Indian J Med Res 147, February 2018, pp 125-127
DOI: 10.4103/ijmr.IJMR_1087_17

Quick Response Code:

Commentary

Adrenal disorders in people with HIV: The highs and lows

According to the National AIDS Control Organization (NACO), the adult HIV prevalence in India in 2015 was 0.26 per cent, with an estimated 2.2 million people being affected[1]. With the availability of newer, more potent antiretroviral therapy (ART) and its increasing accessibility in many regions of the world, the nature of HIV-AIDS is changing from an illness characterized by an early mortality due to opportunistic infections and malignancies, to that of a chronic disorder with high frequency of insulin resistance, metabolic abnormalities and cardiovascular disease[2].

Different components of the endocrine system are frequently affected by HIV infection. This may occur as a result of infiltration of the affected glands by infections or malignancies, alteration of various hypothalamic-pituitary axes due to immune activation and pro-inflammatory cytokines or the side effects of drugs used for ART. Endocrine manifestations of HIV infection include adrenal dysfunction, hypothyroidism, lipodystrophy and insulin resistance, metabolic syndrome, lipid abnormalities (especially elevated triglycerides and low HDL-cholesterol), impaired glucose tolerance and diabetes, hypogonadism (both males and females) and osteoporosis[3]. Of these, changes in the hypothalamic-pituitary-adrenal (HPA) axis are among the most frequent abnormalities.

In individuals with HIV infection, involvement of the HPA axis leads to a wide variety of clinical manifestations. At one end of the spectrum is adrenal insufficiency (AI), resulting from involvement and destruction by HIV, opportunistic infections or malignancies, which may involve either the adrenal glands or the hypothalamus/pituitary[4]. However, more frequently encountered is an elevation in serum cortisol and adrenocorticotropic hormone (ACTH), which occurs due to numerous complex mechanisms[5]. These include activation of the HPA axis due to HIV infection itself or pro-inflammatory cytokines [including interleukin (IL)-1β, IL-2, IL-6 and tumour necrosis factor-alpha (TNF-α)], peripheral increase in the conversion of cortisone to cortisol due to activation of 11-β hydroxysteroid dehydrogenase type 1 in the adipose tissue or decrease in cortisol metabolism[6].

Some of the drugs used for ART, particularly protease inhibitors such as ritonavir, lead to decreased metabolism of endogenous and exogenously co-administered glucocorticoids, resulting in an iatrogenic Cushing's syndrome, with secondary AI when glucocorticoids are withdrawn[7-9]. A small proportion of patients with HIV infection may develop peripheral glucocorticoid resistance, with elevated levels of cortisol and ACTH, but clinical features of AI[7]. These patients have abnormal glucocorticoid receptors with reduced affinity due to the effect of HIV or cytokines. While most patients with elevated cortisol do not need any treatment, those with AI require continuous therapy with glucocorticoids and mineralocorticoids.

AI usually manifests when >80-90 per cent of the adrenal glands are destroyed. In addition to the stage of the illness, the frequency of AI also varies depending on the method of assessing adrenal function and criteria used for its diagnosis. The disorder is most commonly reported in patients with advanced disease and multiple comorbidities, with a frequency ranging from 10 to 20 per cent[10,11]. Due to improvements brought about by highly active antiretroviral therapy (HAART), the prevalence of AI has decreased[6]. The adrenal glands can be affected by HIV itself or, more commonly, by opportunistic infections with cytomegalovirus (CMV), *Mycobacterium avium-intracellulare* and *M. tuberculosis*, and fungal infections (such as *Histoplasma* and *Cryptococcus*), *Pneumocystis carinii* and *Toxoplasma gondii*[4]. Of these, CMV infection is

the most common aetiology[6]. In earlier reports, before the advent of ART, HIV-infected patients with CMV infection had adrenal gland involvement in nearly 80 per cent of cases[12]. Certain drugs used in the treatment of comorbidities associated with AIDS can directly inhibit adrenal steroidogenesis. For example, the antifungal agent ketoconazole can block multiple steps in the adrenal steroid biosynthesis pathway. Other drugs, such as rifampicin, lead to induction of hepatic steroid metabolism. Of practical interest is the fact that many clinical features of AI (anorexia, dizziness, weight loss, abdominal pain, hypotension and hyponatremia) overlap with those frequently present in HIV-infected individuals without this disorder. Hence, making the diagnosis of AI on clinical grounds alone is difficult.

A study published in this issue by Sharma *et al*[13] provides useful information regarding the frequency and risk factors of AI. The investigators studied 359 Indian patients with HIV attending an ART clinic in north India. The patients had no serious comorbidities requiring hospitalization and >90 per cent of patients had CD4 T-cell count of >200 cells/µl. Despite their relatively preserved immune status, nearly a quarter of the patients were diagnosed to have AI on testing with an ACTH stimulation test. These included all patients (3% of those tested) who had a very low morning cortisol (<6 µg/dl) and more than half of the patients with low cortisol (7-11 µg/dl). AI was present in 24.23 per cent patients in this study. Such high frequency is usually reported in severely immunocompromised HIV patients with multiple comorbidities[5,10,11]. A possible reason for this may be the non-availability of the standard aqueous ACTH preparation in India, and hence, the use of a modified porcine gel preparation for testing stimulated cortisol[14]. The ACTH stimulation test using this gel preparation has not been rigorously validated[15]. In addition, the concurrent use of drugs, such as rifampicin, phenytoin and ketoconazole, which may decrease cortisol levels, was not reported. Since plasma ACTH levels and adrenal size were not ascertained, the site of the lesion (adrenal or hypothalamus/pituitary) and the aetiology of AI remained unclear. No specific risk factors for AI could be ascertained in this study, other than a decreased morning cortisol. No patient with AI was hyperpigmented or had an episode of acute adrenal crisis, and CD4 T-cell counts were similar among those with or without AI.

In the current study, one-fifth of patients had a morning plasma cortisol >18 µg/dl. However, in the absence of cortisol levels from a control healthy population and simultaneously measured ACTH, it is difficult to interpret these values. As discussed earlier, elevated levels of cortisol have been frequently reported in studies on patients with HIV infection[10], including a small report from Chandigarh[16].

Which patients with HIV infection should be tested for AI and how should we clinically manage patients with an abnormal cortisol? Previous studies, as well as the current study, do not provide many clinical clues as to which patients should be targeted and how frequently should they be tested. A morning serum cortisol is simple test to perform, but is useful only if it is very low (<6 µg/dl) or >18 µg/dl. However, diagnostic low values were only present in three per cent of patients tested in the current study. Thus, for the majority of patients with HIV, an ACTH-stimulated cortisol value will be required to make a definitive diagnosis of AI. However, in view of the cost of this test, non-availability of the standard aqueous ACTH in India and inadequate validation of ACTH stimulation test using porcine ACTH gel, it would be prudent to conduct the test only for patients with advanced disease and comorbidities, symptoms and signs consistent with AI (especially hyperkalaemia) and those receiving drugs which may impair adrenal function or decrease cortisol action. Regarding management, all symptomatic patients with a morning plasma cortisol <5 µg/dl or ACTH-stimulated cortisol <18 µg/dl, especially if associated with elevated plasma ACTH, should be treated with daily oral hydrocortisone or prednisolone and fludrocortisone. Alternatively, asymptomatic patients with stimulated serum cortisol near to normal (15-18 µg/dl) could be carefully followed without daily replacement, with advice to take stress doses of glucocorticoids whenever required.

In summary, there is a wide spectrum of alterations in HPA axis in patients with HIV infection, ranging from hypercortisolaemia to AI. The current study[13] provides useful information on the frequency of AI in Indian patients with HIV infection. However, the high frequency of AI noted in this study requires further confirmation. Additional research is required to delineate the participants who should be targeted for testing and to determine which patients with AI would benefit most from continuous replacement with glucocorticoids.

***Conflicts of Interest*:** None.

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Received June 29, 2017

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