CASE REPORT

A case of nausea and vomiting to remember

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SUMMARY

Nausea and vomiting are the most common overlooked debilitating symptoms that significantly impact the quality of life and acute care we provide as physicians. The duo has an extensive aetiology ranging from common known causes to uncommon idiopathic reasons. Our case illustrates the fact that identifying the aetiology of nausea and vomiting can be lifesaving, given the characteristics of the patient. This case is about a 31-year-old Caucasian woman, with history significant for insulin-dependent diabetes mellitus on insulin pump since the age 2, Hypothyroidism, diabetic peripheral neuropathy with no significant known family history, who was admitted with intractable nausea and vomiting. She was discharged twice from hospital after temporary symptom control with presumed diagnosis of diabetic gastroparesis. Her third hospital visit enabled us to identify the cause of her symptoms being Addison's crisis rather than gastroparesis.

BACKGROUND

Adrenal insufficiency is a life-threatening disorder with variable clinical presentation depending on whether the onset is acute or chronic. In the western world autoimmune adrenal insufficiency is responsible for 70–90% of cases with female preponderance of 70–80%.[1–3] Morbidity and mortality associated with Addison's disease is due to failure or delay in making the diagnosis and instituting appropriate treatment.

There are case reports of adrenal insufficiency as cause for hypoglycaemia in patients with diabetes,[4 5] but very few to none cases listed as a cause for intractable nausea and vomiting creating a diagnostic dilemma.

Especially in patients with diabetes, Addison's disease presenting as nausea and vomiting can masquerade as diabetic gastroparesis since both these diagnoses are usually suspected on clinical grounds with different treatment options. Also, critical level of clinical suspicion for autoimmune polyglandular syndrome is essential, especially in female patients with ages from 20 to 40 years and with medical history of endocrine autoimmune diseases like insulin-dependent diabetes mellitus (IDDM)/autoimmune thyroid disease/primary hypogonadism.[6–8]

CASE PRESENTATION

A 31-year-old Caucasian woman with history significant for IIDM on insulin pump since the age 2, hypothyroidism, diabetic peripheral neuropathy with non-significant known family history was admitted with intractable nausea and vomiting for 2 weeks PTA. According to patient's mother, she was discharged from another facility 1 week back for diabetic ketoacidosis (DKA). She has associated non-bloody non-mucous loose stools, fatigue and generalised abdominal discomfort and unknown degree of unintentional weight loss. On examination her body mass index was 20.5, has stable vitals with no signs of dehydration and minimal generalised abdominal tenderness with no signs of acute abdomen. Complete blood count/BMP/liver function test/thyroid-stimulating hormone were WNL with BHB of 23.5.

Endocrinology was consulted. She is presumed to have diabetic gastroparesis and was treated with intravenous fluids/intravenous macrolides/antiemetic. She was subsequently discharged home after 3 days of hospital stay, on proton-pump inhibitors/antiemetic's/erythromycin suspension. A day after discharge she got admitted with intractable nausea and vomiting and was discharged after 2 days of similar hospital course as mentioned above.

After 15 days of hospital discharge, she was readmitted with intractable nausea/vomiting/generalised abdominal discomfort with failed outpatient management. Her primary care physician sent her to the facility. Ultrasonography of the abdomen performed outpatient to r/o acute cholecystitis was unremarkable. She has associated unintentional weight loss of 25 lbs. and fatigue. On examination she is noted to have dry skin and mucous membranes, HR of 120/min with BP of 90/50 mm Hg and minimal generalised abdominal tenderness with no signs of acute abdomen. She was not in DKA. Endocrinology and Gastroenterology was consulted. Diagnostic impression was diabetic gastroparesis.

She was started on total parental nutrition (TPN) for nutrition. Random cortisol and adrenocorticotropic hormone (ACTH) ordered 3 days after hospital stay are suggestive of adrenal insufficiency and intravenous methylprednisolone in stress doses were initiated, which was subsequently tapered to oral prednisone after her symptoms resolved. She was discharged on prednisone and fludrocortisone with an impression of Addison's crisis.

INVESTIGATIONS

The patient had a blood glucose of 297 mg/dL. Her haemoglobin was 18.4 g/dL, total leucocyte count of 7100/mm^3 with differential count of neutrophils 23%, lymphocytes 51%, eosinophil's 13%. Her electrolyte panel significant for sodium of 132, potassium of 4.4, chloride of 98, bicarbonate of 18 with AG of 16 with rest of the electrolyte panel with in normal range. Urine ketones were 3+. Her BHB was 32.8, lactic acid of 2.8, pH venous 7.39. Other biochemical tests like liver, renal function, thyroid functions tests were within normal range.

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Upper gastrointestinal endoscopy was unremarkable.

Hepatobiliary iminodiacetic acid scan was negative for acute cholecystitis.

Early morning random cortisol of 0 µg/dL and elevated ACTH of 433 pg/mL.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis has been explained in Table 1.

TREATMENT

She was initially managed with intravenous fluids, antiemetic's (alternating with intravenous reglan and intravenous zofran), and intravenous macrolides. TPN was started which was continued till she tolerated oral feeds. Intravenous methyl prednisone at stress doses was continued for 3 days. Her symptoms resolved and she was discharged on oral prednisone 7.5 mg daily and fludrocortisone 0.1 mg daily.

OUTCOME AND FOLLOW-UP

The patient is doing well with regular follow-up and no subsequent hospitalisations. She is being evaluated for autoimmune polyglandular syndrome type 2.

DISCUSSION

Adrenal insufficiency is a clinical and bio chemical entity characterised by partial or complete loss of secretion of adrenocortical steroids. The prevalence of adrenal insufficiency is 5 in 10 000 in general population. Hypothalamic-pituitary origin has a prevalence of 3 in 10 000 and primary adrenal insufficiency with 2 in 10 000.[7 8 10 11] The most common cause in adults is the use of exogenous glucocorticoids administered chronically for the treatment of various medical conditions that lead to suppression of hypothalamic–pituitary–adrenal (HPA) axis.

Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis with isolated autoimmune adrenalitis accounting for 30–40% cases and 60–70% develop as part of autoimmune polyglandular syndromes (APS).[5 6 7 8] Primary adrenal insufficiency is described in approximately 0.5% of patients with type 1 diabetes mellitus (T1DM)[12 13]: it is more frequent in females and occurs in middle aged patients, usually several years after the onset of T1DM as part of APS type 2. There has been no association described between primary adrenal insufficiency and T2DM.

Secondary adrenal insufficiency is a consequence of dysfunction of HPA axis (tables 2 and 3).

Clinical features of primary adrenal insufficiency are characterised by loss of both glucocorticoid and mineralocorticoid secretion. In secondary/central adrenal insufficiency, only glucocorticoid deficiency is present and is amenable for regulation by renin-angiotensin system.[2 3 10 17]

In primary adrenal insufficiency serum cortisol and aldosterone levels are low, but plasma renin and ACTH levels are increased. In secondary adrenal insufficiency, serum cortisol levels are low with low to normal ACTH, normal renin and aldosterone levels. Random free cortisol levels vary depending on the time of the day due to pulsatile nature of ACTH and normal diurnal variation of cortisol level. A minimal or no response to serum cortisol levels from baseline in response to cosyntropin stimulation, preferably performed in the morning confirms the diagnosis. Healthy persons increase the serum cortisol to >18 µg/dL after 250 µg of cosyntropin intravenous. Serum levels of dehydroepiandrosterone and dehydroepiandrosterone-sulfate are characteristically low with both primary and secondary adrenal insufficiency. If the diagnosis of secondary adrenal insufficiency is suspected based on biochemical findings, imaging of the pituitary should be performed (MRI of pituitary; table 4).[18]

Table 1 Differential diagnosis of adrenal insufficiency

Acute adrenal insufficiency	Chronic adrenal insufficiency
Sepsis	Apathetic hyperthyroidism in elderly
Hypovolaemic shock	Myopathies
Acute gastroenteritis	Malignancies
Our case	Major depression
	Anorexia nervosa
	Salt losing nephropathy
	Chronic infections: TB/AIDS

Adapted from
Arlt and Allolio;[2]
Oelkers;[3]
Bornstein;[8]
Ten *et al*.[9]
TB, tuberculosis

Table 2 Causes of autoimmune adrenal insufficiency

Diagnosis	GENE	Features (order of frequency)
APS 1	AIRE	Hypothyroidism, Chronic mucocutaneus candidiasis Adrenal insufficiency Primary hypogonadism Malabsorbtion syndromes Type 1 DM Others
APS 2	HLA-DR3 CTLA-4	Adrenal insufficiency Autoimmune thyroid disease Type 1 DM Primary hypogonadism Vitiligo
Isolated Autoimmune adrenalitis	HLA-DR3 CTLA-4	

Adapted from:
Arlt and Allolio;[2]
Oelkers;[3]
Bornstein;[8]
Leshin;[11]
Dittmar *et al*;[10]
Neufeld *et al*.[6]

Table 3 Clinical manifestations and laboratory findings of primary adrenal insufficiency

Symptoms	Signs	Labs
Weakness, fatigue (100%)	Dehydration (acute onset)	Hyponatraemia
Anorexia (100%)	Weight loss (100%)	Hyperkalaemia
GI symtoms:	Hyperpigmentation (94%)	Hypercalcaemia
Nausea (86%)	Hypotension (SBP<110)	Metabolic acidosis (acute onset)
Vomiting (75%)	shock (acute onset)	hypoglycaemia
Constipation (33%)	Vitiligo	Azotemia (acute Onset)
Abdominal pain		Anaemia
Diarrhea		Lymphocytosis
Fever(acute onset)		eosinophilia
Salt craving		
Postural dizziness		
Myalgia		
Arthralgia		

Adapted from: Arlt W and Allolio;[2] Oelkers W;[3]
Burke;[14] Varadaraj *et al*;[15] Stacpoole *et al*.[16]
GI, gastrointestinal; SBP, systolic blood pressure.

Table 4 Glucocorticoid replacement therapy in adrenal sufficiency

Condition	Hydrocortisone	Prednisone	Dexametha -Sone
Daily dose (oral)	15–25 mg daily in divided doses	3–5 mg daily in divided doses	0.375 to 0.75 mg daily in one dose
Minor stress (cold) Oral	30–50 mg/daily in 3 divided doses for 2–3 days	8–15 mg/daily in 2 divided doses for 2–3 days	1 to 2 mg/d in 2 divided doses for 2–3 days
Moderate stress (minor or moderate surgical procedure) oral or intravenous	45–75 mg/daily in 3 divided doses for 2–3 days	15–20 mg/daily in 2 divided doses for 2–3 days	2–3 mg/d in 2 divided doses for 2–3 days
Severe stress (major surgery/sepsis)	100–200 mg/daily in 4 divided doses for 1 day taper to physiological dose over 3–5 days	Same as hydrocortisone regimen	Follow hydro-cortisone regimen
Septic shock	150–200 mg/daily in 4 divided doses, taper as clinically tolerated	Follow hydrocortisone regimen	Follow hydro –cortisone regimen

Adapted from ref. 19
Oelkers *et al*.;[20]
Debono *et al*.;[21]

The standard drug for mineralocorticoid replacement in patients with primary adrenal insufficiency is fludrocortisone, 0.05–0.1 mg/day. Patients with either primary or secondary adrenal insufficiency are deficient in adrenal androgens, but adrenal androgen replacement therapy is not essential for survival, and the data are not clear that replacement offers clear benefit.

Learning points

- Adrenal insufficiency is a life-threatening disorder and delay in diagnosis leads to increased morbidity and mortality.
- Adrenal insufficiency should be considered in the differential diagnosis of intractable nausea and vomiting especially in patients with diabetes.
- The combination of autoimmune adrenal insufficiency with other autoimmune endocrine disorders is referred to as the polyglandular autoimmune syndrome types I and II and patients with high degree of suspicion need to be evaluated.

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Competing interests None.

Patient consent Obtained.

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Reminder of important clinical lesson