A case report of central adrenal insufficiency: hiding in persistent, refractory nausea and vomiting

Jia Yang
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Xiao Wang
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Jin Tang
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Ziling Hu
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Tingting Xu
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Hongwei Wang
Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Lei Wang
Shanghai Putuo District People's Hospital

Yanmei Cheng (✉ yyq22@163.com)
Shanghai University of Traditional Chinese Medicine

Case Report

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Abstract

Background

Central adrenal insufficiency (CAI) is defined as the inability of the adrenal glands to release sufficient corticosteroids due to a series of diseases or injuries of the hypothalamus or pituitary. Signs and symptoms of CAI are insidious, ambiguous, and debilitating. Preceding studies suggest that elderly patients with CAI may present with hyponatremia as a characteristic manifestation, but little is mentioned about gastrointestinal (GI) symptoms. Herein we report a rare case of an elderly male patient with a radio-chemotherapy history for nasopharyngeal carcinoma, in whom prolonged exogenous glucocorticoid replacement and infectious stress from two bouts of bacterial pneumonia combined to cause severe CAI with prodromal symptoms of persistent, intractable nausea and vomiting.

Case presentation

A 71-year-old man presented to the gastroenterology department with persistent nausea and vomiting. Gastroscopy, brain magnetic resonance imaging (MRI), and contrast-enhanced abdominal computed tomography (CT) were performed to exclude organic lesions. The diagnosis of CAI was confirmed by checking the levels of basal cortisol and adrenocorticotropic hormone. After replacement therapy with hydrocortisone, the patient's GI symptoms resolved rapidly, hyponatremia was corrected. At subsequent follow-ups, he was doing well with no hospitalizations.

Conclusion

CAI in elderly patients can start with persistent, refractory nausea and vomiting, and is featured by uncorrectable and insidious hyponatremia. Timely hydrocortisone replacement therapy averts life-threatening adrenal crises.

Background

The inadequate glucocorticoid secretion springs from decreased adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) caused by hypothalamic-pituitary disease or injury that characterizes CAI. The proportion of elders treated with glucocorticoids increases by 1.5 times compared to younger and middle-aged adults, this potentially suppresses the hypothalamic-pituitary-adrenal (HPA) axis and renders the onset of CAI more likely[1]. Elderly patients with CAI may have insidious hyponatremia that is hard to correct[2], and when accompanied by other GI symptoms with electrolyte loss, it becomes more arduous to confirm the cause-effect relationship and reach the diagnosis.

Case Presentation

A 71-year-old man presented to the gastroenterology department with a complaint of persistent nausea and vomiting lasting for over eight months. He vomited 4–5 episodes daily, which worsened
postprandially, mostly undigested or semi-digested food. Vomiting was non-bloody, non-bilious, and non-projectile, accompanied by heartburn, acid regurgitation, loss of appetite, generalized fatigue, without dizziness or headache, and no weight loss. He had got bacterial pneumonia twice in the past year. His background history included life-long asthma and locoregional radiotherapy with chemotherapy for nasopharyngeal carcinoma.

The outpatient medical report showed low serum sodium (120mmol/L) six months ago, and hospitalized laboratory results also indicated hyponatremia (124mmol/L), which seemed unsuspicious after vomiting. Other general biochemical tests like tumor markers, liver and kidney function were within normal range. MRI of his brain was performed to evaluate the presence of brain lesions, which revealed intracranial atherosclerosis along with multiple small ischemic lesions in bilateral basal ganglia and corona radiata (Fig. 1). Contrast-enhanced abdominal CT found bilateral renal cysts, and adrenal glands were normal in size (Fig. 2). Gastroscopy was unremarkable. After the exclusion of organic pathologic changes, he was diagnosed with non-erosive reflux disease (NERD). However, antiemetics, proton pump inhibitors, and prokinetic agents combined with 10% sodium chloride only provided limited symptomatic relief, while nausea and vomiting were still recurrent. Hyponatremia remained intractable (Fig. 3), questioning the initial clinical diagnosis. Reviewing his medical history, the patient reported taking inhaled budesonide 640µg daily for asthma control over the past 20 years. During the chemotherapy for nasopharyngeal carcinoma, he accepted several times of intravenous drips of dexamethasone. It was eight months earlier that he got his first bacterial pneumonia. Eventually, Basal cortisol level measurements showed that early morning (8:00) serum cortisol was 21.08nmol/L (06:00–10:00 166-507nmol/L), adrenocorticotropic hormone test measured 3.68pg/mL (7.2-63.4pg/mL), proving strong evidence that hyponatremia was secondary to adrenal insufficiency. Getting confirmed CAI, he was given oral hydrocortisone immediately, with 10 mg at 8:00 and 5 mg at 14:00. Soon, his digestive symptoms decreased, and hyponatremia was corrected. The patient was discharged home after three days, continuing hydrocortisone replacement treatment. He is now regularly followed up and doing well with no subsequent hospitalizations.

**Discussion and conclusion**

This is the first case of CAI with intractable nausea and vomiting as the primary presentation in an elderly male. CAI has a prevalence of 0.15 to 0.28% in the general public[3], and its etiology involves tumors, surgery, infections, trauma, and glucocorticoid replacement therapy. Exogenous glucocorticoids closely relate to the suppression of ACTH and CRH, resulting in adrenal cortex atrophy, which has been proven to be one of the most common reasons for cortisol deficiency[4]. It is estimated that 1% of populations are treated with regimens of glucocorticoids, 2.5% of those over 70 years old[1], the prevalence of glucocorticoid-induced adrenal insufficiency remains unknown and may vary with the formulations. Under physiological and unstressed conditions, daily production rates of cortisol are calculated at 22.56 +/- 3.60 mg/d in males and 9.12 +/- 3.36 mg/d in females[5]. There is no doubt that long-term or frequent short-course, high-dose glucocorticoid treatment often brings about a higher risk for CAI. However, even being treated with a low physiological dose can also give rise to hypoadrenalism, especially during prolonged treatment for chronic diseases such as asthma, chronic obstructive pulmonary disease, and...
rheumatoid arthritis[6]. Therapy entails an equivalent dose of ≥ 5mg prednisolone for not less than four weeks will predispose to drug-induced adrenal insufficiency[7]. Glucocorticoids exert negative feedback on the corticotropin-releasing factor-producing neurons in the hypothalamus paraventricular nucleus through systemic absorption by direct or indirect entrance into the pulmonary and systemic circulation, inducing generalized side effects[8]. Not only systemic glucocorticoids but locally applied formulations, including intranasal, intraarticular, inhaled, percutaneous and ocular glucocorticoids, have been reported to have a certain degree of systemic absorption, which can also potentially generate adrenal suppression[9–11]. HPA axis dysfunction presents in nearly half of patients taking inhaled glucocorticoid therapy[12, 13]. The adrenal glands might generate sufficient cortisol to meet the body’s daily requirements despite being in a suppressed period[14]. Yet, stress exposure due to severe infection, trauma, negative life events, burns, or surgery could at least triple or even sextuple the need for cortisol, rendering cortisol production hardly matches the level of requirement during stressful episodes[15].

Among all types of hypopituitarism, 64.3 to 80.6% of elderly patients manifested hyponatremia, remarkably greater than young and middle-aged individuals[16, 17]. Besides, the seriousness of hyponatremia negatively correlated with the age of diagnosis confirmation[2]. The pathophysiology of hyponatremia in CAI is as yet under debate. In physiological situations, the permissive role of cortisol regulates overall physiological and metabolic functions, allowing the kidney to function optimally[18]. Proximal tubule sodium reabsorption and renal free water clearance could be enhanced by serum cortisol. When there is a lack of glucocorticoids, renal water handling tends to be dampened. In the meantime, inappropriate continuing arginine vasopressin (AVP) secretion also plays an essential role in hyponatremic genesis, primarily occasioned by lack of hypotonic inhibition from glucocorticoids and secondarily intensified by non-osmotic stressors, including nausea, pain, hypotension, and hypoglycemia[19, 20]. Additionally, aging may bring gerontological alteration, enclosing decreased renal water excretion, over-releasing AVP from the neurohypophysis, and over-responding to AVP release-related stressors[17, 21]. This means cortisol reduction tonifies AVP secretion, impairing renal water excretion and resulting in dilutional hyponatremia. Though CAI presents debilitating yet insidious and unspecific clinical manifestations, refractory hyponatremia may be considered a revealing feature in diagnosing CAI, especially in elderly patients[22].

Regarding the mechanism of gastrointestinal symptoms in hyponatremia, one classical theory suggests plasma hypotonicity engendering a water movement from intravascular space into the relatively hypertonic brain cells, elevating intracranial pressure by cerebral edema. Apart from nausea and vomiting, headache, reduced consciousness or confusion, and coma are also typical accompanying signs. Supported by current evidence, another major theory emerged. GI tract is an electromechanical organ. Its unique electrophysiological properties are reflected in diversified cell types represented by interstitial cells of Cajal (ICC), smooth muscle cells (SMC), and enteric neurons, which regulate and optimize GI motility. ICC are crucial for pacing and propagating cyclic electrical activity, and SMC are hubs in electromechanical coupling[23]. Voltage-gated ion channels provide an indispensable molecular basis in excitable cells, underlying coordinated electrical activity, and they determine the membrane potential and mediate activate-needed ion flux[23]. Of all members of voltage-gated ion channels involved in multiple
GI functions, voltage-gated sodium channels are widely expressed in the ICC and SMC of human GI tract to facilitate the setting of membrane potential and modulate the upstroke velocity and frequency of slow waves, and are involved in gastric motor functions, sensory and pain transmission[24–26]. In the activation phase, serum Na\(^{+}\) ions trans-membrane through voltage-gated sodium channels rapidly, taking with abundant positive voltage to depolarize ICC for seconds. This electrical event repeats periodically and tirelessly, named slow waves. Gap junctions form the electrical coupling between ICC and SMC, permitting slow waves subsequently transmit to SMC, which elicits identical cyclic depolarization. SMC depolarization triggers the opening of voltage-gated L-type calcium channels. The influx and internal release of Ca\(^{2+}\) ions together form a calcium-mediated action potential, with GI smooth muscle constricting, the entire process of excitation-contraction coupling completed. ICC, acting as the pacemaker cells, generate and propagate slow waves cyclically to maintain a normal electrical rhythm, providing essential GI motility for peristalsis in different segments of GI tract, thus maintaining regular digestive functionality. Hence, Hyponatremic conditions are very likely to bring GI sensory and motor dysfunctions, and the symptoms span a broad range, containing indigestion, nausea, vomiting, abdominal bloating or pain. In the meantime, Chronic nausea and vomiting cause extrarenal sodium loss, which further exacerbates hyponatremia. To wrap up, GI symptoms and CAI-induced hyponatremia are in a vicious circle.

The clinical presentation of CAI is insidious and nonspecific, which tends to overlap with symptoms of other diseases. Its diagnosis relies on heightened clinical suspicion, sometimes exclusionary. Missed, misdiagnosed or delayed diagnosis is not rare. If left untreated, an adrenal crisis would be the ultimate end of CAI, an acute, life-threatening severe complication with a prevalence of 8% and a mortality of 0.5%, which are still increasing[3]. Physicians should be aware of the risk and provide timely as well as accurate clinical management. In addition, precautionary procedures should be taken. Patients with CAI and their families must be educated about the sick day rules of stress dose administration, equipped with steroid emergency cards and rescuing injectable hydrocortisone, and recommended regular screening for cortisol levels if necessary.

Nausea and vomiting are exceptionally common GI complaints, whereas the causes rarely mention CAI. Even though CAI is an endocrine disorder, it could appear with GI symptoms as the initial manifestation. Patients may first be referred to the gastroenterology department, and it is typically the gastroenterologist who first needs to suspect CAI. When accompanied by acid regurgitation, heartburn, and negative endoscopic findings, it seems rather reasonable to attribute all clinical manifestations to NERD, shifting concerns from hyponatremia and its true etiology. Moreover, We have observed that chronic vomiting due to CAI-mediated hyponatremia is relatively mild, usually non-projectile, seldom preceded by abdominal cramps, hardly followed up with post-vomiting lacrimation and hyperventilation, which makes it more like an intermediate between reflux and violent vomiting, therefore prone to masquerade as gastroesophageal reflux disease, gastroparesis or rumination disorder. CAI, on the other hand, has an entirely distinguished treatment approach from the above-mentioned digestive diseases. Erroneous diagnosis and inadequate treatment could aggravate CAI into a potentially fatal adrenal crisis. This case highlights that, in
diagnosing a disease presenting intractable nausea and vomiting with a history of recurrent, long-term glucocorticoid application, if failed to find organic lesions, a high degree of clinical vigilance is still required for screening the levels of cortisol and electrolyte. Thorough evaluations of electrolyte imbalance can be life-saving.

**Abbreviations**

CAI: Central adrenal insufficiency

GI: Gastrointestinal

MRI: Magnetic resonance imaging

CT: Computed tomography

ACTH: Adrenocorticotropic hormone

CRH: Corticotropin-releasing hormone

HPA: Hypothalamic-pituitary-adrenal

NERD: Non-erosive reflux disease

AVP: Arginine vasopressin

ICC: Interstitial cells of Cajal

SMC: Smooth muscle cells

**Declarations**

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent to publish was obtained from the patient using our institutional consent form.

Competing interests

All the authors declare that they have no competing interests.

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Availability of data and materials

The clinical data presented in this case report are from medical records in our institution, further inquiry can be directed to the corresponding author.

Authors’ contributions

Jia Yang and Xiao Wang are shared first authors.

JY and XW drafted the manuscript, collected and analyzed the clinical data. JT provided geriatric expertise and confirmed the diagnosis. ZH obtained the patient’s medical history. TX, HW, LW, and YC revised the manuscript. Before submitting, all authors read and approved the final version of the manuscript.

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References


Figures

Figure 1

Brain MRI (T2-weighted) demonstrates a normal pituitary (A, transverse plane; B, sagittal plane).

Figure 2

Contrast-enhanced abdominal CT showing both sides of adrenal glands are normal in size.
Figure 3

Graph depicts serum electrolyte concentrations over time. Serum sodium level was transiently corrected with hypertonic saline treatment but plummeted after discontinuation of hypertonic saline. The patient's hyponatremia was completely corrected after hydrocortisone supplementation.