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Research Article

Prevalence aetiology and clinical spectrum of abnormal adrenal functions in human immunodeficiency virus infection

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Abstract:

Aim: To find Prevalence, Aetiology and Clinical Spectrum of abnormal adrenal functions in Human Immunodeficiency Virus infection. To diagnose and treat adrenal dysfunction in various stages of HIV infection and see the response to treatment if required.

Material & Methods: 100 patients with HIV infection being admitted to our hospital was evaluated for abnormal adreno cortical functions. Immune dysfunction was assessed with CD4 count. Statistical tests (chi squared test) were applied to the collected data to find out any significant correlations.

Results: The overall prevalence of adrenocortical abnormalities in HIV positive patients was 14% which included hypocortisolemia in 3% and hypercortisolemia in 11% of patients. Frequency of hypocortisolemia was significantly associated with presence of HIV infection with opportunistic infections and low CD4 counts (less than 50cells). In patients having hypercortisolemia, ONDST (Over night dexamethasone suppression test) was done and it showed reduction of serum cortisol to expected level (suppressed to <1.8 mcg/dl). Adjustment disorders and drugs mainly efavirnz more than nevirapine was incriminated in the same.

Conclusion: HPA axis dysfunction is frequently encountered in HIV infected patients. The commonest dysfunction was hypercortisolemia probably due to elevated cytokines. Hypercortisolemia is a feature of early stage HIV infection. The likelihood of adrenal insufficiency increases as the disease advances and patient enters a more immunocompromised state. Hypocortisolemia should be treated regardless of the existence of associated symptoms. Hypercortisolemia in the absence of features of Cushing's syndrome is common and should not promote treatment or specific studies.

Keywords: HIV Infection, Adrenal dysfunctions, antiretroviral therapy.

Introduction

Hypothalamo-Pituitary Adrenal axis in HIV patients:

The basal and stress-related homeostasis[1] are maintained by peripheral branches of stress system which includes HPA axis and the systemic sympathetic/adrenomedullary (sympathoadrenal) system. Stress response is the biologic, physical or psychologic activationi of the stress system, including the HPA axis. The primary mediator of stress response is corticotropin-releasing hormone (CRH), a 41-amino acid peptide that plays a central role in coordinating the HPA axis and the systemic response to stress, [2] acting as the main physiologic ACTH stimulus.[3] ACTH leads to secretion of cortical and other adrenal steroids, such as dehydroepiandrosterone (DHEA) and aldosterone.

The evaluation of AIDS and HIV infected patients has revealed varied involvement of HPA axis ranging from High or normal[4,5] basal cortisol levels and high,[5,6] low[6] or normal[7] ACTH plasma levels. Depending on stages of HIV infection, derangement of HPA axis ranging from subclinical alterations in cortisol levels to frank adrenal insufficiency has been observed during evaluation using CRH and/or ACTH.

Pathogenesis of HPA Axis Dysfunction:

Hypercortisolemia in AIDS patients*:* A large number of AIDS patients has been documented with elevated basal cortisol levels,[7] which has been likely attributed to a chronic stress-related shift of steroid production from adrenal androgens toward cortisol. Alternative explanation was the increasing plasma concentrations of cortisol-binding globulin (CBG) observed with the the disease progression.[8] The cytokines IL-1β and IL-6 has been implicated to direct stimulation of the adrenal glucocorticoid synthesis pathway leading to High cortisol levels associated with low ACTH in HIV infection. Concomitant high levels of ACTH and cortisol often observed in these patients suggest a stimulatory effect of these cytokines on CRH release. Recent data suggest the likely role of the HIV envelope protein gp-120 in inducing HPA axis hyperactivity.[9] The relevance of observed high cortisol levels,(beneficial, due to the anti-inflammatory properties, or deleterious,due to its immunosuppressive properties), remains unclear. However, as in other forms of acute or chronic illness, it might reflect an adaptive, albeit allostatic, stress response.

Glucocorticoid resistance: A subset of AIDS patients , probably due to altered cytokine action have clinical manifestations indicative of adrenal insufficiency (fatigue, hypotension, skin and mucosal pigmentation) along with a biochemically hyperfunctioning HPA axis characterized by hypercortisolemia and a moderate increase of ACTH.[10] A state of partial glucocorticoid resistance state as indicated by reduced glucocorticoid affinity to its ligand and the glucocorticoid receptor (GR) number was increased in these patients. A similar glucocorticoid resistance state is present in glucocorticoid resistant asthma type 2 patients due to specific cytokine pattern consisting mainly of elevated IL-2 and IL-4 and also exhibit reduced glucocorticoid affinity to its ligand, closely resembling the glucocorticoid resistance state found in AIDS patients.[11] Another possible explanation for the relative glucocorticoid resistance of these patients is the increased expression of the GRβ splicing variant of the glucocorticoid receptor relatively to the expression of the GRα isoform.[12] The GRα isoform is the main mediator of glucocorticoid activity and the GRβ isoform is known to inhibit GRα action. Thus, the increased intracellular proportion of GRβ isoform leads to a decreased glucocorticoid effect.[13,14]

Adrenal androgens: HIV-infected patients, exhibits a shift of steroid metabolism from adrenal androgens and 17-deoxysteroids towards cortisol[15], similar to pattern of shunting away from adrenal androgens towards cortisol observed in acute and chronic illness, as well as in malnutrition among non-HIV patients.[16] The high cortisol and reduced DHEA may be due to a decreased adrenal 17,20-lyase activity.[17] In a study investigating ovarian and adrenal function in HIV-infected women with AIDS, significantly reduced DHEA and increased cortisol responses to ACTH were demonstrated. The ratio of the DHEA to cortisol response (an index of shunting away from adrenal androgen secretion and towards increased cortisol production) was significantly decreased in women with AIDS-related wasting syndrome compared to control subjects. In contrast, the same study demonstrated intact ovarian androgen responsiveness to HCG stimulation.[18,19]

1. 2.

Altered steroid production and immune status in AIDS: Plasma DHEA concentrations correlate positively with the CD4 cell count.[20] A negative linear correlation between CD4 count and cortisol levels,[21] is demonstrated by some studies, while others do not.[20] .The pattern of high cortisol/low DHEA-S levels is associated with HIV illness markers, including viral load, and that this finding carries a negative prognostic value.[21] A reduced DHEA-S/cortisol ratio is associated with a deterioration of the immune status of HIV-infected patients due to a shift from a Th1- to a Th2-driven immune response. Thus, AIDS patients with diminished DHEA-S levels display an excessive production of cytokines by Th2 cells (IL-4, IL-5, IL-6, IL-10) and a suppression of cytokines (IL-2, IFN-γ, IL-12) secreted by Th1 cells, the latter apparently negatively affecting the clinical course of the disease. DHEA-S supplementation appears to restore cytokine production in animal models.

1. 2. 3. 4. 5.

Adrenal Insufficiency in HIV-Infected Patients: Adrenal function is compromised by action at several levels of HPA axis in patients with HIV and concomitant opportunistic infections. Both adrenal and pituitary infection leads to subclinical or overt adrenal insufficiency with the progression towards AIDS.[22] Direct HIV infection of adrenals / adrenal neoplasm (Kaposi's sarcoma, lymphoma) can impair adrenal function. Anti-adrenal antibodies detected in HIV patients, probably reflecting thymic dysfunction or an epiphenomenon linked to nonspecific B-cell activation.[23] Medications implicated in adrenal function include, ketoconazole inhibiting steroidogenesis, rifampin and phenytoin enhancing steroid metabolism and may unmask adrenal insufficiency in patients with a decreased adrenal reserve.[24-26] Megestrol acetate exhibits intrinsic glucocorticoid activity and prolonged administration can induce secondary adrenal insufficiency and abrupt withdrawal can precipitate acute adrenal insufficiency

Corticotropin-releasing hormone (CRH) is secreted in response to physiologic and psychologic stressors in pulsatile fashion in healthy individuals by the hypothalamus, as well as circadian stimuli, which then leads to ACTH secretion from the anterior pituitary. In response to ACTH, cortisol is released by the adrenal cortex, leading to alterations in cellular metabolism throughout the body. Cortisol also provides negative feedback to the hypothalamus and pituitary to limit secretion of CRH and ACTH.

Material and Methods

Material

100 patients with HIV infection being admitted to our hospital was evaluated for abnormal adreno-cortical functions with basal Serum Cortisol.

Inclusion Criteria

Age more than 18 years.

Triple enzyme linked immunosorbent assay (ELISA) proven HIV infection.

Exclusion Criteria

Patients with prior history of adrenal dysfunction.

Patients who are under treatment for adrenal dysfunction.

Methods

History pertaining to adrenocortical dysfunction and symptoms and features suggestive of opportunistic infections was taken.

Complete physical examination was carried out. Clinical features suggestive of adrenal insufficiency and features of opportunistic infections were looked for.

Serum cortisol was measured by ELIZA. In cases with high basal serum cortisol, stress response was excluded by ONDST (Overnight dexamethasone suppression test).

Immune dysfunction was assessed with CD4 count.

Appropriate specific investigations were done to confirm the presence/absence of opportunistic infections and other AIDS defining illness.

Statistical tests (chi squared test) were applied to the collected data to find out any significant correlations.

Results and Discussion

This study included 100 patients who were admitted at our tertiary care hospital. Out of those 100 patients 19 (19%) were of age group less than 30, 51 (51%) were of age group between 30-40 and rest 30 cases (30%) were of age greater than 40 yrs. The youngest was of age 23 yrs. and oldest was having age of 52 yrs. Out of 100 patients six (6%) had CD4 count < 100 cells, 70 (70%) had CD4 count between 100-300 cells and 24 (24%) had CD4 >300 cells.

It was observed that out of 100 patients three (3%) had serum cortisol level <50 ng/ml, 11(11%) had serum cortisol level >230 ng/ml and 86(86%) had serum cortisol within the normal range i.e. (50-230 ng/ml) (Fig 1).

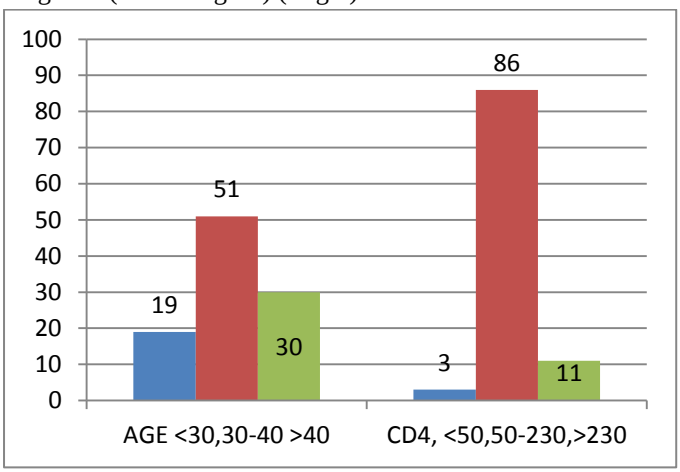


Figure 1

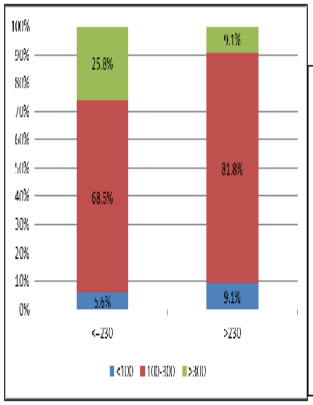
A correlation analysis was done between the serum cortisol and the CD4 count. It was observed that both didn't have any statistically significant correlation (P value of 0.651). The serum cortisol across different cortisol groups were compared and it was found that in CD4 level less than 100cells the mean cortisol level was 110.83ng/ml, CD4 100-300 cells mean serum cortisol 158.25ng/ml and CD4 > 300 cells the mean serum cortisol level was 142.67 ng/ml . It was observed that no significant difference in mean cortisol level existed across different CD4 groups with P value of 0.145 as show in **Table 1.**

S Cortisol	CD4				P value	Significance
	<100	100-300	>300	Total		
S Cortisol Mean ±± Std. Deviation	110.83 ± 94.34	158.25 ± 62.16	142.67 ± 50.38	150.37	0.145	Not Significant

There is no statistically significant difference in Mean Serum Cortisol across different CD4 Groups (P value >0.05).

It was further observed that patients with CD4 less than 100 cells had the lowest mean serum cortisol level.

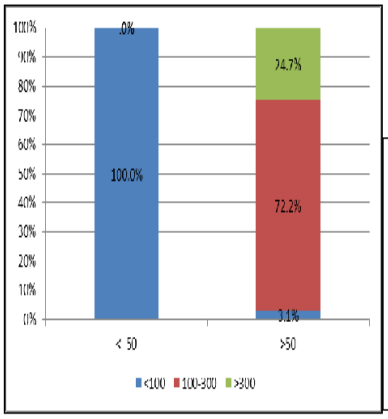
A comparison was made between serum cortisol levels in patients with CD4 count less than 100 cells, 100-300 cells and greater than 300 cells. It was observed that in patients with CD4 level less than 100 cells, five (5.6%) patients had serum cortisol less than 230ng/ml and out of which three had cortisol level less than 50ng/ml. One (9.1%) patient had cortisol level greater than 230ng/ml. In the group with CD4 count between 100-300 cells 61(68.5%) patients had serum cortisol less than 230ng/ml but none had serum cortisol level less than 50ng/ml, i.e. all patients were in eucortisolemic level. It was observed that nine (81.8%) patients had serum cortisol level greater than 230ng/ml i.e. hypercortisolemia. In patients with CD4 count greater than 300 cells it was observed that 23(25.8%) patients had serum cortisol level in eucortisolemic level i.e. between 50-230 ng/ml. One (9.1%) had serum cortisol greater than 230ng/ml. There was no statistically significant difference in the distribution of serum cortisol level greater than 230ng/ml and CD4 count with a P value of 0.452 as depicted in figure 2.



There is no statistically significant difference in the distribution of S Cortisol >230 & and CD4 Count (P value >0.05)

Figure 2

In comparison of patients with serum cortisol less than 50ng/ml it was noticed that all patients had CD4 count less than 100 cells and it was observed to have a statistically significant correlation between patients having CD4 count less than 100 cells and patient having cortisol level less than 50 ng/ml. The P value was less than 0.001 as depicted in figure 3.



There is statistically significant difference in the distribution of S CORTISOL <50 & and CD4 count. P value <0.001)

Figure 3

Out of 100 patients 28 (28%) patients were not on ART, rest i.e. 72 (72%) were on ART. Out of 28 patients not on ART it was observed that 27(30.3%) had serum cortisol normal range (50-230ng/ml). One patient had cortisol level greater than 230 ng/ml .

Out of the 72(72%) patient on ART, one (9.1%) patient on 3 drugs stavudine, lamivudine and nevirapine (SLN) had serum cortisol level greater than 230ng/ml. Of patients on stavudine, lamivudine, nevirapine and septran (SLNP) one (9.1%) patient had serum cortisol level greater than 230ng/ml. Patients on SLNP along with azithromycin and fluconazole (AF) it was observed that two (66.7%) cases had serum cortisol level less than 50ng/ml and no patients had serum cortisol greater than

230ng/ml .

Out of 29(29%) patient on zidovudine, lamivudine and nevirapine(ZLN), six (54.5%) patient had serum cortisol level greater than 230ng/ml and no patient had cortisol level less than 50ng/ml. 31(31%) patients received ZLN and septran (P), out of which two (18.2%) had hypercortisolemia. Patients on ZLNPAF one (33.3%) had serum cortisol level less than 50ng/ml. It was observed that there was a statistically significant correlation between the drug usage and cortisol levels, both hypo and hypercortisolemia.

It was observed that out of 11 cases of serum cortisol level >230 ng/ml, five cases were subjected to ONDST and it was found out that post ONDST the level of serum cortisol showed reduction in cortisol level to less than 1.8 mcg/dl . Psychiatric evaluation was done in those patients for adjustment disorder. It was noticed that in those patient after counseling and on further follow up there was reduction in serum cortisol levels by expected levels substantiating that stress was the cause of raise in cortisol. It was also noticed that the rise in serum cortisol were also due to ART usage. It has been found that NNRTI especially efavirenz, more than nevirapine has been shown to be associated with high serum cortisol level and in stable patients over a period of time along with ART usage the level of serum cortisol has been increased. It was noticed that values had normalized on modification of ART.

The finding of high cortisol in patients of AIDS has been seen in different studies even though prevalence of hypocortisolemia has been reported more. The study conducted by Uma Sinha et al in Indian Journal of Endocrinology and Metabolism; Oct-Dec 2011:15(4) are in accordance with our study where we found higher prevalence of hypercortisolemic rather than hypocortisolemic patients.

The ONDST test was not performed in rest of patients as they were asymptomatic and had no symptoms, signs or clinical evidence suggestive of hypercortisolemia.

Studies conducted by Vichit Prasanthai et al.[28] Prevalence of adrenal insufficiency in critically ill patients with AIDS in J Med Assoc Thai 2007:90(9):1768-74; in 26 patients showed adrenal insufficiency more prevalent in AIDS patients. The study also showed prevalence of mycobacteriosis as common cause along with CMV.

Studies also observed a significant correlation between serum cortisol and drugs. It has been observed that ketoconazole (by decreasing steroidogenesis), rifampicin (by enhancing cortisol metabolism) causes decrease in cortisol level.

The infection per say or the usage of drug, rifampicin was the probable explanation for adrenal insufficiency. Rifampicin induces the activity of cytochrome P-450 enzymes and thus increases the metabolism of cortisol. HIV may also decrease the secretion of cortisol from adrenal glands via the effects of cytokines like tumor necrosis factor (TNF). TNF is produced by macrophages which are stimulated by HIV infections. It impairs corticotrophin-releasing hormone, ACTH, and adrenal cortisol synthesis. The plasma from patients in setting of critical illness contains mediators that impair the synthesis of corticosteroids. It has also been noticed that a functional or relative adrenal insufficiency may be responsible for hypoadrenalism which can occur without obvious structural defect in HPA axis in some patients with acute iiness. Even though the cortisol is high, it is insufficient to control inflammatory responses. Treatment with supplementation of corticosteroids may be beneficial.

In this study it was observed that three patients (3%) had serum cortisol level <50ng/ml, and it was observed that all patients were terminally ill with CD4 counts <50cells. It was observed that the two patients had tuberculosis and one had other opportunistic infections (PCP). The cause of adrenal insufficiency was infection per say and the rifampicin based ATT. It was also observed that all the three cases had CD4 counts less than 50 cells/mcl.

Conclusion

HPA axis dysfunction is usually encountered in HIV infected patients. The commonest dysfunction was hypercortisolemia probably due to elevated cytokines. Hypercortisolemia is a feature of early stage HIV infection. The likelihood of adrenal insufficiency increases as the disease advances and patient enters a more immunocompromised state.

The overall prevalence of adrenocortical abnormalities in HIV positive patients was 14% which included hypocortisolemia in 3% and hypercortisolemia in 11% of patients.

Frequency of hypocortisolemia was significantly associated with presence of HIV infection and low CD4counts (less than 50cells). Presences of opportunistic infections, tuberculosis were mostly responsible for low serum cortisol levels. Hypocortisolemia should be treated regardless of the existence of associated symptoms.

In patients having hypercortisolemia, ONDST was done and it showed reduction of serum cortisol to expected level (suppressed to <1.8 mcg/dl). Adjustment disorders and drugs mainly efavirnz more than nevirapine was incriminated in the same. Thus we conclude hypercortisolemia in the absence of features of Cushing syndrome is common and should not promote treatment or specific studies.

Our study showed more prevalence of hypercortisolemia and it was seen more in early HIV infection. The prevalence of hypocortisolemia was more in late advanced stages with low CD4 counts. The incidence in this study was less compared to hypercortisolemia which has been supported by other studies as well. Drugs were found to have significant correlation with cortisol level in this study in both hypo and hypercortisolemia.

Drawbacks of the study:

The study group had only few cases of advanced cases with CD4 counts below 100cells. Hence the prevalence of hypocortisolemia might have been underestimated. Hence a larger study group with more subset of advanced cases will be required to assess the prevalence.

Recommendations:

1. As adrenocortical axis is frequently involved in HIV infection, the adrenal test should be done in all patients with early HIV infection and advanced disease.
2. All patients with hypercortisolism and early HIV infection to be referred to psychiatrist for psychoanalysis.
3. Patients with hypercortisolism need to undergo ONDST only if they have symptoms, signs or clinical evidence of cushing's syndrome, as majority of them will not require treatment except modification in ART or psychotherapy.
4. In early stages of HIV infection, ONDST rather than basal serum cortisol assay to be preferred as it will obviate the stress and other factors causing increased serum cortisol levels.
5. All patients with hypocortisolism need to be treated irrespective of whether they have clinical signs or not.

Competing Interests

The authors declare that they have no competing interests.

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