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Plasma ACTH in Addison’s Disease: Therapeutic Implications
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ABSTRACT
Addison’s disease is a rare disorder characterized by the failure of the adrenal cortex to produce sufficient amounts of cortisol and aldosterone. Uncontrolled Addison’s disease is associated with detrimental physiological and metabolic effects such as severe abdominal pain, dehydration, hypotension, syncope, and hypoglycemia. Administration of synthetic glucocorticoids and mineralcorticoids – a standard therapy for Addison’s disease – has shown to improve the patient’s prognosis and quality of life. However, it is not uncommon for patients on steroid replacement therapy to experience multiple side effects. Often, these side effects lead to self-adjustment of medication dosage and even discontinuation of treatment. We report a patient who fulfilled the criteria for the diagnosis of primary adrenocortical failure (Addison’s disease) but was inclined to stop her medications since she was unconvinced of the diagnosis and concerned about the side-effects of steroid therapy. The demonstration of persistent plasma adrenocorticotropic hormone (ACTH) elevation while on replacement steroids and explanation of the pathophysiology involved convinced the patient of the diagnosis of Addison’s disease and persuaded her to stay on her replacement therapy. We suggest that in patients with Addison’s disease on replacement corticosteroids, a persistently elevated plasma ACTH can serve as a confirmatory test. We postulate that the lack of pulsatility in hormone replacement regimens is likely responsible for the persistent ACTH elevation. The cost of the ACTH assay has declined over the years, and we encourage providers to consider it in conjunction with measuring plasma cortisol. A suppressed ACTH in patients with Addison’s disease may indicate overzealous glucocorticoid treatment.

INTRODUCTION
Addison’s disease is a relatively uncommon condition affecting one in 100,000 people in the U.S. Addison’s patients normally present with orthostatic hypotension, muscle weakness and fatigue, nausea, hypoglycemia, weight loss, salt craving, and hyperpigmentation of the skin. In patients with adrenal failure, plasma ACTH is always elevated (>70 pg/mL). A cosyntropin test has been a traditional way to demonstrate adrenocortical failure when plasma cortisol fails to reach the normal peak values of 18-20 mg/dL. However, the comparison of plasma ACTH to cortisol can also be very helpful in the diagnosis of adrenal dysfunction. Elevated plasma ACTH combined with diminished cortisol values may be useful in confirming the diagnosis of primary adrenal insufficiency.

While synthetic corticosteroids effectively compensate for the impaired adrenal function, their excessive use has been linked to various adverse effects such as weight gain, dyslipidemia, hypertension, osteoporosis, and type II diabetes mellitus. Also, the majority of treated Addison’s patients report decline in the quality of life, decreased perception of wellbeing, depression and anxiety. In some cases, the potential physical and psychological discomfort, as well as awareness of harmful consequences of overtreatment, may lead patients to discontinue essential replacement medications.
We report a patient who was inclined to stop all medications related to Addison’s disease and requested additional proof of diagnosis. We describe the utility of obtaining plasma ACTH measurements in this unique situation. The ability to interpret plasma ACTH values while the patient is on steroid replacement is an added benefit to testing under these circumstances.

CASE HISTORY
A 63-year-old female was hospitalized following a syncopal episode. She had a family history of coronary artery disease, diabetes mellitus, and melanoma. Her medical history included hypothyroidism as a result of total thyroidectomy. Her medications regimen consisted of levothyroxine (50 mg QD), omeprazole (20 mg QD), proventil (90 mg/ACT aerosol solution inhalation), Aspirin (81 mg as needed), multivitamins, and Caltrate 600+D Plus (600 calcium and 400 IU Vitamin D3 BID). Apart from skin and buccal hyperpigmentation and a thyroidectomy scar, no other findings were noted on physical examination. The patient’s blood pressure was 113/56 with no significant postural changes. Basic metabolic panel revealed mild hyponatremia of 136 mmol/L and borderline high potassium of 5 mmol/L. Cosyntropin stimulation test showed the patient’s cortisol level of less than 0.4 mg/dL at baseline (2.3-19.4), 1.5 mg/dL at 30 min, and 1.7 mg/dL at 60 min (18-20). Adrenal CT with and without contrast was unremarkable. The patient was treated with hydrocortisone (10 mg BID), and fludrocortisone (0.1 mg QD). Adrenal function workup also included positive 21-Hydroxylase antibodies of 1:40 (<1:10).

On follow-up, our patient was noted to have reduced her hydrocortisone without medical consultation. She explained her lack of compliance by expressing concern that weight gain could occur with hydrocortisone use. She was reluctant to continue hydrocortisone treatment. The patient repeatedly complained of dizziness and fatigue and admitted to salt cravings. Despite counseling, the patient continued to self-adjust her medication and at times skipped hydrocortisone entirely for a few days, since she remained unconvincing that steroid replacement was essential. On account of her imminent discontinuation of both her glucocorticoid and mineralcorticoid medications, the patient agreed to have an ACTH value measured after a detailed explanation of its role in confirming the diagnosis of Addison’s disease. Plasma ACTH was measured by LabCorp using the technique of electrochemiluminescence immunoassay (ECLIA). The patient’s plasma ACTH level was 459 pg/mL (7.2-63.3). It was explained to the patient that persistent ACTH elevation added further weight to the diagnosis of Addison’s disease. Despite her ongoing concerns about the side effects of steroid replacement therapy, she agreed to continue taking hydrocortisone and fludrocortisone after she was counseled on the significance of elevated ACTH in her condition. She is currently taking hydrocortisone (10 mg BID), fludrocortisone (0.1 mg daily), and her consistency with medications has improved noticeably.

DISCUSSION
Plasma ACTH values have not been routinely required for the diagnosis of Addison’s disease with the diagnostic emphasis on cortisol values post cosyntropin. In our case, the measurement of ACTH helped convince the patient of the need to comply with replacement medications. The consistency of ACTH elevation in patients with Addison’s on replacement glucocorticoids is noteworthy and is likely to be of diagnostic and therapeutic use.

Non-compliance is often observed in patients and is associated with adverse health outcomes and escalation of healthcare costs. In many cases, face-to-face counseling and health education encouragement may help reduce the incidence of non-compliance.

These measures often fall short when the patient is not convinced that his or her diagnosis is accurate and prescribed treatment is relevant. Our patient intended to stop taking her medications
unless we could provide additional confirmatory evidence of Addison’s disease. Measuring plasma ACTH concentration and explaining the significance of persistently elevated levels of this hormone to the patient was sufficient to ensure the patient’s ongoing compliance.

The value of the ACTH assay in patients with Addison’s disease on replacement has been overlooked in the past. Only three studies have investigated the patterns of ACTH release in patients with Addison’s, and none has addressed the utility of plasma ACTH levels in this particular setting.\textsuperscript{4,5,6} It is not customary to monitor plasma ACTH in patients on hydrocortisone because it is widely assumed that ACTH is suppressed as a result of negative feedback. While synthetic steroid replacement may mimic cortisol in structure and mechanism of action, the traditional two-dose hydrocortisone administration does not replicate pulsatile secretion of adrenal cortical hormones. This pulsatility of glucocorticoid feedback is responsible for adequate suppression of ACTH release by the corticotrophs of the anterior pituitary in healthy subjects. In those on steroid replacement therapy, ACTH increase is unrestrained because their plasma cortisol levels are undetectable during the night and early morning before administration of the a.m. dose of hydrocortisone. The study by Ekman et al., reported median ACTH level of 844 pg/mL at 07:30 with some values reaching as high as 2,249 pg/mL.\textsuperscript{6}

An important benefit of using ACTH as a clinical tool is that therapeutic process does not need to be interrupted by taking the patient off hydrocortisone, since the presence of replacement steroids does not interfere with the test results. It should be noted that while elevated morning plasma ACTH in patients on hydrocortisone almost unmistakably confirms Addison’s disease, low or normal ACTH levels cannot be used to rule it out due to the large inter-individual variation in hydrocortisone metabolism, sensitivity, and tolerance. Likewise, hydrocortisone dosage should not be adjusted on the basis of ACTH concentration, with the exception of ACTH levels in the normal range that may be a sign of excessive treatment.\textsuperscript{7}

The measurement of ACTH in our patient likely helped avoid hospital admission for Addisonian crisis, which would have occurred if she had stopped her replacement therapy. The value of this test in persuading the patient to remain on glucocorticoid replacement and helping her understand her illness was undeniable. Consequently, primary care providers may want to consider using plasma ACTH levels as a tool for confirming the diagnosis in patients with suspected Addison’s disease receiving glucocorticoid replacement. With the progressive decline in costs of ACTH assay over the years and close relationship between ACTH and cortisol levels, ACTH test is possibly an underutilized tool in the work-up of patients with adrenocortical failure.

**References:**

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