

NORMAL SHORT SYNACTHEN TEST IN PATIENTS WITH SECONDARY ADRENAL FAILURE

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The short synacthen test (SST), first introduced by Wood et al.¹ in 1965, is widely used to confirm the diagnosis of primary adrenal insufficiency. The optimum method for the diagnosis of secondary adrenal insufficiency remains controversial. The insulin tolerance test (ITT) is accepted by most endocrinologists as the gold standard² for the assessment of the hypothalamic-pituitary-adrenal (HPA) axis, but is hazardous at times, with some morbidity and occasional mortality. The short synacthen test is gaining popularity, and by 1994, up to 50% of UK endocrinologists were using it to assess the HPA axis.³ We describe two cases presenting with hyponatremia in whom hypoadrenalism was suspected, but with normal SST. The secondary adrenal insufficiency was later confirmed in these cases on clinical features, associated hormonal deficiencies, ancillary investigations and most important of all, the therapeutic response to replacement steroids.

Case 1

A 63-year-old male presented with a history of six to seven episodes of fainting/loss of consciousness over the previous year-and-a-half. These episodes were never preceded by any palpitations or associated with seizure activity and/or incontinence of urine or feces. He also experienced occasional nausea with vomiting. He was labelled to have ischemic heart disease on the basis of ECG changes, but did not have angina and was taking diltiazem, moduretic (amiloride and hydrochlorothiazide), ranitidine and amitriptyline regularly. He appeared unwell upon admission, and was pale-looking, with a pulse of 90/min. His blood pressure was in the range of 120-140 mm Hg systolic and 70 mm Hg diastolic, but with a significant postural drop of 20 mm Hg. The rest of the examination was unremarkable. Routine investigations revealed serum sodium of 112 mmol/L, potassium of 3.3 mmol/L, and creatinine of 1.0 mg/dL. It was thought that electrolyte imbalance was due to diuretics and associated vomiting. He was rehydrated with normal saline and the

arrhythmia. A CT scan of the brain showed pituitary macroadenoma, which extended just above the sella but did not compress the chiasma or extend into the cavernous sinuses. While some of the investigations were being done on an outpatient basis, he was readmitted with further episodes of dizziness/unconsciousness. The patient again showed symptoms of hyponatremia, with serum sodium of 117 mmol/L and potassium of 4.3 mmol/L. A hormonal workup was done this time that included the short synacthen test. Baseline values showed secondary hypothyroidism with a low T₃ of 0.44 ng/mL (normal being 0.86-1.87), T₄ of 3.6 µg/dL (4.5-12.5) and TSH of 2 (0.3-4.5). There was evidence of hypogonadism with a low testosterone of 27 ng/dL (270-1070) and normal FSH of 9.3 mIU/mL (up to 20) and LH of 2.9 mIU/mL (up to 20). Insulin hypoglycemia test was not done due to associated ischemic heart disease. The short synacthen test was done with the following values: baseline cortisol 9.9 µg/dL; 30 minutes post 250 µg intramuscular synacthen, 16 µg/dL; and 60 minutes post synacthen, 20 µg/dL.

As the clinical suspicion of hypoadrenalism was very high, the patient was started on replacement steroids and low-dose thyroxine. Three years of follow-up has not shown any further episodes of unconsciousness, nausea/vomiting has settled and the serum sodium has repeatedly been within normal limits. His pituitary adenoma has stopped growing, and his prolactin (24.6 ng/mL) and growth hormone (<0.1 ng/mL) were essentially normal and being followed by repeated CT scanning. The patient has refused an operation for his pituitary adenoma.

Case 2

A 55-year-old female who was a known diabetic and hypertensive with ischemic heart disease presented with a three-month history of nausea, vomiting and retching which had lately worsened, necessitating hospital admission. She was treated symptomatically at another hospital and became drowsy a day prior to presentation to our hospital. She was taking metformin 500 mg three times a day and sublingual nitrates when required, and was not on diuretics. On examination she was drowsy and responded minimally to verbal commands. Her pulse was 90/min and blood pressure was 130/70 mm Hg. The rest of the examination was unremarkable. Routine investigations revealed a sodium of 108 mmol/L, potassium 3.3 mmol/L, chloride 80 mmol/L, bicarbonate 19.9 mmol/L, creatinine 1.2 mg/dL,

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Accepted for publication 7 December 1997. Received 21 June 1997. diuretics were discontinued. As a workup for his faintness, a 24-hour halter monitoring was done to pick up any

and blood glucose of 130 mg/dL. Urinary spot sodium was 60 mmol/L and the urine osmolality 385 mOsm/L. Hypoadrenalism was suspected and hormonal workup revealed a very low total T₃ of 0.3 ng/mL (0.8-2.0) and T₄ of 1.2 µg/dL (4.5-12.0), with a thyroid-stimulating hormone (3.12 uIU/mL) within the normal range. Follicle-stimulating hormone (1.7 µIU/mL) and luteinizing hormone (1.96 µIU/mL) were very low for a postmenopausal woman (her periods stopped at the age of 43). The short synacthen test showed a baseline cortisol of 12.5 µg/dL; 30 minutes post 250 µg intramuscular synacthen of 24.6 µg/dL; and 60 minutes post synacthen of 30 µg/dL.

As the clinical and hormonal workup suggested hypopituitarism, insulin hypoglycemia test was considered to prove this, but was not done due to the patient's history of ischemic heart disease. She was started on replacement steroids and low-dose thyroxine. CT scan of the pituitary and paraspituitary region was normal. She has been feeling well with no weakness or any nausea or vomiting, and there has been no recurrence of hyponatremia.

Discussion

The short synacthen test is an excellent diagnostic test for patients suspected of having adrenal insufficiency.^{1,4-6} Although this test directly measures the integrity of the adrenals, it also provides an assessment of the hypothalamic-pituitary-adrenal axis. An inadequate response to adrenal stimulation is almost always seen in patients of primary adrenal failure. However, when hypoadrenalism is due to lack of stimulation by adrenocorticotrophic hormone (ACTH) (secondary adrenal failure), adrenal hyporesponsiveness may not be a constant finding, as highlighted in our two cases and a few others.⁷⁻¹⁰ In primary adrenal failure, sometimes mineralocorticoid deficiency can precede glucocorticoid deficiency and can give a normal SST.¹¹ Cunningham et al. and others have shown that in two categories of secondary hypoadrenalism, the SST may be normal while the other test assessing hypothalamic-pituitary-adrenal axis (ITT and metyrapone test) might be abnormal.¹² One of these situations is post-hypophysectomy, in which there is a window period of a few weeks after the onset of pituitary dysfunction during which the adrenal gland is still capable of responding to exogenous ACTH. The value of SST after chronic steroid usage to assess the HPA axis is still debated, with studies both for and against it.¹²⁻¹⁴ Even in certain situations other than the above two settings, the short synacthen test may be normal.⁷⁻¹⁰

Low doses of ACTH have been reported to be sufficient to cause the release of cortisol.¹⁵ The low "physiological dose" may thus unmask subtle disturbances of the HPA axis which are passed as normal by the standard high-dose short synacthen test, as in our cases. Recent studies have shown a close association between peak serum cortisol responses to ACTH, metyrapone or ITT and the low-dose

synacthen test.^{16,17} Rasmuson et al.¹⁸ have shown in their study of 27 patients that the low-dose ACTH test seems to follow the ITT more closely than the standard ACTH test.

The short synacthen test should be used to screen for hypoadrenalism, until the low-dose synacthen test replaces it, as it is a simple and inexpensive test. Insulin tolerance test and metyrapone have the advantage of assessing the integrity of hypothalamus and pituitary glands, but unfortunately are unpleasant, expensive and have contraindications. In a patient presenting with hyponatremia of undetermined cause, the diagnosis of adrenal insufficiency should be entertained. If the clinical suspicion is high for secondary hypoadrenalism and the SST is normal, further investigations should be done in the form of low-dose synacthen test, ITT, metyrapone test, associated pituitary hormonal measurements, and even pituitary imaging.

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