CASE REPORT

Pituitary apoplexy presenting with anorexia and hyponatraemia

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Accepted 26 February 2015

SUMMARY

Pituitary apoplexy, a syndrome caused by haemorrhage into the pituitary gland, typically manifests as sudden severe headache, visual symptoms and hypopituitarism, including adrenal insufficiency. We report a case of a 65-year-old man with adrenal insufficiency due to pituitary apoplexy presenting with anorexia following temporal headache and diagnosed through evaluation for hyponatraemia. MRI focusing on the pituitary gland helped to confirm the diagnosis. Our experience serves as a useful reminder of this atypical presentation of pituitary apoplexy, also known as 'subclinical pituitary apoplexy,' and underscores the importance of careful evaluation for hyponatraemia using serial urine osmolality, which is useful to distinguish hypovolaemic hyponatraemia from euvolaemic hyponatraemia. Clinicians should consider pituitary apoplexy as a differential diagnosis in cases of anorexia, loss of energy or hyponatraemia, following headache even when the patient is lacking classical symptoms such as severe headache or visual symptoms.

BACKGROUND

Hyponatraemia is a ubiquitous problem that is caused by many aetiologies. Adrenal insufficiency is an important differential diagnosis of hyponatraemia because of its potential fatality. Adrenal insufficiency is the clinical manifestation of the deficient production or action of the glucocorticoids, which can result from either primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis. One cause of secondary adrenal insufficiency is pituitary apoplexy. Pituitary apoplexy, a syndrome caused by sudden haemorrhage into the pituitary gland,¹ typically manifests as a combination of sudden severe headache, visual symptoms and hypopituitarism, including acute adrenal insufficiency.^{1 2} Although most cases require emergent evaluation for severe headache or visual symptoms, cases with atypical manifestation, also known as 'subclinical pituitary apoplexy', were frequently overlooked in the past but are now increasingly being recognised with advances in neuroimaging technologies.² We report a case of pituitary apoplexy that was diagnosed through evaluation for anorexia, loss of energy and hyponatraemia. Our report underscores the importance of recognising 'subclinical pituitary apoplexy' as a differential diagnosis of hyponatraemia and the importance of careful evaluation of hyponatraemia using serial urine osmolality monitoring.³

CASE PRESENTATION

A 65-year-old man was admitted to our facility for an evaluation of anorexia and loss of energy for 2 weeks following a headache. Three weeks prior to admission, he reported an acute right temporal headache and vomited once. He visited another hospital and underwent MRI (figure 1) and a CT of the brain, which was unremarkable. The headache gradually improved for a week. However, he became less energetic and spent the majority of his time lying in bed. He had eaten much less than usual over the previous 3 weeks, taking only a few bites at each meal. He had also stopped drinking beer during these 3 weeks although he was a habitual drinker (he consumed 1.4 L of beer a night). Two days prior to admission, he developed a fever of 38°C without any focal symptoms, and he visited our department. Although his fever had subsided by the time of the visit, he was admitted for evaluation of anorexia and low energy. At that time, he did not report of headache, nausea or vomiting. He denied visual symptoms, depressive mood and insomnia. A thorough review revealed no additional symptoms.

The patient had been treated at another hospital for an earlier brain infarction and cerebellar haemorrhage associated with atherosclerotic changes, which had occurred 2 years previously and from which he had recovered without apparent neurological sequelae. He had also been treated for hypertension, chronic kidney disease, hyperuricaemia, emphysema and constipation. He took a low-dose aspirin with prophylactic use of a proton pump inhibitor, an angiotensin receptor blocker, diuretics, a calcium blocker, a uric acid lowering agent and an anticholinergic inhaler. His family history was unremarkable. He managed a handyman company. He had a smoking history of 86 packs per year until 2 years ago.

INVESTIGATIONS

On physical examination, the patient was fully oriented but appeared apathetic. His body temperature was 36.9°C, blood pressure was 106/76 mm Hg, heart rate was 72 bpm and regular, and respiratory rate was 16 breaths/min. His conjunctivae looked slightly pale but not icteric. His neck was supple without meningeal signs. Thoracic and abdominal examinations were intact. There was no oedema, lymphadenopathy or pigmentation. A neurological examination was also normal.

Laboratory data on admission (table 1) were remarkable for hyponatraemia (126 mEq/L) and mild hyperkalaemia (4.9 mEq/L). Initially, we diagnosed

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To cite: Sasaki Y, Nakata K, Suzuki K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209120

Figure 1 MRI of the brain performed at the previous hospital. Retrospectively, the low-intensity area seen in T2-weighted imaging (A, green arrow) and the high-intensity area seen in T1-weighted imaging (B, green arrow) at the pituitary fossa suggest haemorrhage into the pituitary gland. These findings are not sufficiently definitive for diagnosis, however. Although T2-weighted imaging (C, red arrow) is a highly sensitive modality for the detection of haemorrhage, here, an artefact caused by the air in the sphenoid sinus prevents us from using it to make the correct diagnosis.

the patient with hypovolaemic hyponatraemia due to anorexia and hydrated him with normal saline. However, hyponatraemia (133 mEq/L) persisted with hypertonic urine (464 mOsm/kg) despite volume repletion over 48 h. Given the combination of saline-resistant hyponatraemia with hypertonic urine and acute loss of energy, we suspected euvolaemic hyponatraemia due to adrenal insufficiency or hypothyroidism. We measured the patient's thyroid, adrenal and pituitary hormones, and found an undetectable level of serum adrenocorticotrophic hormone (ACTH) and low serum cortisol with mildly impaired response to

a rapid ACTH stress test (table 2). Serum thyroid-stimulating hormone (TSH) was intact. MRI focusing on the pituitary gland with gadolinium enhancement revealed haemorrhage into the pituitary gland resulting in swelling of the gland without evidence of pituitary tumour (figure 2). On the basis of these results, we diagnosed him with secondary adrenal insufficiency due to hypopituitarism caused by pituitary apoplexy.

TREATMENT

We initiated oral hydrocortisone 10 mg two times a day and discontinued aspirin. After this change, the patient became energetic and his appetite fully recovered. Five days of hydrocortisone replacement raised his serum sodium to 144 mEq/L and lowered his serum potassium to 4 mEq/L. Ophthalmological evaluation detected no visual impairment. There was no sign of intrinsic bleeding tendency. Although our measurements of other pituitary hormones suggested impaired secretion of growth hormone (GH) and luteinising hormone, that is, hypopituitarism (table 2), he was discharged after 11 days of hospitalisation without further stress tests for confirmation of hypopituitarism because his signs and symptoms had fully improved.

OUTCOME AND FOLLOW-UP

After discharge, the patient was under the follow-up of an endocrinologist and a neurosurgeon. Pituitary MRI performed 1 month after discharge revealed improved swelling of the pituitary gland. Serum cortisol was maintained around 8–10 µg/dL with continuous administration of hydrocortisone 10 mg two times a day. Ten weeks after admission, serum ACTH spontaneously recovered from an undetectable level to 7.7 pg/mL (table 2). Given this improvement in hormone levels, indicating restored secretion, along with reduced pituitary gland compression as seen in pituitary MRI, we plan to taper off and discontinue replacement therapy in the near future.

DISCUSSION

This case offers important lessons about the evaluation of hyponatraemia through measurement of urine osmolality, the various possible clinical presentations of adrenal insufficiency and the diagnosis of pituitary apoplexy.

Hyponatraemia, the most common and most complicated electrolyte disturbance, reportedly affects 22% of hospitalised

Table 1 Laboratory data on admission

Blood counts	
WCC (/mm ³)	3900
Hb (g/dL)	17
Ht (%)	45.8
PLT (10 ³ /mm ³)	133
Chemistry	
Sodium (mEq/L)	126
Potassium (mEq/L)	4.9
Chloride (mEq/L)	96
Calcium (mg/dL)	9.1
Phosphorus (mg/dL)	3.8
BUN (mg/dL)	22
Creatinine (mg/dL)	1.15
eGFR (mL/min/1.73 m ²)	50.2
Glucose (mg/dL)	111
AST (IU/L)	30
ALT (IU/L)	24
LDH (U/L)	183
CK (U/L)	181
Albumin (g/dL)	3.7
CRP (mg/dL)	0.4
Coagulation function	
PT-INR	1.1
aPTT (s)	38.3

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; Ht, haematocrit; LDH, lactate dehydrogenase; PLT, platelet; PT-INR, prothrombin time-international normalised ratio; WCC, white cell count.

Table 2 Results of hormone study

	Before ACTH administration	30 Min after ACTH administration	60 Min after ACTH administration	4 Weeks after hospitalisation	10 Weeks after hospitalisation
Cortisol (µg/dL)	1.1	9.1	12.8	10.1	8.2
Aldosterone (pg/mL)	133	169	147		
PRA (ng/mL/h)	1.7				
ACTH (pg/mL)	<2.0			3.6	7.7
TSH (µU/mL)	0.85			1.8	
FSH (mIU/mL)	3.2			6.6	
LH (mIU/mL)	0.4			4.9	
GH (ng/mL)	0.3			0.19	
IGF-1 (ng/mL)	70			105	
PRL (ng/mL)	4.4			4.7	

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinising hormone; PRA, plasma renin activity; PRL, prolactin; TSH, thyroid-stimulating hormone.

patients.¹ Aetiologies of hyponatraemia are generally subdivided by a patient's volume status: hypovolaemia, euvolaemia or hypervolaemia. Hypovolaemic hyponatraemia is a common aetiology and responds well to volume repletion with normal saline.³ Euvolaemic hyponatraemia is mainly caused by SIADH, hypothyroidism, mineralocorticoid deficiency (primary adrenal insufficiency) or polydipsia. It is sometimes difficult to distinguish mild hypovolaemia from euvolaemia. In this situation, serial monitoring of urine osmolality after volume repletion is useful for discrimination, as persistent hypertonic urine after hydration is suggestive of SIADH.³ In this case, persistent hyponatraemia and hypertonic urine after hydration was the clue that indicated 'SIADH-pattern' hyponatraemia.

Lack of energy, anorexia and weight loss is seen in all patients with adrenal insufficiency. Nausea and vomiting is reportedly seen in 92% of patients with adrenal insufficiency.⁴ Hyponatraemia is the most common electrolyte disturbance and is seen in 70–80% of such patients, followed by hyperkalaemia, which is seen in 30–40% of patients with primary or secondary adrenal insufficiency.⁴ The aetiologies of hyponatraemia differ between primary and secondary adrenal insufficiency. In primary adrenal insufficiency, hyponatraemia is caused by hypoaldosteronism (ie, decreased secretion of mineralocorticoid from the adrenal cortex). Hypoaldosteronism results in hyponatraemia accompanied by hypotension, especially orthostatic hypotension, due to impaired renal reabsorption of sodium and water. Mineralocorticoid secretion is normally preserved in secondary adrenal insufficiency. However, secondary adrenal insufficiency can cause hyponatraemia because of SIADH due to the decreased inhibition of ADH by cortisol as well as the decreased mineralocorticoid effect of cortisol.^{2,4}

Pituitary apoplexy is classically defined as a syndrome characterised by sudden onset of headache, vomiting, visual impairment and decreased consciousness, caused by haemorrhage and/or infarction of the pituitary gland. Its presentation can vary

from this pattern, however, and any symptoms caused by sudden haemorrhage into the pituitary gland are regarded as pituitary apoplexy regardless of whether the typical symptoms such as sudden-onset severe headache or visual impairment are involved.¹ Owing to advances in neuroimaging, asymptomatic pituitary haemorrhage is now being reported in up to 25% of cases and is called 'subclinical pituitary apoplexy'.² There are some reports of cases with atypical presentation that have been diagnosed through the evaluation of hyponatraemia.^{5–9} Precipitating factors have been identified in up to 40% of cases of pituitary apoplexy.² Previous reports of atypical cases have identified several precipitating factors such as orthopaedic operation,^{7,9} cardiac operation⁸ and pregnancy.⁶ Long-standing hypertension, the most common (26%) predisposing factor,² seemed to be a precipitating factor in our case.

Headache is the most common symptom of pituitary apoplexy, and the headaches associated with pituitary apoplexy are classically sudden, severe and retro-orbital, though they can be bifrontal or diffuse and may be accompanied by nausea and vomiting. The quality of our patient's headache was atypical; he suffered from persistent right temporal headache. ACTH deficiency has been reported in up to 70% of cases of pituitary apoplexy,² while hyponatraemia has been reported in up to 40% of patients.² As for the transient fever that our patient experienced a few days prior to admission, we could not find any sign of recent infectious or inflammatory disease. According to a recent review, adrenal insufficiency itself can reportedly cause fever in some cases due to the lack of cortisol and its effects.⁴ Hence, the transient fever that our patient experienced may have been related to adrenal insufficiency.

MRI reportedly confirms the diagnosis of pituitary apoplexy in over 90% of patients. Although CT scan is the most commonly used modality in acute clinical settings, it is reported to be diagnostic in only 21–28% of pituitary apoplexy cases.² Our

Figure 2 MRI of the pituitary gland. The high-intensity area seen in T1-weighted imaging (A) and the low-intensity area seen in T2-weighted imaging (B) at the pituitary gland suggest haemorrhage into the pituitary gland. T1-weighted imaging with gadolinium enhancement (C) showing a well-enhanced pituitary gland (green arrow) compressed by a poorly enhanced haematoma (red arrow).

team, including three radiologists, discussed whether the diagnosis could have been made based solely on the CT scan and brain MRI, without gadolinium enhancement, that were performed at the patient's visit to the first hospital, and concluded that this would have been difficult (figure 1). Thus, neuroimaging focused on the pituitary gland, especially MRI with gadolinium enhancement, is required for diagnosis.

In retrospect, we should have performed a comprehensive evaluation including stress tests for pituitary hormones, especially GH, because concurrent GH secretion impairment could have explained the patient's symptoms, such as loss of energy and apathetic appearance. However, we believe that adrenal insufficiency was the primary condition. The combination of hypoactive symptoms and concurrent hyponatraemia responding rapidly to cortisol replacement supports our diagnosis.

Learning points

- ▶ Pituitary apoplexy can manifest as hyponatraemia due to secondary adrenal insufficiency in the absence of classic symptoms such as headache or visual symptoms.
- ▶ Clinicians should consider subclinical pituitary apoplexy as a differential diagnosis for hyponatraemia and anorexia.
- ▶ Once suspected, MRI focusing on the pituitary gland should be obtained for diagnosis because of the low sensitivity of non-focused neuroimaging.
- ▶ Serial urine osmolality monitoring after fluid administration may be useful to distinguish non-apparent hypovolaemic hyponatraemia from euvolaemic hyponatraemia.

Acknowledgements The authors thank Dr Takahiro Sato (Department of General Medicine and Emergency Care), Dr Nobuyuki Shiraga (Department of Radiology), Dr Masahiro Kobayashi (Department of Radiology) and Dr Yoshihisa Urita (Department of General Medicine and Emergency Care) for their contributions to this article.

Contributors YS managed the patient, obtained consent from the patient and wrote the article as the first author. KN managed the patient, and contributed to the article by researching and reviewing previous studies. KS contributed by reviewing all images related to the case, confirming the diagnosing of pituitary apoplexy and advising the other authors as a radiologist. YA managed the patient and gave important advice to the other authors as an endocrinologist.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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