ASSESSMENT OF ADRENAL DYSFUNCTION IN PATIENTS WITH HIV INFECTIONS

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CERTIFICATE

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CONTENTS

INTRODUCTION

The adrenal gland is frequently involved in patients infected with human immunodeficiency virus (HIV). Although clinical manifestations of adrenal dysfunction are uncommon in patients infected with HIV, subclinical functional abnormalities of the hypothalamic - pituitary - adrenal axis are frequent[1]. Patients with acquired immuno deficiency syndrome are found to have increased basal cortisol and reduced stimulated cortisol release. This imbalance may be related to progression of the infection by inducing a shift from T(H)1 to T(H)2 immunologic responses. Also 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.

Patients with AIDs are also at risk of acquiring opportunistic infections like tuberculosis, cytomegalovirus infections etc, which may involve adrenal gland and result in adrenal hypofunction. Cortisol levels are also subject to variations in HIV infected patients who are on antibiotics such as ketoconazole, rifampicin, etc.

Taking into consideration the various factors which alter the HPA axis and plasma cortisol levels, the study was conducted to assess the adequacy of function of the HPA axis by estimation of basal cortisol level, since a basal cortisol value >15 µg / dl invariably indicates an intact HPA axis[2]. Adrenal dysfunction also could contribute to morbidity and mortality in HIV infected patients.

AIM OF THE STUDY

Assessment of adrenal dysfunction in patients with HIV infections.

MATERIALS AND METHODS

Study design

Prospective, cross - sectional study.

Subjects

Patients admitted in medical wards of Government General Hospital, Chennai, who were detected to have HIV infection (HIV-1 and HIV-2) by ELISA were enrolled in the study.

The study group consisted of 61 patients (45 males, 16 females). The control group was formed by age and sex matched 20 normal individuals.

Informed consent was obtained from patients and controls.

All patients tested positive for HIV infection by ELISA over 12 years of age were included in the study.

Exclusion Criteria

1. Patients who were concurrently taking any of the following drugs:

   Phenytoin

   Rifampicin

   Ketoconazole

Corticosteroids

Oral contraceptive pills

2. Pregnancy
3. Liver disease

METHODOLOGY

Detailed history, symptoms and signs of adrenal hypofunction were noted[3]. All patients were completely examined and routine urine and blood investigations were taken.

Clinical evaluation of adrenal insufficiency included the following symptoms.

* Fatigue and postural dizziness

* Gastrointestinal symptoms:

nausea, vomiting

diarrhoea

abdominal pain

constipation

Measurement of blood pressure to detect postural hypotension (defined as a postural decrease from the supine to standing position of atleast 20 mmHg of systolic pressure or 10

mmHg of diastolic pressure, within 3 minutes of standing up).

Estimation of serum sodium, serum potassium, blood glucose and eosinophil count was done in all patients as part of evaluation of adrenal insufficiency. The patients were staged in accordance to WHO guidelines and the nature of concurrent diseases or infections were noted.

Estimation of serum cortisol:

Serum cortisol was estimated by competitive immunoenzymatic colorimetric method (DiaMetra kit).

Principle : Cortisol (antigen) in the sample competes with horseradish peroxidase - cortisol (enzyme - labeled antigen) for binding on to the limited number of anti - cortisol (antibody) sites on the microplates (solidphase).

After incubation, the bound free separation was performed by a simple solid - phase washing.

The enzyme substrate (H_2O_2) and the TMB - substrate (TMB) were added. After an appropriate time had elapsed for maximum colour development, the enzyme reaction was stopped and the absorbances were determined.

Cortisol concentration in the sample was calculated based on a series by a set of standards. The colour intensity was inversely proportional to the cortisol concentration in the sample.

Detection of HIV Infection:

The detection of HIV infection was done by ELISA (Enzyme Linked Immuno Sorbent assay). The kit contains antigens for both HIV-1 and HIV-2. These kits use both natural and receombinant antigens.

CD4 cell count:

CD4 cell count was done by flow cytometry (Becton and Dickinson equipment). The FACS count method was used and laser principle technique was applied in it.

ACTH Stimulation test:

Screening with ACTH stimulation test for all patients would have been ideal. The short Synacthen test was done only on those patients with basal cortisol levels less than 15 µg / dl since a value of more than 15 µg / dl invariably indicates an intact HPA axis. The major deterrent to subjecting every patient to this test was resources crunch. The test involved intravenous administration of 250 mcg of tetracosactrin (Synacthen), comprising the first 24 aminoacids of normally secreted ACTH 1 - 39[4]. Plasma cortisol levels were measured at 0 and 30 minutes after Synacthen administration, and a normal response defined by a peak plasma cortisol level of more than 19 µg / dL (525 nmol/L)[5].

STATISTICAL ANALYSIS

Mean basal plasma cortisol levels were compared between study and control groups. Statistical significance of the clinical features of adrenal dysfunction were analysed using

student's t-test. Correlation between cortisol levels and variables like serum sodium, serum potassium, blood glucose and eosinophil count were done using Pearson's correlation method.

REVIEW OF LITERATURE

HIV AND ADRENAL INSUFFICIENCY

The adrenals are frequently involved in patients with acquired immunodeficiency syndrome (AIDS); adrenalitis may occur after infection with CMV or atypical mycobacterium, and Kaposi's sarcoma may result in adrenal infiltration. The onset is often insidious,[6] but if tested, over 10% of patients with AIDS demonstrate a subnormal cortisol response following a short Synacthen test. Adrenal insufficiency may be precipitated through the concomitant administration of appropriate anti-infectives such as ketoconazole (inhibits cortisol synthesis) or rifampicin (increases cortisol metabolism). Rarely, patients with AIDs and features of adrenal insufficiency are found to have elevated circulating ACTH and cortisol concentrations that are not suppressed normally by lowdose dexemathasone administration. This is thought to reflect an acquired form of glucocorticoid resistance related to reduced glucocorticoid receptor affinity, but the underlying cause remains unknown[7].

MYCOBACTERIUM TUBERCULOSIS

Patients with HIV are at greater risk of reactivating latent infection (7-10% annual risk compared to 5-10% lifetime risk in an HIV -uninfected individual), of acquiring TB from an open contact (10-20% compared to 5-10%), of developing progressive primary disease (30-40% compared to 5-10%) and of developing disseminated, miliary or extrapulmonary disease (>60% compared to <25%). Patients are also at risk of developing

second episodes of TB from exogenous infection as demonstrated by isolate typing.

In addition to the devastating effect of HIV on TB, M. tuberculosis affects HIV adversely with enhanced replication and acceleration of the disease process.

The clinical presentation depends mainly on immune function. When the CD4 count is >200 cells / mm^3, disease is more likely to be reactivated upper - lobe open cavitatory disease; as immunosuppression increases, miliary, atypical pulmonary and extrapulmonary (especially pericardial, abdominal and meningeal) TB become progressively more common, as does mycobacteraemia. Constitutional symptoms of fever and night sweats are usually present. Approximately 5% of patients with smear positive pulmonary TB have normal chest radiographs. Confirmation of the clinical diagnosis when the immune system is relatively preserved is by sputum microscopy (Ziehl - Neelsen and auramine stains) and radiometric culture. Rapid diagnostic tests involving nucleic acid amplification are being employed more frequently for sputum analysis in smear - negative pulmonary cases, in culture speciation and for rifampicin resistance testing. In patients with late - stage HIV and low CD4 counts, diagnosis in usually made by mycobacterial culture of blood, bone marrow or tissue.

Tuberculous Addison's disease results from hematogenous spread of the infection from elsewhere in the body, and extra adrenal disease is usually evident[8] The adrenals are initially enlarged with extensive epithelioid granulomas and caseation, and both the cortex and the medulla are affected. Fibrosis ensues, and the adrenals become normal or smaller in

size with calcification evident in 50% of cases.

THE HYPOTHALAMIC - PITUITARY - ADRENAL AXIS[9]

Cortisol is the predominant corticosteroid secreted from the adrenal cortex in humans. In a healthy, unstressed person, cortisol is secreted according to a diurnal pattern under the influence of corticotropin released from the pituitary gland. Corticotropin secretion, in turn, is under the influence of hypothalamic corticotropin - releasing hormone (Fig.A), and both hormones are subject to negative feedback control by cortisol itself. Circulating cortisol is bound to corticosteroid - binding globulin, with less than 10 percent in the free, bioavailable form. With severe infection, trauma, burns, illness, or surgery, there is an increase in cortisol production by as much as a factor of six that is roughly proportional to the severity of the illness (Fig. B). Diurnal variation in cortisol secretion is also lost. These effects are due to increased production of corticotropin - releasing hormone and corticotropin and a reduction in negative feedback from cortisol[10]. Stimulation of the hypothalamic - pituitary - adrenal axis in this context is caused by elevated levels of circulating cytokines, among other factors[11].

Adrenal responsiveness to exogenous corticotropin is normally maintained during acute illness. In addition, during critical illness, levels of corticosteroid - binding globulin decrease rapidly, leading to increased levels of circulating free corticosteroids. Levels of free cortisol may also increase at sites of inflammation owing to the cleavage of corticosteroid - binding globulin by neutrophil elastase, an effect that liberates cortisol. In addition to having systemic actions, inflammatory cytokines can increase tissue cortisol

levels through changes in peripheral cortisol metabolism and can increase the affinity of glucocorticoid receptors for cortisol. These changes in cortisol action appear to be important adaptive mechanisms regulating the inflammatory response.

During severe illness, many factors, can impair the normal corticosteroid response (Fig.C). These factors include preexisting conditions affecting the hypothalamic - pituitary - adrenal axis but, corticosteroid insufficiency can also occur during the course of acute illness. Responses involving corticotropin - releasing hormone and corticotropin can be impaired by head injury, central nervous system depressants, or pituitary infarction. Adrenal cortisol synthesis can be impaired by multiple mechanisms. The anesthetic agent etomidate and the antifungal agent ketoconazole inhibit the activity of enzymes involved in cortisol synthesis. Adrenal hemorrhage can occur in sick patients, especially those with septicemia and underlying coagulopathy, and adrenal insufficiency can occur when there is extensive destruction of adrenal tissue caused by tumors or infection. The high levels of inflammatory cytokines in patients with sepsis can also directly inhibit adrenal cortisol synthesis.

Object 3

FEATURES SUGGESTING CORTICOSTEROID INSUFFICIENCY

Symptoms

- Weakness and fatigue
- Anorexia, nausea, vomiting
- Abdominal pain
- Myalgia or arthralgia
- Postural dizziness
- Craving for salt
- Headaches
- Memory impairment
- Depression

Findings on physical examination

- Increased pigmentation
- Hypotension (postural)
- Tachycardia
- Fever
- Decreased body hair
- Vitiligo

Features of hypopituitarism

Amenorrhoea

Intolerance to cold

Clinical problems

Hemodynamic instability

Hyperdynamic (common)

Hypodynamic (rare)

Ongoing inflammation with no obvious source

Multiple-organ dysfunction

Hypoglycemia

Laboratory findings

Hyponatremia

Hyperkalemia

Hypoglycemia

Eosinophilia

Elevated thyrotropin levels

CLINICAL FEATURES OF ADRENAL INSUFFICIENCY

Patients with primary adrenal failure usually have both glucocorticoid and mineralocorticoid deficiency. In contrast, those with secondary adrenal insufficiency have an intact renin-angiotensin-aldosterone system. This accounts for differences in salt and water balance in the two groups of patients, which in turn result in different clinical presentations. The most obvious feature that differentiates primary from secondary hypoadrenalism is skin pigmentation, which is nearly always present in primary adrenal insufficiency (unless of short duration) and absent in secondary insufficiency. The pigmentation is seen in sun-exposed areas, recent rather than old scars, axillae, nipples, palmar creases, pressure points, and in mucous membranes (buccal, vaginal, vulval, anal). The cause of the pigmentation has long been debated, but it is thought to reflect increased stimulation of the melanocortin-2 receptor by ACTH itself. In autoimmune Addison's disease there may be associated vitiligo.

The clinical features are related to the rate of onset and severity of adrenal deficiency[12,13]. In many cases, the disease has an insidious onset and a diagnosis is made only when the patient presents with an acute crisis during an intercurrent illness. Acute adrenal insufficiency or an adrenal or Addisonian crisis is a medical emergency manifesting as hypotension and acute circulatory failure. Anorexia may be an early feature, which progresses to nausea, vomiting, diarrhoea, and sometimes abdominal pain. Fever may be present, and hypoglycemia may occur. Patients presenting acutely with adrenal hemorrhage have hypotension; abdominal, flank, or lower chest pain; anorexia; and vomiting. The

condition is difficult to diagnose, but evidence of occult hemorrhage (rapidly falling hemoglobin), progressive hyperkalemia, and shock should alert the clinician to the diagnosis.

Alternatively, the patient may present with vague features of chronic adrenal insufficiency - weakness, tiredness, weight loss, nausea, intermittent vomiting, abdominal pain, diarrhoea or constipation, general malaise, muscle cramps, arthralgia, and symptoms suggestive of postural hypotension. Salt craving may be a feature, and there may be a low grade fever. Supine blood pressure is usually normal, but almost invariably there is a fall in blood pressure on standing. Although adrenal androgen secretion is lost, this is clinically more apparent in women, who may complain of loss of axillary and pubic hair. Psychiatric symptoms may occur in long-standing cases and include memory impairment, depression, and psychosis[14]. Patients may be inappropriately diagnosed as suffering from chronic fatigue syndrome or anorexia nervosa. These features regress upon treatment with replacement corticosteroids.

In secondary adrenal insufficiency associated with hypopituitarism, the presentation may be related to deficiency of hormones other than ACTH, notably LH or FSH (infertility, oligomenorrhea or amenorrhea, poor libido) and TSH (weight gain, cold intolerance). Fasting hypoglycemia occurs because of loss of the gluconeogenic effects of cortisol. It is rare in adults unless there is concomitant alcohol abuse or additional GH deficiency. However, hypoglycemia is a common presenting feature of ACTH or adrenal insufficiency in childhood. In addition, patients with ACTH deficiency present with malaise, weight loss,

and other features of chronic adrenal insufficiency. Rarely, the presentation may be more acute in patients with pituitary apoplexy.

INVESTIGATION OF HYPOADRENALISM

Routine Biochemical Profile

In established primary adrenal insufficiency, hyponatremia is present in about 90% of cases and hyperkalemia in 65%. The blood urea concentration is usually elevated. Hyperkalemia occurs because of aldosterone deficiency and is therefore usually absent in patients with secondary adrenal failure. Hyponatremia may be depletional in an addisonian crisis, but in addition vasopressin levels are elevated, resulting in increased free water retention. Thus in secondary adrenal insufficiency there may be a dilutional hyponatremia with normal or low blood urea. Reversible abnormalities in liver transaminases frequently occur. Hypercalcemia occurs in 6% of all cases and may be particularly marked in patients with coexisting thyrotoxicosis. However, free thyroxine concentrations are usually low or normal but TSH values are frequently moderately elevated. This is a direct effect of glucocorticoid deficiency and reverses with replacement therapy. Persistent elevation of TSH in association with positive thyroid autoantibodies suggests concomitant autoimmune thyroid diseases.

ASSESSING ADEQUACY OF FUNCTION OF THE HYPOTHALAMO-PITUITARY-ADRENAL AXIS

Clinical suspicion of the diagnosis should be confirmed with definitive diagnostic

tests. Basal plasma cortisol and urinary free cortisol levels are often in the low normal range and cannot be used to exclude the diagnosis. However, a basal cortisol value greater than 400nmol/L (15 μg/dl) invariably indicates an intact HPA axis. In practice, rather than waiting for results of insensitive basal tests, all patients suspected of having adrenal insufficiency should have an ACTH stimulation test, although in patients with an Addisonian crisis treatment should be initiated immediately and stimulation tests conducted at a later stage.

The ACTH stimulation test involves intramuscular or intravenous administration of 250 μg of tetracosactrin (Synacthen), comprising the first 24 amino acids of normally secreted ACTH 1 to 39. Plasma cortisol levels are measured at 0 and 30 minutes after ACTH, and a normal response is defined by a peak plasma cortisol level greater than 525 nmol/L (19 μg/dL). This value equates to the fifth percentile response in normal subjects but is assay-dependent, with different cortisol radioimmunoassays giving different results. Incremental responses (i.e., the difference between peak and basal values) are of no value in defining a pass response and should not be used. Response is unaffected by the time of day of the test, and the test can be performed in patients who have commenced corticosteroid replacement therapy provided this is of short duration and does not include hydrocortisone (which would cross-react in the cortisol assay).

TESTS OF PITUITARY-ADRENAL RESPONSIVENESS Stimuli such as insulin-induced hypoglycemia, AVP, and pyrogens induce the release of ACTH from the pituitary by an action on higher neural centers or on the pituitary itself. Insulin-induced

hypoglycemia is particularly useful, because it stimulates the release of both growth hormone and ACTH[15]. In this test, regular insulin (0.05 to 0.1 U/kg body weight) is given intravenously as a bolus to reduce the fasting glucose level to at least 50% below basal. The normal cortisol response is a rise to >500 nmol/L (18 μg/dL). Glucose levels must be monitored during insulin-induced hypoglycemia, and it should be terminated by feeding or intravenous glucose, if subjects develop symptoms of hypoglycemia. This test is contraindicated in individuals with coronary artery disease or a seizure disorder.

Two other tests have been advocated to assess adequacy of function of the HPA axis, but their use in modern clinical practice should be restricted to difficult diagnostic cases. In the overnight metyrapone test, metyrapone is given at 30 mg/kg (maximum 3 g) at midnight and plasma cortisol and 11-deoxycortisol are measured at 8 AM the following morning. In patients with an intact axis, ACTH levels rise after the blockade of cortisol synthesis by metyrapone and a normal result is signified by a peak 11-deoxycortisol value greater than 200 nmol/L (7 μg/dL). The CRH stimulation test has been used to diagnose adrenal insufficiency and, unlike the metyrapone tests, differentiates primary from secondary causes. Patients with primary adrenal failure have high level ACTH levels that rise further after CRH. Conversely, patients with secondary adrenal failure have low ACTH levels that fail to respond to CRH. Patients with hypothalamic disease show a steady rise in ACTH levels after CRH.

HIV VIRUS AND AIDS

The etiologic agent of AIDS is HIV, which belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses.

VIROLOGY PATHOGENESIS

Each virion is spherical in shape; it has a lipid membrane lined by a matrix protein and studded with a glycoprotein (gp 120) and gp 41 spikes surrounding a coneshaped protein core. This core houses two copies of the ss RNA genome and viral enzymes. The virus infects the CD4 cell in a complicated sequence of events involving initial attachment and receptor engagement through the viral gp 120 and the CD4 cell receptor. Free or cell - associated virus is then disseminated widely through the blood with seeding of CNS, spleen, testes, intestinal mucosal lymphoid tissue and latent CD4 cell population, resulting in increasing impairment of cell mediated immunity with consequent susceptibility to opportunistic infections.

NATURAL HISTORY AND CLASSIFICATION OF HIV

Primary Infection

Primary infection is symptomatic in 70-80% of cases and usually occurs 2-4 weeks after exposure. The major clinical manifestations are fever (80%) and erythematous maculopapular rash mainly over the trunk (60%), fatigue (80%), pharyngitis with cervical lymphadenitis (50%), myalgia and arthralgia (50%), headache with retro-orbital pain (40%)

and mucosal ulceration (mouth 20%, genital 10%). This coincides with a surge in plasma HIV RNA levels to >1 million copies / ml (peak between 4 and 8 weeks), and a fall in the CD4 count to 300-400 cells / mm^3 but occasionally to below 200 when opportunistic infections occur.

Symptomatic recovery occurs after 1-2 weeks but occasionally may take up to 10 weeks and parallels the return of the CD4 count and fall in the viral load. In many patients the illness is mild and only identified by retrospective enquiry at later presentation. However, the CD4 count rarely recovers to its previous value.

The appearance of specific anti - HIV antibodies in serum (seroconversion) takes place later 3-12 weeks (median 8 weeks), although very rarely seroconversion may take place after 3 months.

VIROLOGICAL AND IMMUNOLOGICAL PROGRESSION OF HIV INFECTION.

Asymptomatic infection

Asymptormatic infection (category A disease) follows for a variable period, during which the infected individual remains well with no evidence of disease except for the possible presence of persistent generalised lymphadenopathy (PGL; defined as enlarged glands at $\geq$ 2 extra - inguinal sites). At this stage the bulk of virus replication takes place within lymphoid tissue (e.g. follicular dendritic cells). There is sustained viraemia with a decline in CD4 count dependent on the height of the viral load but usually between 50 and 150 cells / year.

Mildly symptomatic disease

Mildly symptomatic disease (category B disease) then develops in the majority, indicating some impairment of the cellular immune system. These diseases correspond to AIDS - related complex conditions but by definition are not AIDS - defining. Included in this category are chronic weight loss, fever or diarrhoea (but not fulfilling criteria for AIDS), oral or vaginal candidiasis, oral hairy leucoplakia, recurrent herpes zoster infections, severe pelvic inflammatory disease, bacillary angiomatosis, cervical dysplasia and idiopathic thrombocytopenic purpura. The median interval from infection to the development of symptoms is around 7 - 10 years.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (category C disease) is defined by the development of specified opportunitic infections, tumours etc.

Common AIDS - Defining Conditions

* Oesophageal candidiasis
* Cryptococcal meningitis
* Chronic cryptosporidial diarrhoea
* CMV retinitis
* Chronic mucocutaneous herpes simplex

* Disseminated Mycobacterium avium intracellulare
* Miliary or extrapulmonary tuberculosis
* Pneumocystis carinii pneumonia
* Cerebral toxoplasmosis
* Kaposi's sarcoma

Definition

The current CDC classification system for HIV infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts. The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories.

Using this system, any HIV - infected individual with a CD4 + T cell count of 200/ μL has AIDS by definition, regardless of the presence of symptoms of opportunistic diseases. Once individuals have had a clinical condition in category B, their disease cannot again be classified as category A, even if the condition resolves; the same holds true for category C in relation to category B.

WHO staging of HIV infection

Clinical group-I

Acute HIV infection

PGL

Asymptomatic

Normal activity

Clinical group-2 (Early stage disease)

Weight loss <10%

Muco-cutaneous problem

Herpes zoster

Recurrent URI

Normal activity

Clinical group-3 (Intermediate disease)

Weight loss <10%

Chronic diarrhoea

Prolonged fever 1 month

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis

Severe bacterial infections

Bed ridden <50% of day (previous month)

Clinical group-4 (Late stage disease)

Definitive or presumptive diagnosis of AIDS

Bed ridden >50% of day (previous month)

1993 Revised Classification System for HIV infection and Expanded AIDs Surveillance Case Definition for Adolescents and Adults			
	Clinical Categories		
CD4 + T cell categories	**A Symptomatic, acute (Primary) HIV or PGL**	**B symptomatic, Not A or C conditions**	**C AIDs - indicator conditions**
> 500/μL	A1	B1	C1
200-499/μL	A2	B2	C2
<200/μL	A3	B3	C3

PGL, progressive generalized lymphadenopathy.

The diagnosis of HIV infection depends upon the demonstration of antibodies to HIV and / or the direct detection of HIV or one of its components.

The standard screening test of HIV infection is the ELISA, also referred to as an enzyme immunoassay (EIA). This solid - phase assay is an extremely good screening test with a sensitivity of >99.5%. Most diagnostic laboratories use a commercial EIA kit that contains antigens from both HIV-1 and HIV-2 and thus are able to detect either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensitivity to newly discovered species, such as group O viruses. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially

reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity.

The most commonly used confirmatory test is the western blot. This assay takes advantage of the fact that multiple HIV antigens of different, well - characterized molecular weight elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the western blot. A negative western blot is one in which no bands are present at molecular weights corresponding to HIV gene products.

While the western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20 to 30% may show one or more bands on western blot. While these bands are usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RNA PCR, the (b) DNA assay, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which is the product of the percent of CD4 + T cells (determined by flow cytometry) and the total lymphocyte count (determined by the white blood cell count (WBC) and the differential percent) has been shown to correlate very well with the level of

immunologic competence.

Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3 to 6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to most guidelines, a CD4 T cell count <350/μL is an indication for consideration of initiating antiretroviral therapy, and a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy. Once the CD4+ T cell count is <200/μL, patients should be placed on a regimen for P. carinii prophylaxis, and once the count is <50/μL, primary prophylaxis for MAC infection is indicated.

CORRELATIONS BETWEEN CD4 COUNT AND HIV-ASSOCIATED DISEASES

> 500cells/mm^3

* Acute primary infection
* Progressive generalised lymphadenopathy
* Recurrent vaginal candidiasis

200-500 cells / mm^3

* Pulmonary tuberculosis
* Herpes zoster

* Oropharyngeal candidiasis
* Oral hairy leucoplakia
* Salmonellosis
* Kaposi's sarcoma

<200 cells / mm^3

* Pneumocystic carinii penumonia
* Mucocutaneous herpes simplex
* Cryptosporidium
* Microsporidium
* Oesophageal candidasis
* Miliary / extrapulmonary tuberculosis

<100 cells / mm^3

* Cerebral toxoplasmosis
* Cryptococcal meningitis

<50 cells / mm^3

* CMV retinitis / gastrointestinal disease

* Disseminated Mycobacterium avium intracellulare

HIV and infectious diseases associated with adrenal insufficiency.

Bacterial	:	Tuberculosis
		Atypical mycobacteria
Fungal	:	Histoplasmosis
		Cryptococcosis
		Coccidioidomycosis
Viral	:	Cytomegalo virus
		HIV

There are several studies of adrenal function in HIV infected patients.

Bansali et al[16]., (2000) observed patients to have elevated basal plasma cortisol levels with abnormal circadian rhythm in some and normal adrenocortical reverse irrespective of the symptoms/signs of adrenal insufficiency. Similar results were obtained in a study done by Mayo et al[1]. (2002). They also found lower serum dehydroepiandrosterone levels in HIV infected individuals.

Abbott et al., (1995)[17] studied patients with advanced HIV disease and found cortisol deficiency to be common, but symptoms of fatigue and postural hypotension, as well as biochemical findings to be poor predictors of cortisol deficiency.

A study done in critically ill patients found a high incidence of adrenal insufficiency. They also compared low dose-ACTH stimulation test (1 mcg) and high dose ACTH stimulation test (249 mcg) and found the low dose test to be more sensitive than the high dose test for diagnosing adrenal in sufficiency (Marik et al[18]., in 2002). Another study screened all AIDS patients with 10 mcg cosyntropin and found prevalence of glucocortical insufficiency to be 21.2%[19].

A study done in Kenya to determine the prevalence of adrenocortical insufficiency in HIV infected and non-infected patients with tuberculosis found no significant differences among the two groups, though an impaired cortisol response in tuberculosis was observed (Hawkin et al., in 1996[20]).

Dobs et al. in 1988[21], evaluated gonadal, adrenal and thyroid function in HIV infected patients and found 92% to have normal adrenocortical reserve, normal thyroid function and hypogonadism to be common in men.

OBSERVATION

The study group consisted of 61 patients with HIV infection (45 males and 16 females). 51 patients in the study group had stage IV infection (83.6%). The following tabular column gives information about the age and sex distribution of the study group.

AGE AND SEX DISTRIBUTION

Age (Years)	Male	Female
10 - 19	-	-
20 - 29	4	4
30 - 39	24	5
40 - 49	13	3
50 - 59	3	3
≥ 60	1	1

Observations were made for the presence of clinical and biochemical parameters of adrenal hypofunction in HIV infected patients.

33 patients in the study group had symptoms of adrenal insufficiency (54%) and 17 patients had postural hypotension (27.8%).

4 patients had hyponatraemia (6.5%) and all of them were detected to have low basal cortisol levels. One patient had both hypontraemia and hyperkalemia, but he had acute renal

failure which could have contributed to his hyperkalaemia. 14.7% of patients had eosinophilia.

The control group consisted of 20 normal individuals who were age and sex matched with the study group. The control group consisted of 15 males and 5 females.

COMPARISON OF AGE AND SEX OF STUDY VS CONTROL GROUP

SEX:

Sex	Study Group (average %)	Control Group (average %)
Males	74	75
Females	26	25

AGE:

Sex	Study Group - Age (average years %)	Control Group - Age (average years %)
Males	39	38
Females	39	40

There is no statistical significance for age and sex between the study and control groups.

COMPARISON OF BASAL CORTISOL LEVEL BETWEEN THE STUDY AND CONTROL GROUPS.

The basal cortisol level was compared between the study group and control group by estimating the mean basal cortisol level and the statistical significance analyzed by students t-test.

	Group	N	Mean	Std. Deviation	t-test
Cortisol mcg/dl 8 am	Study	61	33.139	16.4048	t=4.03 P=0.01
	Control	20	18.210	3.3576	

The mean basal cortisol level in the study group was found to be high (33.139) when compared to the control group (18.21), and was found to be statistically significant (p =0.01) in difference between the two groups.

ASSOCIATION OF SYMPTOMS OF ADRENAL INSUFFICIENCY WITH CORTISOL LEVEL.

	Symptoms	N	Mean	Std. Deviation	t-test
Cortisol mcg/dl 8 am	Absent	28	37.693	14.8112	t=2.05 P=0.05
	Present	33	29.276	16.9104	

Symptoms of adrenal insufficiency included gastrointestinal symptoms like abdominalpain, vomiting, anorexia, and easy fatigueability. Symptoms were present in 33 patients and absent in 28 patients. The mean cortisol value was 29.27 and 37.69 respectively. The significance of symptoms of adrenal insufficiency with cortisol level was analyzed between in the two groups using student's t-test and was found to be statistically significant ($p = 0.05$).

ASSOCIATION OF POSTURAL HYPOTENSION WITH CORTISOL LEVEL

Postural hypotension is an important clinical sign of adrenal insufficiency. 17 patients who had postural hypotension had mean cortisol value of 24.28, and 44 patients who did not have hypotension had mean cortisol of 36.559. This has statistical significance between the two groups with cortisol level since p = 0.01.

	Postural Hypotension	N	Mean	Std. Deviation	t-test
Cortisol mcg/dl 8 am	Absent	44	36.559	14.4184	t=2.76 P=0.01
	Present	17	24.288	18.3052	

ELECTROLYTE ABNORMALITIES, AND THEIR CORRELATION WITH CORTISOL LEVEL

		Na+ meq/L	K+ meq/L
Cortisol mcg/dl 8 am	Pearson Correlation	.389(**)	-.129
	Sig. (2-tailed)	.002	.320
	N	61	61

Hyponatraemia and hyperkalaemia are electrolyte abnormalities which may occur in patients with adrenal insufficiency. Hyerkalaemia occurs because of aldosterone deficiency and is therefore usually absent in patients with secondary adrenal failure. 4 patients in our study group had hyponatraemia, and 1 patient had hyperkalaemia with acute renal failure. Using Pearsons correlation test we analysed whether these electrolyte abnormalities had correlation with cortisol level. Hyponatraemia was found to have correlation with low cortisol level, which was statistically significant ($p = 0.002$). Potassium levels did not have correlation with cortisol level.

Since hypoglycaemia and eosinophilia may be present in patients with adrenal insufficiency, we tested whether these two variables have correlation with cortisol level. We found no significance for glucose level ($p = 0.241$) and eosinophil count ($p = 0.057$).

		Glucose mg/dl	**Eosinophil Count %**
Cortisol mcg/dl 8 am	Pearson Correlation	.152	-.183
	Sig. (2-tailed)	.241	.057
	N	61	61

CORRELATION BETWEEN CD4 CELL COUNT AND

CORTISOL LEVEL

Opportunistic infections occur with increasing frequency as the CD4 cell count declines. Since some of these infections may also involve the adrenal gland (tuberculosis, cytomegalovirus etc), adrenal insufficiency may occur. Hence we correlated if low CD4 cell count was associated with hypocortisolaemia using Pearsons correlation test. We found that low CD4 cell cound was related to hypocortisolaemia and had statistical significance (P=0.003).

		CD4+ cell Count / uL
Cortisol mcg/dl 8 am	Pearson Correlation	.376(**)
	Sig. (2-tailed)	.003
	N	61

COMPARISON OF MEAN BASAL CORTISOL LEVEL IN HIV PATIENTS WITH AND WITHOUT ASSOCIATED TUBERCULOSIS

		N	Mean	Std. Deviation	T-TEST
Cortisol mcg/dl 8 am	HIV	49	32.590	17.3331	t=2.76 P=0.01
	TB+HIV	12	35.383	12.2506	

The mean basal cortisol level in patients with HIV and tuberculosis was 35.38 compared with HIV alone (32.59), which was statistically significant ($p = 0.01$), between the two groups tested.

ASSESSMENT OF ADEQUACY OF FUNCTION OF THE HYPOTHALAMO - PITUITARY - ADRENAL AXIS

Clinical suspicion of the diagnosis of adrenal insufficiency should be confirmed with definitive diagnostic tests like the Synacthen stimulation test. Basal plasma cortiso levels are often in the low normal range, but may also be insensitive for diagnosing adrenal insufficiency. However, a basal cortisol value greater than 15 mcg/dl (400 nmol/L) invariably indicates an intact HPA axis, and therefore we did short synacthen test for those patients who had basal cortisol levels less than 15 mcg/dl.

S.No.*	Basal cortisol (0min) mcg/dl at 8 am	Stimulated cortisol (30 min) mcg/dl
1.	7.9	26.7
2.	7	14
3.	7.6	23.1
22	7.2	19.8
23	0.9	3.4
S.No.*	**Basal cortisol (0min) mcg/dl at 8 am**	**Stimulated cortisol (30 min) mcg/dl**
32	3.5	8
41	10.1	21.4
47	1.2	6.4
50	7.4	15.4
53	8.2	20.5
56	6.9	16.5
61	3.1	10.2

* Master Chart

12 out of 61 patients had basal cortisol level <15 mcg/dl. (basal cortisol >15mcg/dl indicates intact HPA axis). Short synacthen test was done for these patients. Basal cortisol values (0 minutes) and stimulated cortisol values after (30 minutes) were obtained. 7 patients (11%) had subnormal cortisol response. (a normal response is defined by a peakplasma cortisol level > 19mcg/dl) and 5 had normal responses.

DISCUSSION

61 patients seropositive for HIV infection (the study group) and 20 age and sex - matched controls were studied. The observations were made for basal cortisol levels in the study and control group. Within the study group, we analysed whether the clinical features (symptoms and postural hypotension) and biochemical profiles (electrolytes, glucose, eosinophil count) of adrenal insufficiency could have positive association with serum cortisol levels.

BASAL CORTISOL LEVELS IN THE STUDY GROUP VS CONTROL GROUP

There was statistical significance (p = 0.01) for the cortisol level when it was compared between the study and control groups.

Our observations were similar to the one reported by Bhansali et al., in 2000[16].

	N	Present study mean basal cortisol value	N	Bhansali et al., Median basal cortisol value
Study group	61	13.139 mcg/dl	15	19.5 mcg/dl (540 nmol/L)
Control group	20	18.210 mcg/dl	12	15 mcg/dl (415 nmol/L)
Significance		p = 0.01		P < 0.005

N = Number of patients

Mayo et al., 2002[1], also observed that patients with HIV infections had higher basal

cortisol levels than controls.

CLINICAL FEATURES OF ADRENAL INSUFFICIENCY

The association of symptoms and signs (postural hypotension) of adrenal insufficiency with cortisol levels had statistical significance in our study. (Symptoms, $p = 0.05$; postural hypotension, $p = 0.01$).

Studies done by Mayo et al., (2002) and Abbott et al., (1995)[17] have reported that clinically evident adrenal insufficiency is uncommon in HIV infected patients. Abbott et al., also added that although cortisol deficiency is common in late stage HIV infections, symptoms and signs are poor predictors of adrenal insufficiency. Mayo et al.,[1] observed that when clinically evident adrenal insufficiency is present it is observed in advanced stages of the infection. This observation is consistent with the result obtained in our study since patients with stage IV disease constitute 84% of our study group.

BIOCHEMICAL PROFILE

Electrolyte abnormalities :

Our study found positive correlation between serum sodium and cortisol levels, and which was statistically significant.

On the contrary Abbott et al., observed that cortisol deficiency was not predicted by electrolyte abnormalities (hyponatraemia, hyperkalaemia) even in late stage HIV infections.

Other parameters like hypoglycaemia, eosinophilia did not have correlation with hypocortisolaemia in our study, which is consistent with observations made by Abbott et al.

CORRELATION BETWEEN HYPOCORTISOLAEMIA AND LOW CD4 CELL COUNT

Our study found correlation between low cortisol levels and low CD4 were count which was statistically significant ($p = 0.003$).

Abbott et al., have reported similar observations in patients with CD4 cell count $\leq$ 50 / µl. They studied cortisol responses to synacthen test in 42 patients and found adrenal insufficiency in 16% of the patients. They have recommended routine screening by a rapid ACTH stimulation test in HIV patients will CD4 counts $\leq$ 50 cells / µl.

BASAL CORTISOL LEVELS IN PATIENTS WITH HIV INFECTIONS WITH / WITHOUT TUBERCULOSIS

Patients with concurrent tuberculosis had higher mean basal cortisol levels (35.38) than those with HIV alone (32.59). It also attained statistical significance (p 0.01) in difference between the two groups.

There have been no studies comparing basal cortisol levels in patients with HIV with or without tuberculosis. Hawken et al., (1996) undertook a study to determine the prevalence of adrenocortical insufficiency in HIV infected and non - infected patients with tuberculosis[20]. They observed no increased prevalence of adrenocortical insufficiency in HIV - associated tuberculosis.

The increase in basal cortisol level in patients with HIV and associated tuberculosis than in patients with HIV alone could be due to subclinical functional abnormalities of the HPA axis. The possible influences that alterations of the adrenal function could have on the patients immune status merits further research.

PREVALENCE OF ADRENOCROTICAL HYPOFUNCTION IN HIV INFECTIONS

* Based on the short synacthen test which we did on patients with basal cortisol <15 mcg/dl (value of >15 mcg/dl indicates an intact HPA axis), we found 11% of the patients to have adrenal hypofunction.

* Abbott et al., reported the prevalence of cortisol deficiency in late HIV disease to be 16%.

* Gonzalez - Gonzalez et al.,[19] reported the prevalence of glucocorticoid insufficiency by the 10 mcg. Cosyntropin test to be 21.2%.

* Hilton et al., in 1988[22] found a normal response to the synacthen test in 11 consecutive patients with AIDS ($p < 0.0005$).

We observed that adrenal dysfunction was characterized in our study by elevated basal serum cortisol levels in HIV infections, and clinically and biochemically evident adrenal insufficiency when present was seen in advanced stages of HIV infection with very low CD4 cell count.

CONCLUSIONS

* 61 patients and 20 controls were studied for clinical and biochemical evidence of adrenal dysfunction in HIV infections.

* The patients whom we evaluated in the medical wards comprised predominantly of males (74%).

* 84% of the patients admitted during the study period were in stage - IV disease (WHO clinical stage).

* Basal cortisol levels were significantly elevated in patients with HIV infections compared to controls. Patients who had concurrent tuberculosis had significantly higher basal cortisol levels than those with HIV infection alone.

* Symptoms and signs of adrenal hypofunction had significant association with hypocortisolemia.

* Hyponatraemia had statistically significant correlation with low cortisol levels.

* Low CD4 cell count had significant correlation with hypocortisolemia and therefore may predict adrenal insufficiency.

SUMMARY

The adrenal gland is frequently involved in patients with HIV infections. Structural and functional alterations of the adrenal glands, and involvement of the HPA axis can occur. Our study on patients infected with HIV has shown that adrenal dysfunction is common resulting in higher basal serum cortisol level. There is a significant association of clinical features of adrenal insufficiency, CD4 cell count with hypocortisolaenia. Adrenal insufficiency is observed in advanced stages of the infection. Hence hypocortisolemia should be treated regardless of the existence of associated symptoms, whereas hypercortisolemia in the absence of features of Cushings syndrome is common and should not promote treatment nor specific studies.

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PROFORMA

Name Address Occupation

Age Marital Status

Sex

MRD.No.

MEDICAL HISTORY INCLUDING HISTORY SUGGESTIVE OF ADRENAL INSUFFICIENCY:

Fatigue
Weightloss
Anorexia
Abdominal pain
Nausea, vomiting
Diarrhoea, constipation

COMORBID CONDITIONS / INFECTION : HT/DM/TB/STD. etc.

TREATMENT HISTORY:

SEXUAL HISTORY; BLOOD TRANSFUSION:
SMOKER; ALCOHOL INTAKE

EXAMINATION:

Body habitus
Pallor, cyanosis

Fever,

Oral thrush

Lymphadenopathy

Pedal oedema

Skin pigmentation

Vitiligo

Pulse rate

BP - supine

- Standing

Respiratory rate

CVS :

RS :

CNS :

Abdomen :

INVESTIGATION:

- Urine analysis
- Blood - haemogram
  glucose
- Serum Urea
  Creatinine
  electrolytes
- Liver function tests.
- HIV (ELISA)
- CD4 cell count
- Basal cortisol
- ACTH stimulation test - 0 min, 30 min
- Other investigations :

  Chest X-ray, ECG, Sputum for AFB etc.

ABBREVIATIONS

HIV	:	Human Immuno deficiency virus
AIDS	:	Acquired Immuno deficiency syndrome
TB-P	:	Pulmonary tuberculosis
TB-E	:	Extrapulmonary tuberculosis
C	:	Candidiasis (Oral)
SD	:	Seborrheic dermatitis
PA	:	Psoriatic arthropathy
L	:	Large cell lymphoma
MC	:	Molluscum contagiosum
P	:	Pneumonia
LA	:	Amoebic liver abscess
DM	:	Diabetes mellitus
NS	:	Neurosyphilis
GBS	:	Guillain-Barre Syndrome
PML	:	Progressive multifocal leukoencephalopathy
SS/ARF	:	Septic shock/Acute renal failure
HZ	:	Herpes zoster
PSY	:	Acute psychosis
Chr-D	:	Chronic diarrhoea
DCM	:	Dilated Cardiomyopathy
PHT	**:**	**Pulmonary Hypertension**