

Adrenal Function in the Human Immunodeficiency Virus–Infected Patient

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Although clinical manifestations of adrenal dysfunction are uncommon in patients infected with human immunodeficiency virus (HIV), subclinical functional abnormalities of the hypothalamic-pituitary-adrenal axis are frequent. Patients infected with HIV usually have higher basal serum cortisol and lower serum dehydroepiandrosterone concentrations than HIV-seronegative individuals. This imbalance has been related to progression of the infection by inducing a shift from T_H1 to T_H2 immunologic responses. Although, adrenal reserve may be marginal in HIV-infected patients, clinically evident adrenal insufficiency is uncommon and, when present, it is observed in advanced stages of the infection. Hypocortisolemia should be treated regardless of the existence of associated symptoms. On the contrary, hypercortisolemia in the absence of features of Cushing syndrome is common and should not promote treatment nor specific studies. The possible influence that alterations of the adrenal function could have on the patients' immune status and the eventual effect of antiretrovirals on these alterations merit further investigation.

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Adrenal gland involvement has been documented in as many as two thirds of patients with acquired immunodeficiency syndrome (AIDS) at postmortem examination.¹ However, adrenal insufficiency is seldom diagnosed in clinical practice because symptoms do not appear until more than 80% of the gland has been destroyed, and the extent of necrosis in the most frequent autopsy finding, cytomegalovirus adrenalitis, rarely exceeds 60%.^{2,3} Nevertheless, 2 (3%) of 75 autopsies performed in unselected patients with AIDS at a single center revealed greater than 80% destruction of the adrenal cortex by cytomegalovirus⁴; this is in agreement with the 3% of patients who had an antemortem diagnosis of adrenal insufficiency in another necropsy series.¹

Less common pathological processes include other opportunistic infections (*Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis carinii*, and *Toxo-*

plasma gondii), neoplasms (Kaposi sarcoma and lymphoma), hemorrhage, fibrosis, infarction, and more subtle abnormalities such as cortical lipid depletion, a likely surrogate of long-lasting severe stress.^{2,3,5,6} Adrenocortical antibodies are detected in a substantial proportion of patients with AIDS,^{3,5} probably as an epiphenomenon linked to nonspecific B-cell activation and devoid of clinical significance. Finally, several drugs have been found to be responsible for adrenal insufficiency by decreasing steroidogenesis (ketoconazole), enhancing cortisol metabolism (rifampin), or suppressing pituitary secretion of corticotropin due to their intrinsic glucocorticoid activity (megestrol acetate).^{3,7} In fact, Cushing syndrome induced by continuous administration of megestrol acetate has been reported.⁸

DYSFUNCTION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Subclinical functional abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis

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are much more prevalent than clinical manifestations of these disturbances. Basal serum cortisol levels seem to be higher in patients infected with human immunodeficiency virus (HIV) than in controls,^{9,10} with a negative linear correlation between CD4 cell counts and cortisol found in some,¹¹ but not all,¹² studies. This elevation is usually associated with normal levels of 17-deoxysteroids (ie, corticosterone, deoxycorticosterone, and 18-OH-deoxycorticosterone), subnormal increase of both 17-deoxysteroids⁹ and cortisol^{9,13-15} in response to cosyntropin, and an altered circadian rhythm of pituitary and adrenocortical hormone secretion.^{10,16} These patients also have a normal suppression of cortisol synthesis by dexamethasone, and lower levels of corticotropin¹⁰ and dehydroepiandrosterone (DHEA),^{10-12,17} an adrenal androgen that has a positive correlation with CD4 cell counts.^{11,12,17}

Although basal aldosterone levels tend to be lower in HIV-infected individuals, and both hyporeninemic and hyperreninemic hypoaldosteronism have been reported,¹⁸ response of plasma aldosterone to angiotensin III infusion and postural stimulation was normal in a study⁹; these findings have been interpreted as a preferential involvement of the zona fasciculata over the zona glomerulosa.^{2,3,5} There are 2 case reports of primary aldosteronism in HIV-infected patients,¹⁹ perhaps mediated through a reninlike activity of the HIV aspartic protease, but the causal relationship is far from clear.

PATHOGENESIS

Several pathogenic mechanisms have been proposed to explain the relative hypercortisolemia present in untreated HIV-positive individuals. First, the shift of steroid metabolism from aldosterone, DHEA, and 17-deoxysteroids to cortisol may represent an adaptive response to stress.^{2,3,5,6} Second, the cortisol-binding globulin of HIV-infected patients shows a higher number of binding sites compared with controls.²⁰ Some authors have also found increased plasma concentrations of cortisol-binding globulin associ-

ated with progression of the disease,²¹ whereas others found normal levels of cortisol-binding globulin in all HIV disease stages.²² Third, the increased cortisol synthesis in the absence of an increase in corticotropin suggests that some nonpituitary factors derived from infected immune cells, such as interleukin (IL)-1 β and IL-6,^{10,23,24} might directly stimulate the adrenal cortex. In patients with hypercortisolemia and increased corticotropin levels, these abnormalities may result from a stimulatory effect of cytokines (eg, interferon- α , IL-1 β , IL-2, and IL-6)²⁵ or the HIV envelope protein gp120²⁶ on the hypothalamic corticotropin-releasing hormone release. However, patients with advanced HIV disease often have reduced or blunted pituitary-adrenal responsiveness to corticotropin-releasing hormone infusion,²⁷ and cases of secondary adrenal insufficiency with normal corticotropin stimulation tests have been described.²⁸ Fourth, some patients with AIDS have a syndrome of peripheral cortisol resistance due to acquired abnormalities of the glucocorticoid receptor (GR), characterized by an increase in GR density and a decrease in GR affinity for the substrate.²⁹ These individuals have a high-cortisol, low-corticotropin state with paradoxical Addisonian features, but it is conceivable that a clinical spectrum exists, ranging from subclinical alterations to overt adrenal failure. Finally, the HIV vpr gene product has been reported to act as a GR coactivator in human lymphoid and muscle-derived cell lines,³⁰ which could result in an enhanced effect of glucocorticoids on the target cells.

It has been suggested that this pattern of high cortisol and low DHEA levels could induce a worsening in immune status by shifting the cytokine production from the so-called T_H1 or cellular-type response (interferon- γ , IL-2, and IL-12) to the T_H2 or humoral-type response (IL-4, IL-5, IL-6, and IL-10),³¹ a hallmark of HIV disease progression. In fact, cortisol suppresses interferon- γ and IL-2 production, favors IL-4 production, and stimulates programmed cell death (apoptosis).³¹ In this regard, cortisol-resistant AIDS patients have

a type 1 cytokine profile.³² In contrast, DHEA appears to enhance immune function,¹² probably by antagonizing some effects of cortisol on lymphocytes³; indeed, both decreased concentrations of DHEA^{33,34} and increased cortisol/DHEA ratio³⁵ are independent predictors of progression to AIDS in some studies.

EFFECTS OF ANTIRETROVIRAL TREATMENT

How and whether highly active antiretroviral therapy modifies this profile is largely unknown. Shortly after the release of protease inhibitors (PIs) for clinical use, disorders in the body adipose tissue distribution, including truncal obesity, visceral fat deposition, peripheral wasting, breast hypertrophy, and enlargement of the dorsocervical pad ("buffalo hump"), often associated with hyperlipidemia, hyperinsulinemia, and insulin resistance, were recognized.^{36,37} The similarities in their phenotypic characteristics led some authors to use the term *pseudo-Cushing syndrome* to denominate this clinical picture,³⁸ but soon it became clear that, unlike the pseudo-Cushing syndrome seen in alcoholism or severe depression, the vast majority of PI-treated patients had normal or slightly elevated cortisol levels in the morning serum or in the 24-hour urinary determinations, and showed normal dexamethasone suppression tests.^{37,39-42} Due to a number of clinical and laboratory features shared with classic generalized lipodystrophic syndromes, these changes in fat distribution and metabolic profile have been commonly referred to as antiretroviral-associated lipodystrophy. Lately, lipodystrophy has been linked to antiretrovirals other than PIs (eg, nucleoside-analogue reverse-transcriptase inhibitors) or even to the HIV infection itself,⁴³ and ascribed to a large array of pathogenic mechanisms, such as inhibition by the PIs of several host-cell proteins involved in lipid and carbohydrate metabolism,⁴⁴ PI-induced subcutaneous adipocyte apoptosis,⁴⁵ mitochondrial damage attributable to nucleoside-analogue reverse-transcriptase inhibitors,⁴⁶ and cytokine

dysregulation in the setting of immune recovery,⁴⁷ among others.

In a cross-sectional study,⁴⁸ the serum steroid hormone concentrations of patients taking highly active antiretroviral therapy who presented symptoms of lipodystrophy, according to a subjective clinical score, were compared with those of nonlipodystrophic individuals. Serum cortisol levels were elevated in patients compared with HIV-negative controls, but no differences were found between individuals with or without lipodystrophy. However, serum DHEA levels were significantly lower and cortisol/DHEA ratio higher in patients with lipodystrophy, and cortisol/DHEA ratio correlated positively with both dyslipidemia and the subjective clinical score. Christeff et al⁴⁸ speculated that the increased cortisol and decreased DHEA concentrations were due to the effect of PIs on cytochrome P450 isoforms involved in steroid metabolism, producing an imbalance between lipolysis and lipogenesis that could account for the peripheral fat loss and central fat accumulation.⁴⁸

In another study,⁴⁹ patients with antiretroviral-related lipodystrophy, defined by changes in body shape and abdominal computed tomographic scan findings, were compared with HIV-negative controls for multiple parameters of the HPA axis; unfortunately, there was no group of untreated HIV-positive individuals. Lipodystrophic patients showed normal values of serum cortisol levels, cortisol response after corticotropin-releasing hormone stimulation, cortisol-binding globulin concentration, and GR number and affinity, ruling out hyperactivity of the HPA axis as a cause of lipodystrophy. However, basal and corticotropin-releasing hormone-stimulated plasma corticotropin concentration, as well as 24-hour urinary 17-OH-corticosteroid concentrations, were significantly greater, whereas urinary free cortisol excretion was significantly lower in patients than in controls. The authors hypothesized that 1 or more of the antiretroviral drugs taken by these patients alter the metabolism of cortisol by enhancing the renal 11-ketosteroid reductase activity or by partially inhibiting the adrenal 11-

hydroxylase. According to this study, lipodystrophy cannot be attributed to hypercortisolism, and other possible mechanisms, such as selective changes in the glucocorticoid sensitivity of different adipose tissue depots, are worth exploring.⁴⁹ We are aware of a single study that compared serum cortisol levels in nucleoside-analogue reverse-transcriptase inhibitor-treated and naive HIV-infected patients, excluding therefore the effect of PI, and no difference was found between the 2 groups.⁵⁰

SUMMARY

Clinically evident adrenal insufficiency constitutes an uncommon event in HIV infection. When present, it usually involves patients in advanced stages of the infection, with cytomegalovirus disease or under treatment with drugs that interfere with cortisol metabolism. Even in this setting, the rate of adrenal insufficiency is probably lower than 5%. However, adrenal reserve may be marginal, as suggested by a subnormal response to corticotropin stimulation tests in many cases, and this diagnosis should be kept in mind whenever a patient who undergoes stressing conditions, such as infection or trauma, develops hypotension, profound weakness, untreatable fever, or electrolyte abnormalities. Basal hypocortisolemia, even asymptomatic, should be treated with lifelong substitutive glucocorticoids, but cortisol supplementation for only very stressing situations (eg, surgery) is probably sufficient in patients with normal serum cortisol levels and corticotropin hyposponsiveness.

Hypercortisolemia without clinical features suggestive of Cushing syndrome is frequent enough to not warrant a complete workup of adrenal disease. Antiretroviral-associated lipodystrophy is usually distinguishable from Cushing syndrome on a clinical basis. However, if lipodystrophy coexists with marked hypercortisolemia, measurement of 24-hour free urinary cortisol level and a dexamethasone suppression test would clarify this issue. The extent to which alterations in the HPA axis are related to these patients' immune dysfunction, as well

as the possible changes induced by antiretroviral treatment, should be further investigated. At present, no intervention for these subclinical abnormalities is likely to be useful.

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