

# The Caveats of Corticotropin Stimulation Test in Diagnosing Secondary Adrenal Insufficiency: Case Reports and Literature Review

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## Abstract

Corticotropin stimulation test (CST) is commonly used to diagnose secondary adrenal insufficiency. We present two patients who underwent transsphenoidal pituitary surgery for pituitary macroadenoma. Both patients had additional pituitary hormone deficiencies before and after the surgery. The patients were maintained on glucocorticoid (GC) replacement for at least 3 months after the surgery. In the remote follow-up period, they underwent conventional CST with resultant cortisol levels above 18 µg/dL. This led to discontinuation of GC treatment. Few months later, both patients developed clinically evident adrenal insufficiency. Providers should be cautious interpreting the results of CST in patients with pituitary disorders. The 250-µg CST with standard cortisol cutoff has low sensitivity and can give falsely reassuring results. Thus, it is prudent to use a higher cortisol threshold to define intact hypothalamic-pituitary-adrenal axis.

**Keywords:** Cortisol; Adrenal insufficiency; Corticotropin stimulation test

## Introduction

Adrenal insufficiency (AI) can be primary, due to defect in the adrenal glands, or secondary, due to diminished ACTH secretion from the pituitary gland. Secondary AI is observed in the settings of a mass pressing on the normal pituitary gland, for example, pituitary macroadenoma, Rathke's cyst, or craniopharyngiomas. It is also seen as a result of radiation treatment to the pituitary area, inflammation, or after surgical intervention in the sella turcica. Transsphenoidal pituitary surgery

(TSS) is the first line treatment for most symptomatic pituitary adenomas [1]. The incidence of new AI after TSS is variable depending on the study, ranging from 0.8% to 18.5% [2-6]. The predictors of new pituitary insufficiency are the size of adenoma [3, 4] and preexisting one or more hormonal deficiency [4]. Among the dynamic procedures, corticotropin stimulation test (CST) is often used to assess hypothalamic-pituitary-adrenal (HPA) axis. Here we report two cases of a falsely reassuring standard dose CST at 3 and 6 months after surgery in patients with other pituitary hormone deficiencies.

## Case Reports

### Case 1

A 70-year-old man with prior history of hypertension, hyperlipidemia and coronary artery disease presented with progressive visual loss. Visual field testing demonstrated bilateral hemianopsia and optic atrophy. Magnetic resonance imaging (MRI) of the brain revealed a 4.3 cm pituitary adenoma pressing on the optic chiasm and displacing the optic nerves laterally (Fig. 1a). His preoperative random cortisol was 7.4 µg/dL, and ACTH was 33 pg/mL. He had central hypogonadism based on morning total testosterone of 107 ng/dL (193 - 740 ng/dL), SHBG of 45 nmol/L, and low LH of at 1.6 mIU/mL (1.7 - 8.6 mIU/mL). Other laboratory evaluation revealed central hypothyroidism with low free T4 of 0.7 ng/dL (0.9 - 1.7 ng/dL) and inappropriately normal TSH of 1.63 µIU/mL (0.27 - 4.2 µIU/mL). His prolactin was elevated at 19.9 ng/mL (4.0 - 15.2 ng/mL) and IGF-1 was 162 ng/mL (60 - 220 ng/mL) (Table 1).

The patient underwent TSS. Pathology was consistent with non-functional pituitary adenoma. Intraoperatively, he received hydrocortisone 100 mg due to hypotension and continued on glucocorticoid (GC) upon discharge. Three months postoperatively, his thyroid function normalized (free T4 1.0 ng/dL; TSH 1.76 µIU/mL). However, he had persistent hypogonadism (morning testosterone level 32 ng/dL) requiring testosterone replacement. His morning cortisol levels ranged from 6.8 to 8.2 µg/dL after holding GC for 24 h. He underwent 250-µg CST 3 months postoperatively, which resulted in the cortisol levels rising to 18.6 and 22.8 µg/dL at 30 and 60 min, respectively. The patient was educated about symptoms of AI, and GC replacement was subsequently discontinued. Ten

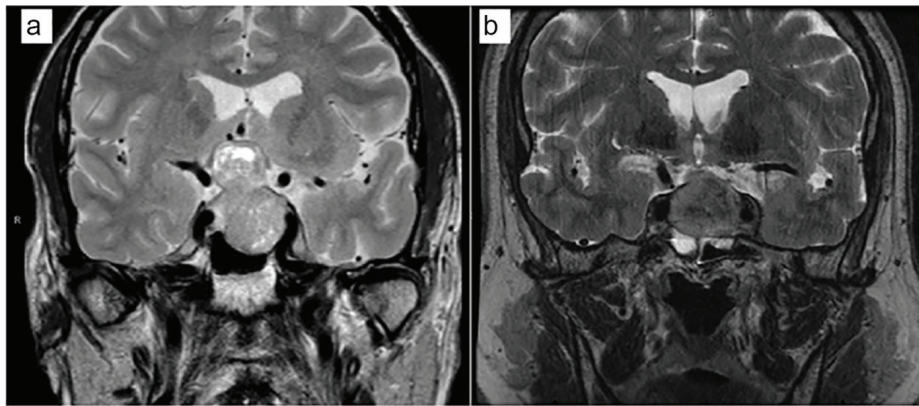
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**Figure 1.** An MRI of the brain at the time of presentation. Coronal T2-weighted images. (a) Case 1. (b) Case 2.

months later, he was re-admitted with sudden onset of nausea and altered mental status. His relatives reported progressive fatigue, shortness of breath, decreased appetite and weight loss over several weeks prior to admission. Laboratory evaluation demonstrated sodium 118 mmol/L (133 - 145 mmol/L), morning cortisol 4.9 µg/dL (6.2 - 19.4 µg/dL), TSH 1.5 µIU/mL and free T4 0.9 ng/dL. He was started on GC replacement with the quick resolution of his symptoms. Head MRI at 3 months after the pituitary surgery and at the time of presentation revealed a stable 1.1 cm residual pituitary lesion.

**Case 2**

A 59-year-old man with no prior history presented to an emergency department with a sudden onset of severe frontal headache, accompanied by nausea, vomiting, double vision, and photophobia. A pituitary MRI showed a 2.9 cm lesion in the sellar and suprasellar regions (Fig 1b). He underwent urgent transsphenoidal surgery; pathology showed extensive acute infarction consistent with pituitary apoplexy. His random pre-operative lab work revealed TSH of 6.19 µIU/mL (0.27 - 4.2 µIU/mL), free T4 of 0.8 ng/dL (0.9 - 1.7 ng/dL), prolactin of

1.7 ng/mL (4.0 - 15.2 ng/mL), LH of 2.1 mIU/mL (1.7 - 8.6 mIU/mL), random total testosterone of 9 ng/dL (193 - 740 ng/dL), and IGF-1 of 237 ng/mL (68 - 245 ng/mL) (Table 1). Peri-operatively, he received stress-dose GCs and was discharged on GC replacement. During follow-up, morning cortisol levels after holding GC for 24 h ranged from 5.0 to 8.1 µg/dL. His testosterone level remained low, but he refused testosterone treatment. In addition, he elected to discontinue GC replacement. Thus, 6 months postoperatively, a 250-µg CST was performed with cortisol levels 18.1 and 22.9 µg/dL at 30 and 60 min, respectively. He was educated about symptoms of AI, and GC replacement was discontinued. Four months later, he presented to his primary care doctor with complaints of joint pain, muscle aches, leg swelling and 20 lb weight loss. His morning cortisol level was 3.0 µg/dL (normal 4.0 - 22.0 µg/dL), morning total testosterone was 44 ng/dL (241 - 927 ng/dL), LH was 1.2 mIU/mL (1.6 - 15.2 mIU/mL), TSH was 3.97 µIU/L (0.35 - 4.94 µIU/L) and free was T4 0.54 ng/dL (0.7 - 1.48 ng/dL), altogether, indicating adrenal insufficiency, central hypothyroidism and hypogonadism. Upon GC treatment, his symptoms quickly resolved. He was also started on testosterone and thyroid replacement. An MRI scan at the time of presentation with adrenal insufficiency showed no evidence of residual or

**Table 1.** Laboratory Findings Before and After the Surgery

	Normal range	Case 1		Case 2	
		Preoperative	3 months postoperative	Preoperative	3 months postoperative
ACTH (pg/mL)	7 - 63	33.0	n/a	n/a	16.0
Cortisol (µg/dL)	AM: 6.2 - 19.4 random: 2.3 - 19.4	7.4 (random)	8.2 (AM)	n/a	6.0 (AM)
TSH (µIU/mL)	0.27 - 4.2	1.63	1.76	6.19	4.54
Free T4 (ng/dL)	0.9 - 1.7	0.7	1.0	0.8	0.72
IGF-1 (ng/mL)	Case 1: 60 - 220 Case 2: 68 - 245	162	124	237	63
Total testosterone (ng/dL)	193 - 740	107 (morning)	32 (morning)	9 (random)	n/a
LH (mIU/mL)	1.7 - 8.6	1.6	2.1	2.1	1.7
Prolactin (ng/mL)	4.0 - 15.2	19.9	13.8	1.7	1.1

AM: morning sample from 6 a.m. to 10 a.m.

recurrent mass.

## Discussion

CST is used to assess HPA axis. It is performed by intravenous or intramuscular injection of corticotropin analog with measurement of cortisol at baseline, 30 and 60 min. Synthetic corticotropin analog, tetracosactide, has 1 - 24 amino acids of the endogenous ACTH and mimics its action. CST is a test of choice for diagnosis of primary adrenal insufficiency [7]. However, for secondary adrenal insufficiency, insulin tolerance test (ITT) and overnight metyrapone suppression test are gold standards. These tests are not commonly available, thus many providers rely on CST as an alternative.

The adrenal cortex relies on the trophic effect of pulsatile ACTH secretion to maintain its integrity. In patients with secondary AI, in the absence of ACTH, the zona fasciculata atrophies within 4 - 6 weeks. This leads to impaired ability to produce cortisol in response to exogenous corticotropin [8]. Given the lag period between the onset of diminished ACTH secretion and the atrophy of the adrenal gland, CST can be falsely normal if performed early in the course of the disease. Also, in patients with partial ACTH deficiency and intact adrenal glands, corticotropin analog can lead to substantial cortisol release and resultant levels above 18 µg/dL.

Experts disagree on the dosing of corticotropin and the cortisol value cutoffs for the diagnosis of secondary AI. A conventional high dose (HD) CST refers to use of 250-µg tetracosactide, while a low dose (LD) CST refers to 1-µg tetracosactide. A peak cortisol level equal or above 18 µg/dL, at any time point, is considered an adequate response [9]. LD CST provides higher sensitivity than HD CST [10-12]. This is explained by the degree of adrenal stimulation with corticotropin. The adrenal cortex is maximally stimulated at the corticotropin levels of 70 - 80 pg/mL [13]. HD CST results in measurable plasma corticotropin levels > 13,000 pg/mL at 10 min and > 150 pg/mL at 60 min. Thus, for 1 h, the adrenal glands are maximally stimulated [14], and cortisol levels continue to rise after 30 min, with the highest at 60 min. LD CST also leads to supra-physiological plasma level of corticotropin (up to > 1,900 pg/mL), but only within 30 min after injection [14]. Therefore, cortisol levels peak at 30 min and later decrease [14]. Although LD CST appears to be more sensitive, the test has technical challenges. The 250-µg vial of corticotropin has to be diluted which can result in inaccurate dosing and a variable cortisol response.

HD CST is not very sensitive for secondary AI. In one study sensitivity of the test was only 57% [15]. Therefore, many authors suggest raising cortisol cutoff level to 20 - 22 µg/dL [16, 17] or even higher [14, 18]. At the cortisol cutoff of 20 µg/dL, the sensitivity increases to 83% [19]. Furthermore, Kazlauskaitė et al calculated that the normal HPA axis is best predicted when cortisol is above 30 µg/dL at 30 min [18]. There is a strong correlation between cortisol levels among LD and HD CST at different time points [7, 14, 20, 21]. For this reason, when adjusted cortisol cutoffs are used, both tests provide equal sensitivity [14, 15, 22, 23]. Mayenknecht et al

found that cortisol cutoff of 19.4 µg/dL (30 min) for LD, and 22.5 µg/dL (30 min) and 26.3 µg/dL (60 min) for HD CST resulted in about 94% sensitivity in patients with pituitary disorders [14].

Neither LD nor HD CST reaches 100% sensitivity with acceptable specificity level. For this reason, an interpretation of CST must rely on other factors, including morning cortisol levels, other pituitary hormone deficiencies as well as clinical suspicion.

## Conclusion

CST is commonly used to evaluate HPA axis. Low dose 1-µg CST is more sensitive, for central adrenal insufficiency at the cortisol cutoff of 18 µg/dL. High dose 250-µg CST has low sensitivity and can give falsely reassuring results with standard cortisol cutoff. Thus, for HD CST, a higher cortisol threshold should be considered to determine intact HPA axis, especially in the settings of other pituitary hormone deficiencies. Some authors suggest cortisol levels of 22 µg/dL at 30 min and 30 µg/dL at 60 min. In the two presented cases, raising the cortisol threshold to 22 µg/dL at 30 min for HD CST would have prevented discontinuation of GC replacement and further complications.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article.

## Author Contributions

EM performed the review of cases and wrote the first draft. IS, MS and LC reviewed the draft and made corrections. EV, KF, and CH participated in the patients' care.

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