*Lesson of the week***Misinterpretation of serum cortisol in a patient with hyponatraemia**

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Primary adrenal insufficiency or Addison's disease is caused by bilateral adrenocortical destruction and is a relatively common endocrinopathy, with a prevalence of about 40-60 per million adults.¹ Adrenal insufficiency is an important consideration in any critically ill patient, as failure to make the diagnosis may have fatal consequences. In contrast, early diagnosis and treatment with appropriate corticosteroid replacement restores health and a normal life expectancy. We present a case in which an unusual presentation of Addison's disease caused diagnostic confusion. Although the possibility of adrenal insufficiency was eventually considered, incorrect interpretation of laboratory investigations led to diagnostic delay.

Case report

A 93 year old man without a significant medical history and taking no regular drugs had become unwell on holiday, 18 months before his admission to our department. At that time, he complained of weight loss, nausea, and vomiting. He was admitted to a local hospital and underwent an upper gastrointestinal endoscopy. This revealed oesophagitis with Barrett's mucosa, and treatment with a proton pump inhibitor was started.

He again became unwell two months later and was admitted to hospital with vomiting, drowsiness, and fever. He was found to be clinically dehydrated, and a chest x ray showed a left lower lobe pneumonia. Biochemical investigations revealed hyponatraemia, with a serum sodium concentration of 121 mmol/l. His serum potassium concentration was 5.0 mmol/l. The hyponatraemia was investigated and ascribed to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). A random serum cortisol concentration was 163 nmol/l. After treatment with intravenous fluids and antibiotics, the patient improved clinically and was discharged from hospital.

He continued to experience nausea and vomiting, with further weight loss, and was referred by his general practitioner to a gastroenterologist. At this stage, his serum sodium level had risen to 134 mmol/l. He seemed unwell and looked thin. A barium swallow was arranged, which showed no significant abnormality. The possibility of Addison's disease was considered at this stage, but, although a short corticotrophin test was contemplated, it was not performed or deemed necessary after a random serum cortisol concentration of 141 nmol/l was obtained. Computed tomography scan of the thorax was also performed, which revealed bilateral apical fibrotic changes with some calcification at the left apex.

At outpatient review, two months later, the patient still complained of predominantly upper gastrointestinal symptoms, and another upper gastrointestinal endoscopy was performed. This investigation

Laboratory investigations of patient

Investigation	Result (laboratory normal range)
Short corticotrophin test:	
Cortisol (nmol/l) at 0 min	256
Cortisol (nmol/l) at 30 min	237
Free thyroxine (pmol/l)	17.8 (10.0-20.0)
Thyroid stimulating hormone (mIU/l)	1.3 (0.3-4.0)
Luteinising hormone (IU/l)	27.2 (2-12)
Follicle stimulating hormone (IU/l)	57.9 (<6)
Testosterone (nmol/l)	5.4 (10-35)
Calcium (mmol/l)	2.46 (2.25-2.70)
Adrenocorticotrophic hormone (ng/l)	842 (5-36)
Renin (pmol/ml/hour)	60 (random 0.5-3.1)

showed only changes of a non-inflamed segment of Barrett's mucosa. Three months later, after using antiemetics drugs, he showed some improvement in his symptom of nausea and was discharged. Three months later, however, he experienced further vomiting and was referred to another gastroenterologist. Endoscopy again revealed only a non-inflamed segment of Barrett's mucosa. Shortly after this investigation, he collapsed at home and was admitted to our hospital as an emergency. He had continued to experience nausea, vomiting, and generalised weakness.

Clinical examination showed him to be unwell, thin, dehydrated, and hypotensive. There was also some skin hyperpigmentation. Biochemical investigations revealed hyponatraemia (123 mmol/l), hyperkalaemia (5.8 mmol/l), and an elevated urea concentration (32 mmol/l). A short corticotrophin test (tetracosactide 250 µg intravenous) showed a flat serum cortisol response, and his plasma adrenocorticotrophic hormone concentration was grossly elevated, confirming primary adrenal insufficiency. The table shows the results of other hormonal investigations. Computed tomography of the adrenal glands revealed both glands to be small and atrophic with evidence of bilateral calcification. Adrenocortical autoantibodies were not detectable, and an intradermal tuberculin PPD (Heaf) test was negative.

Immediately after confirmation of the diagnosis, corticosteroids were administered, together with intravenous 0.9% saline. The patient's clinical condition improved rapidly, and he was discharged from hospital with standard replacement doses of hydrocortisone and fludrocortisone. At review, two months later, he was feeling well, had gained a considerable amount of weight, and denied gastrointestinal symptoms. Repeat tests for serum, urea, and electrolytes were normal.

Discussion

When adrenal insufficiency presents acutely in its classic form, characteristic clinical and biochemical findings usually lead to a prompt diagnosis. However,

The possibility of hypoadrenalism must be considered in unexplained hyponatraemia, and cortisol measurements should be interpreted carefully

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BMJ 2004;328:215-6

in more atypical insidious presentations, such as in the present case, the diagnosis can initially be overlooked when predominant symptoms such as nausea and vomiting are attributed to localised gastrointestinal pathology rather than being recognised as a manifestation of adrenal insufficiency.

Although hyponatraemia is a common electrolyte disturbance in elderly people, its clinical evaluation and investigation are often incomplete.^{2,3} For example, in one retrospective study from a UK teaching hospital involving 47 cases of severe hyponatraemia, adrenal insufficiency was excluded in only one case.² The present case shows the importance of a careful evaluation of hyponatraemia in elderly people. The syndrome of inappropriate antidiuretic hormone secretion should be regarded as a diagnosis of exclusion and cannot be said to occur in the presence of other underlying conditions that may be responsible for hyponatraemia. It is difficult to suggest a threshold of hyponatraemia below which adrenal insufficiency should be formally excluded. Rather, adrenal insufficiency should be considered in any hyponatraemic patient in whom an alternative precipitating cause for hyponatraemia is not apparent.

Although measurement of random serum cortisol can be a useful screening test to exclude adrenal insufficiency,⁴ careful interpretation of the result with regard to the patient's clinical status is required. A morning (8–9 am) cortisol concentration of >500 nmol/l effectively rules out the possibility of adrenal insufficiency in most cases, whereas a concentration of <100 nmol/l (especially in a stressed individual) is highly suggestive of the diagnosis.⁴ For acutely ill patients with major trauma or severe sepsis, a safe cut off is unknown, but cortisol concentrations of >700 nmol/l probably rule out adrenal insufficiency.⁵ With values falling below this level, diagnostic doubt remains and dynamic testing is required. Thus, in the present case a cortisol concentration of 163 nmol/l did not exclude adrenal insufficiency. Furthermore, this level of cortisol should have been regarded as below normal in the presence of an acute illness (pneumonia), during which activation of the hypothalamic-pituitary-adrenal axis would be expected.

The short corticotrophin test is safe and simple to perform, and interpretation of the results is straight-

forward.⁴ There should therefore be a low threshold for performing this investigation in unexplained hyponatraemia. A blunted response to a 250 µg dose in association with elevated plasma adrenocorticotrophic hormone is diagnostic of primary adrenal insufficiency. When adrenal insufficiency is suspected in acutely ill patients, administration of corticosteroids should not be delayed pending results of diagnostic tests. In such patients, hydrocortisone should be given immediately after blood samples are drawn for cortisol and adrenocorticotrophic hormone. The combination of a low serum cortisol (<100 nmol/l) and elevated plasma adrenocorticotrophic hormone (>100 ng/l) is diagnostic in these circumstances.¹

Autoimmune adrenalitis resulting in slow destruction of the gland is responsible for most cases of Addison's disease in Westernised populations.¹ However, adrenal infections with a variety of organisms—including tuberculosis, fungal infections such as histoplasmosis, and opportunistic bacterial infections associated with immunodeficiency states—may lead to Addison's disease.¹ In the present case the absence of adrenal autoantibodies together with the radiological finding of adrenal calcification might indicate previous exposure to tuberculosis. The finding of small atrophic adrenal glands is indicative of previous infection, whereas in active disease adrenal enlargement is almost universal.⁶

Contributors: JCS drafted and revised the manuscript. HS helped with managing the patient and performed the relevant literature searches. RJMC helped with drafting and revising the manuscript. RJMC is the guarantor.

Competing interests: None declared.

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(Accepted 3 July 2003)

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