis including calcium, phosphorus, glucose, total protein, albumin, and globulin were also normal. Estimated glomerular filtration rate was 55.2 mL/min/1.73 m^2. Electrocardiogram showed sinus rhythm at a rate of 82 beats per minute.

As hyponatremia was considered responsible for the patient's symptoms, our attention focused on the investigation of the cause. Plasma osmolality was calculated at 258 mOsm and sodium in a urine sample was 24 mEq/L. Based on the algorithm (Figure 1), differential diagnosis included drug-related hyponatremia, hypothyroidism, AI, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[3]

Citalopram was immediately discontinued and fluid restriction limiting water intake to 1 L/day was initiated. For the next 5 days serum sodium levels were monitored with no signs of recovery (Figure 2). Therefore, laboratory tests to evaluate thyroid and adrenal function were ordered. Results from thyroid tests came back normal while basal morning cortisol was below 100 nmol/L in 2 serial measurements (87 and 92 nmol/L, respectively, normal values: 171–536 nmol/L). Primary AI was suspected and plasma adrenocorticotropin hormone (ACTH) level was measured. The results came back with an ACTH level close to the lower normal value (14.5 pg/mL, normal values for adults: 10–60 pg/mL), making primary AI unlikely as in that case increased ACTH levels would be expected. On day 6 after admission and while serum sodium level was 119 mEq/L a Synacthen test and a corticotropin-releasing hormone (CRH) test were also performed. They resulted in a normal adrenal response to the administration of tetracosactide (confirming the exclusion of primary AI as a possible diagnosis) as well as a normal pituitary response to the exogenous administration of CRH (Figure 3), indicating functionally intact pituitary and adrenals. An antidiuretic hormone (ADH) test was performed resulting in inappropriately normal ADH levels for the existing osmolality and electrolyte status (ADH: 2.1 pcg/mL, normal values: 1–5 pcg/mL). Hypothalamic or pituitary dysfunction was supported by an apparent hypogonadotropic hypogonadism. Our patient's basal testosterone level was measured at 0.09 nmol/L which is significantly lower compared with healthy elderly men.[4] On clinical examination patient's testicles appeared normal for his age (calculated volume of 16 mL). Triggered by the low testosterone levels, we performed a GnRH stimulation test, measuring follicle-stimulating hormone (FSH) and luteinizing hormone (LH) both basal and after GnRH stimulation. Basal FSH and LH were 3.3 and 1.7 mIU/mL, respectively, while these levels after GnRH stimulation were 13 and 27.7 mIU/mL confirming a

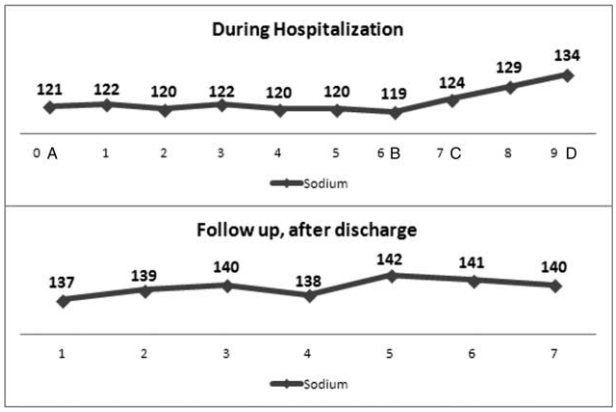

FIGURE 2. Monitoring of sodium levels. Levels of sodium (mEq/L) during hospitalization, from the admission to the discharge date, and levels of sodium during follow up period, from 1 to 7 months. (A) Sodium level on admission was 121mEq/l. (B) Sodium level on day 6 after admission was still 119mEq/l. On day 6 ACTH-stimulation test and CRH test took place, the initial diagnosis was made and the treatment with hydrocortisone started. (C) 24 hours after starting treatment with hydrocortisone sodium level was 124mEq/l. (D) Sodium level on day 9 after admission (Discharge date) was 134mEq/l.

functionally intact pituitary gonadotropin production (Table 1, Figure 3).

A hypothalamus-pituitary magnetic resonance imaging (MRI) scan was then performed that revealed an ectopic posterior pituitary lobe located at the area of the pituitary stalk disrupting the communication between hypothalamus and pituitary along with enlargement of the anterior pituitary gland with no signs of an adenoma (Figure 4).

Therapeutic Intervention

After the initial diagnosis the patient was treated with oral hydrocortisone (10 mg twice per day), which led to the return of serum sodium into the normal range within 3 days.

Outcome and Follow-Up

The serum sodium recovery resulted in direct improvement of the patient's clinical status. He was discharged and followed up in the clinic a week later, when his sodium level was 137 mEq/L. Repeated follow-ups over the next 7 months confirmed the normal electrolyte status under supplementation doses of oral hydrocortisone (Figure 2).

DISCUSSION

Hyponatremia is a usual cause of hospitalization. Mild cases are often asymptomatic and may remain undiagnosed unless randomly detected but severe cases may cause dramatic symptoms and high mortality depending on the underlying cause and the escalation of its severity.[5] In our case, initial clinical examination and laboratory findings indicated the presence of normovolemic low osmolality hyponatremia that might have been caused by hypothyroidism, drug use, glucocorticoid insufficiency, or SIADH (Figure 1).

Hyponatremia and Hypothyroidism

Primary hypothyroidism is sometimes associated with hyponatremia, most frequently in patients with severe hypothyroidism and myxedema.[6] Evaluation of thyroid function in any unexplained hyponatremic patient is included in the diagnostic algorithms. With normal fluid intake hyponatremia results from the inability to decrease urine osmolality below plasma due to failure to suppress maximally the arginine vasopressin hormone.[7] Nevertheless, the mechanism by which hypothyroidism induces hyponatremia is incompletely understood. Recently, new studies comparing euthyroid controls with newly diagnosed hypothyroid patients tend to question the established assumption of hypothyroidism as a traditional cause of hyponatremia.[8]

Drug-Induced Hyponatremia

Drug-induced hyponatremia can be caused by certain drugs such as diuretics, antiepileptics, and antidepressants.[9–19] These drugs have been implicated as established causes of either asymptomatic or symptomatic hyponatremia.[20] The possible mechanisms that lead to this electrolyte abnormality are affected sodium and water homeostasis (excess renal loss of effective solutes compared with water losses, diuretic induced volume depletion that stimulates ADH secretion, coexisting hypokalemia, stimulation of thirst, direct inhibition of urinary dilution, magnesium depletion, and excessive ADH secretion)[9,21–23] or affected water homeostasis alone (increase ADH secretion centrally, potentiate the effect of the endogenous ADH at the renal medulla or reset the osmostat).[13,16,24,25] However, patients may occasionally develop hyponatremia with drugs used in everyday clinical practice (e.g., newer antihypertensive agents, antibiotics, and proton pump inhibitors).[26–29] The diagnosis of drug-induced hyponatremia is based on the history of specific drug use and the finding that hyponatremia resolved after discontinuing the offending agent.[20] Awareness of the adverse events of certain pharmaceutical components on electrolyte levels may help clinicians achieve more effective clinical management.[20]

An uncommon complication of treatment with selective serotonin reuptake inhibitors is hyponatremia secondary to the SIADH.[30,31] Citalopram is a rare cause of this syndrome.[32–37] Female gender and advanced age are considered to be risk factors for selective serotonin reuptake inhibitor-induced hyponatremia.[30,38,39] Several cases have been reported demonstrating that the onset of citalopram-induced hyponatremia ranged from 6 to 20 days after initiation of treatment.[37] In these reports, the need for proper and careful monitor of serum sodium levels, particularly in elderly patients in the first few weeks of therapy, is emphasized.[37]

Hyponatremia and Adrenal Insufficiency

Hyponatremia caused by AI is explained by the dysfunction of hypothalamo-pituitary-adrenal axis. The electrolyte disturbance of hyponatremia in AI is due to diminished secretion of cortisol. Cortisol deficiency results in increased hypothalamic secretion of CRH. CRH plays the role of an additional ADH secretagogue. Normally, cortisol feeds back negatively on both CRH and ACTH. When the defect is either in the anterior pituitary (i.e., adenoma) or in the communication of the hypothalamus with the pituitary ACTH and cortisol production declines but CRH is still produced acting as an ADH secretagogue. CRH may additionally cause an increase in the ADH levels when plasma cortisol levels are low because cortisol appears to directly suppress ADH secretion.[40]

According to the literature, severe hyponatremia due to secondary AI is not as rare as it seems. In a retrospective study Diederich et al[41] screened the files of 185 patients with hyponatremia that had been seen in one endocrine unit over 20 years

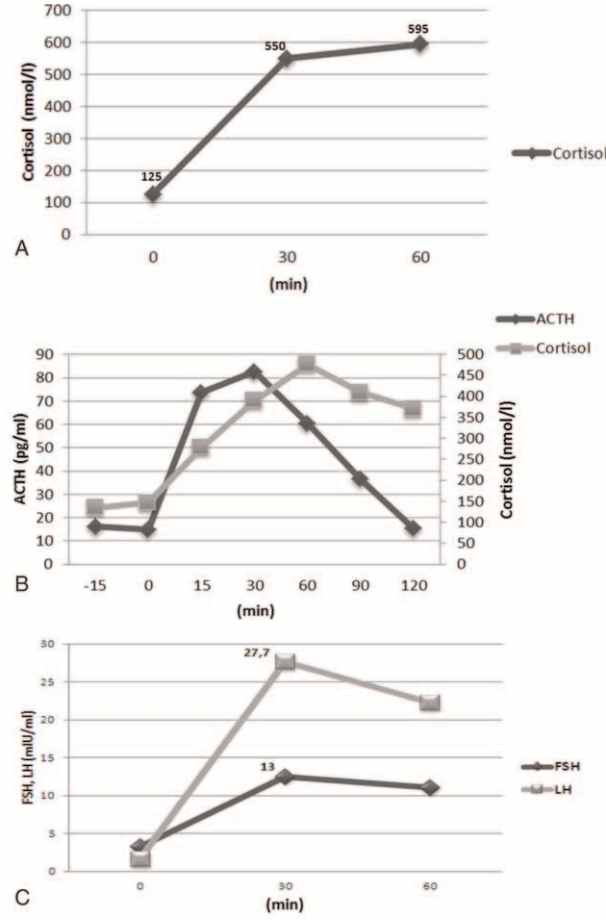

FIGURE 3. Hormone test results. (A) ACTH-stimulation test (0.25 mg i.v. bolus). Results represent normal adrenal response to tetracosactide excluding primary AI as a diagnosis. (B) Corticotropin-releasing hormone test (100 mg i.v. bolus). Results represent normal pituitary response to the exogenous administration of CRH, indicating functionally intact pituitary (C) GnRH-stimulation test (0.1 mg i.v. bolus). Results from exploring the origin of hypogonadotrophic hypogonadism also suggest a normal response from a functional pituitary. ACTH = adrenocorticotropic hormone, AI = adrenal Insufficiency, CRH = corticotropin-releasing hormone.

searching for patients with hyponatremia and hypopituitarism including secondary AI. From 139 cases with adequate available information, 28 patients with severe normovolemic hyponatremia had hypopituitarism and secondary AI, 25 of whom had not been recognized before the hyponatremic episode. Moreover, in 12 cases previous hospital admissions due to hyponatremia were documented. For this reason, high level of suspicion is suggested as the best way to recognize the underlying disorder. Luckily, this was the first hospitalization due to hyponatremia for our patient.

Hyponatremia in the Presented Case

In our patient, thyroid functional tests on admission came back normal. Drug-induced hyponatremia could only be attributed to citalopram as he was receiving no other drugs causing hyponatremia. However, despite the immediate discontinuation of citalopram and the initiation of fluid restriction, serum

TABLE 1. Laboratory Data From Hormone Tests During Hospitalization

Variable	Reference Range Adults	Patient's Hormone Results
TSH, μIU/mL	0.27–4.20	2.74
FT_3, pmol/L	3.1–6.8	**2.4**
FT_4, pmol/L	12.0–22.0	15.86
Cortisol, nmol/L	171–536	**87**
ACTH, pg/mL	10–60	14.5
FSH, mIU/mL	1.5–12.4	3.3
LH, mIU/mL)	1.7–8.6	1.7
Testosterone, nmol/L	8.64–29.0	**0.09**

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, FT_3 = free triiodothyronine, FT_4 = free thyroxine, LH = luluteinizing hormone, TSH = thyroid-stimulating hormone.

sodium levels did not show signs of recovery over the next 6 days making citalopram-induced hyponatremia unlikely in our patient. For certain drugs implicated as established causes of hyponatremia, such as diuretics, full sodium recovery may be delayed for 1 to 2 weeks after drug withdrawal.[20] In the case of citalopram-induced hyponatremia, the exact number of days needed to achieve normonatremia remains unknown.[37] However, in several published cases of patients with hyponatremia due to citalopram, signs of sodium recovery were obvious within 1 to 5 days after drug withdrawal.[32,35,37]

After eliminating thyroid dysfunction and drug-induced hyponatremia as possible diagnoses we focused on adrenal gland dysfunction. Based on the results of hormonal tests our patient suffered from secondary AI. Moreover, evidence of inappropriate ADH secretion was present in our patient at the same time, as ADH levels were inappropriately normal for the existing osmolality and electrolyte status. ACTH-stimulation test, CRH test, and GnRH-stimulation test indicated either hypothalamic dysfunction or disruption of communication between hypothalamus and pituitary as the cause of AI, as pituitary response as well as adrenal response to the exogenous administration of hormone secretagogues was normal.

The hypothalamus-pituitary MRI scan performed revealed an ectopic posterior pituitary gland in combination with enlargement of the anterior pituitary gland with no presence of a pituitary adenoma. This anatomical variation could explain the hypothalamus-pituitary miscommunication by preventing signal transmission through the pituitary stalk with a resulting functional disruption of the hypothalamo-pituitary-adrenal axis. Moreover, previously published case reports indicate pituitary adenomas may mechanically compress the pituitary stalk and the hypothalamus leading to inappropriate arginine vasopressin secretion by the posterior pituitary.[42–45] In the present case, the anatomical variation of the posterior pituitary gland in combination with the enlargement of the anterior pituitary gland could have led to increased secretion of ADH, thus contributing to the induced hyponatremia. A recently appearing pituitary enlargement could have contributed to the anatomical variation, but it could neither be confirmed nor be excluded as there was no prior MRI scan to compare with.

In conclusion, secondary AI is related with hyponatremia through increased ADH secretion. In the case of our patient, ectopic posterior pituitary lobe may have been both the cause of

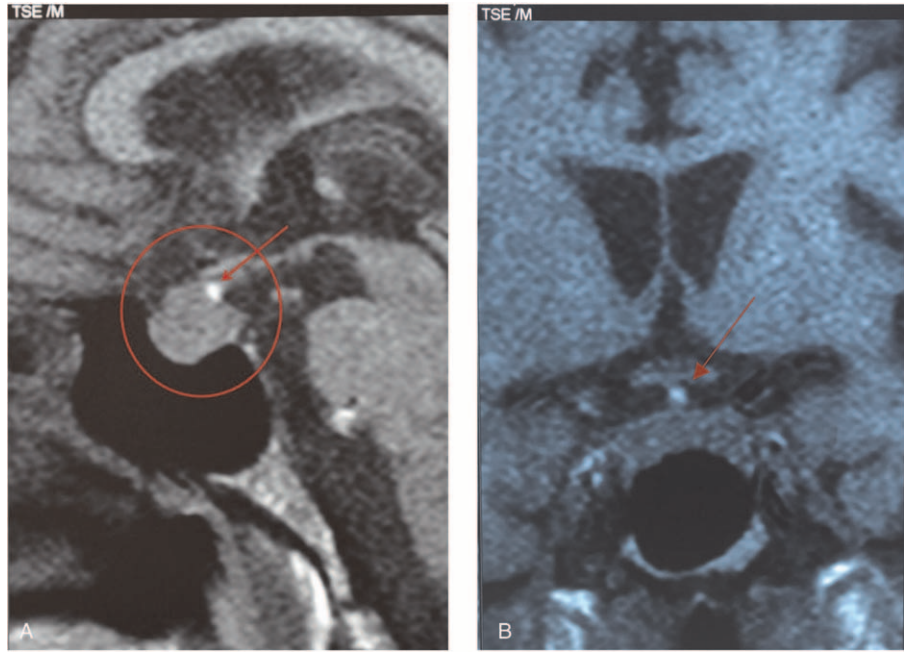

FIGURE 4. Magnetic resonance imaging (MRI) of the hypothalamus and pituitary gland. T1-weighted sagittal (A) and coronal (B) MRI postcontrast images, showing enlarged, isointense anterior pituitary gland (circle) and hyperintense posterior pituitary gland with the bright spot in an abnormal location (arrow).

the disruption in the hypothalamus-pituitary communication resulting in inadequate ACTH production and AI and the origin of inappropriate ADH production clinically manifesting with hyponatremia. High clinical suspicion and diligent follow of the proper diagnostic algorithms contributed to earlier management, diagnosis, and treatment of the patient.

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