

ABNORMAL ACTH-STIMULATION TEST IN A PATIENT WITH AIDS: ADRENAL INSUFFICIENCY OR TOXOPLASMOSIS ?

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We here report a 32-year old homosexuell man with AIDS who had an abnormal ACTH stimulation test while taking megestrol acetate (megace). On further evaluation, he was found to have recurrent Non-Hodgkin lymphoma (spleen) and intracranial toxoplasmosis, perhaps imitating or aggravating symptoms suggestive of adrenal insufficiency (AI). We diagnosed secondary AI due to megace treatment and tapered this medication under simultaneous hydrocortisone replacement therapy. After the patient's intracranial toxoplasmosis had been treated with intravenous bactrim, his symptoms disappeared. We conclude that patients with AIDS on megace therapy should receive special attention in regards to the potential development of AI, especially in stress situations such as infections or pain.

Key words: Megestrol acetate – HIV – ACTH – Adrenal insufficiency – Toxoplasmosis – Stress

Megestrol acetate (Megace) is a progestational agent that is structurally similar to glucocorticoids and is often used for the treatment of patients with endometrial cancer, breast cancer, or cachexia/anorexia. Children and adults treated with megestrol acetate may develop adrenal insufficiency (AI) from a suppression of the pituitary-adrenal axis (FINDLING et al. 1994; SELLMAYER et al. 1996; LOPRINZI et al. 1992; LEINUNG et al. 1995; NAING et al. 1999; STOCKHEIM et al. 1999). We here report a patient with acquired immunodeficiency syndrome (AIDS) whom we evaluated as endocrine consultants for an abnormal adrenocorticotrophic hormone (ACTH)-stimulation test.

Case Report

A 32-year old homosexuell man had been admitted to the Hematology Service of the National Institutes of Health Clinical Center. He had AIDS and a history of Non-Hodgkin lymphoma, for which he

underwent bone marrow transplantation in August 1999. His past medical history also included cytomegaly virus (CMV) colitis and pancytopenia in association with oral and esophageal candidiasis. He did not have any other opportunistic infections and no history of tuberculosis. His family history was unremarkable for endocrinological disorders and he had no allergies. On admission, his current medications were ritonavir, saquinavir, efavirenz, stravidin, bactrim, prilosec, foscarnet, atropin, diphenoxylat, and megestrol acetate (megace) 800 mg/d for more than a year. Three weeks prior, he had been admitted for fever and diarrhea. Despite these symptoms, he continued his medications including megace. Foscarnet was given for presumed recurrent CMV colitis. Plasma CMV antigen was strongly (3+) positiv. An abdominal computed tomogram (CT) including the adrenal glands was unremarkable except for paraaortal lymphadenopathy. A colonoscopy showed inflamed areas with a biopsy suggestive of CMV colitis. During treatment with foscarnet, fever and diar-

rhea improved and plasma CMV antigen became negative. However, the patient developed orthostatic episodes, for which our colleagues from the hematology service performed an ACTH stimulation test. An 8 AM serum cortisol value was undetectable. After injection of 250 µg Cosyntropin, the plasma cortisol value rose to 8.2 µg (30 min) and 10.9 µg (60 min) (normal, > 18 µg/dl). To evaluate this patient for possible adrenal insufficiency, we were then consulted.

On physical examination the patient was orthostatic (pulse, supine: 110 beats per minute, upright: 140 bpm; blood pressure, supine: 110/60 mm Hg, upright: 102/58 mm Hg). He had normal turgor, a stable weight of 80 kg at a height of 184 cm, no signs of hyperpigmentation, a soft abdomen, and a normal neurological examination. Electrolytes, liver function tests, BUN, and creatinine were normal. Thyroid function tests were normal. White blood cell count was 3,500/µl (normal, 3,400-9,600), hemoglobin 7.6 g/dl (stable over a long time period), and platelets 70,000/mm³ (normal, 162 000- 380 000).

Discussion

Do these results justify the diagnosis AI and, if so, what would be the etiology ?

The differential diagnosis in this patient should include deconditioning, volume depletion, anemia, recurrent Non-Hodgkin lymphoma, adrenalitis (e.g. CMV, fungi, etc.), and longstanding pituitary insufficiency for ACTH secretion (suppression).

In our patient, the ACTH stimulation test was clearly abnormal and according to the rule *in dubio pro re*, we decided to administer a one time dose of 50 mg intravenous hydrocortisone. However, this procedure and the application of one liter normal saline did not impact on pulse and blood pressure, the patient remained tachycardic.

According to the literature, clinically relevant adrenal insufficiency in patients with AIDS is exceedingly rare (FINDLING et al. 1994). HIV itself does not exert a destructive role on the adrenal glands (SELLMEYER et al. 1996). Autopsy series of patients with HIV showed that 40-88 % of all patients have CMV inclusion bodies in the adrenal glands with maximally 70% adrenal cortex necrosis. However, more than 90% of the adrenal cortex must be de-

stroyed before clinical symptoms of adrenal insufficiency develop. In the literature, only 2 patients are described who suffered CMV adrenalitis and simultaneously AI. The autopsy of these cases showed a more than 90% destruction of the adrenal gland in association with CMV inclusion bodies (SELLMEYER et al. 1996).

In our patient, primary AI was unlikely, especially with regards to the negative plasma CMV antigen levels and a plasma ACTH level of < 4 pg/ml (normal, 10-60).

Which cause, however, could be responsible for secondary AI, if such should have been present in our patient?

Megace (megestrol acetate) is a progestin similar to medroxyprogesterone acetate. Both compounds have cortisol-like effects. Megace is given to patients with cancer (breast, prostate, ovary) and cachexia for weight gain. Although this compound stimulates appetite like glucocorticoids, the mechanism of weight gain is unknown. First reports on megace denied the possibility to induce secondary AI after abrupt withdrawal of megace (LOPRINZI et al. 1992). More recent reports, however, emphasized the risk of inducing secondary AI (LEINUNG et al. 1995; NAING et al. 1999; STOCKHEIM et al. 1999). Investigators attempted to establish a critical megace "threshold" for this risk. LEINUNG et al. reported that megace in a longterm dose of at least 240 mg/d can lead to AI upon abrupt withdrawal of the medication. NAING et al. (1999) found a even lower "threshold" for the risk of secondary AI, megace in a daily dose of 160 mg/d. Therefore, we decided to taper megace in our patient and to administer temporarily hydrocortisone 15 mg in the morning, and 10 mg in the evening. In addition, we decided to administer short-term "stress doses" of hydrocortisone in situations of "stress" such as severe infections, pain, etc. (SALEM et al. 1994). Under simultaneous application of hydrocortisone, we administered our patient megace 400 mg/d for one week, then 200 mg/d for another week, and finally only hydrocortisone 15 mg in the morning and 10 mg in the evening. However, the patient remained tachycardic and developed again fever and orthostatic episodes after 3 weeks. On admission, he had a palpable spleen (splenomegaly), confirmed by abdominal CT and interpreted as recurrent Non-Hodgkin lymphoma. He was placed on 50 mg intra-

venous hydrocortisone three times a day and underwent splenectomy. Non-Hodgkin lymphoma was histologically confirmed. After 4 days, the patient was dismissed on 15 mg oral hydrocortisone in the morning and 10 mg in the evening. After another 3 weeks, he developed again fever and orthostasis. Brain CT and magnetic resonance imaging showed multiple brain lesions. The pituitary area was unremarkable. Short-term therapy with dexamethasone did not change the size of the brain lesions and thus making the diagnosis of lymphoma unlikely. Subsequently, the patient was treated with intravenous bactrim for the presumed diagnosis toxoplasmosis which was confirmed by stereotactic brain biopsy. During the next days, the brain lesions shrunk and fever and orthostatic episodes disappeared. Bactrim therapy was continued orally.

Retrospectively, the question arises whether the patient's symptoms during the whole course were really related to AI, although the diagnosis of secondary AI was established by an abnormal ACTH stimulation test. In this scope, it is important to remember that the patient was on megace treatment in a dose probably equivalent to 25 mg hydrocortisone daily. Thus, an abnormal ACTH stimulation test may not necessarily imply clinical AI, if the respective individual is on appropriate "glucocorticoid-like" therapy. However, in developing stress situations, "stress doses" of hydrocortisone or glucocorticoids should be administered to such patients. For minor stress (e.g. laparoscopic surgeries) a total of 50 mg hydrocortisone per day may be sufficient, whereas severe stress situations (e.g. coronary artery bypass graft surgery) may require hydrocortisone dosages up to 150 mg per day. Dosages above the latter (150 mg) are nowadays not recommended anymore.

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