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CD4 count as a predictor of adrenocortical insufficiency in persons with human immunodeficiency virus infection: How useful?

Ifedayo A. Odeniyi, Olufemi A. Fasanmade, Michael O. Ajala,[1] and Augustin E. Ohwovoriole

Department of Medicine, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Surulere, Nigeria
[1]*Department of Chemical Pathology, General Hospital, Lagos, Nigeria*

Corresponding Author: Dr. Ifedayo A. Odeniyi, Department of Medicine, Faculty of Clinical Sciences, College of Medicine, University of Lagos, PMB 12003, Surulere, Lagos, Nigeria. E-mail: iodeniyi@unilag.edu.ng

Abstract

Objective:

To determine the usefulness of CD4 count in predicting adrenocortical insufficiency (AI) in persons with HIV infection.

Design:

Experimental study involving people with HIV infection and healthy people.

Participants:

The participants were recruited from the Lagos University Teaching Hospital. Forty-three newly diagnosed, treatment naive persons with HIV (23 males and 20 females) and 70 (35 males and 35 females) HIV negative subjects completed the study.

Intervention:

One microgram Synacthen® was given intravenously to stimulate the adrenal glands.

Main Outcome Measures:

Blood was collected for cortisol at 0 and 30 min after the injection of adrenocorticotropic hormone (ACTH) and CD4 count.

Results:

Mean basal cortisol was 154.9 ± 27.2 nmol/L and 239.9 ± 31.6 nmol/L ($P < 0.001$); the 30-min post ACTH test, cortisol level was 354.8 ± 19.9 nmol/L and 870.9 ± 163.5 nmol/L ($P < 0.001$); the increment was 100.0 ± 17.2 nmol/L and 588.8 ± 143.4 nmol/L ($P < 0.001$) in HIV and healthy subject group; respectively. Using the diagnostic criteria for diagnosis of AI in this study, fifteen (34.8%) persons with HIV had AI.

There was no significant correlation between basal cortisol levels and CD4 count in patients with HIV infection (r = -0.2, *P* = 0.198). There was no significant correlation between stimulated cortisol level and CD4 count in patients with HIV infection (r = -0.09, *P* = 0.516).

Conclusion:

CD4 count does not predict the presence or absence of AI. ACTH stimulation of the adrenal gland remains the acceptable standard.

Keywords: Adrenocorticotropic hormone, CD4 count, cortisol, human immunodeficiency virus

Introduction

Human immunodeficiency virus (HIV) infection is a significant risk factor for the occurrence of adrenocortical insufficiency (AI).[1] Adrenal gland involvement has been documented in as many as two-thirds of patients with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) at postmortem examination.[2] However, adrenal insufficiency is seldom diagnosed in clinical practice because symptoms do not appear until more than 80% of the gland has been destroyed.[2]

Adrenal dysfunction can increase morbidity and mortality among patients with HIV infection.[3] Adrenal insufficiency is a potentially modifiable comorbidity, especially as the biochemical abnormality (cortisol deficiency) is readily corrected by cortisol replacement.[4,5] AI should be suspected in patients with otherwise unexplained symptoms and signs compatible with adrenal insufficiency; such as anorexia, nausea, weight loss, and fatigue; and especially in patients with more specific manifestations of adrenal insufficiency, such as postural hypotension, hyponatremia, or hyperkalemia.[3,6]

Subclinical alterations in cortisol levels to frank primary adrenal insufficiency, using adrenocorticotropic hormone (ACTH) stimulation test, have been found in patients with HIV infection without symptoms or signs suggestive of adrenal insufficiency. In these patients, baseline cortisol levels are typically normal or elevated.[5,7,8,9,10,11] Some patients (8-14%) were found to have subnormal stimulation with ACTH in some studies.[7,8,12,13]

Although the adrenal gland is the most commonly affected endocrine organ in HIV,[14] the clinical diagnosis of adrenal insufficiency is made difficult because HIV infection and AI share similar features.[3] The classic clinical features and electrolyte derangements of AI have been shown to be poorly predictive of AI with regards to HIV infection.[11] Symptoms such as weight loss, malaise, weakness, and diarrhea are common to both HIV infection and AI. Hyponatremia, a characteristic feature of AI, is common in HIV infection, where it may be due to inappropriate antidiuretic hormone secretion or gastrointestinal loss resulting from vomiting and diarrhea. Hyperkalemia, another characteristic biochemical feature of AI, can occur as a side effect of cotrimoxazole therapy in HIV patients. A deliberate search for AI will be required to identify AI in HIV patients. The standard for diagnosing AI is the dynamic testing of the adrenal gland using adrenocorticotropic hormone (ACTH); Synacthen®.

The progression of HIV infection is accompanied by immunodepression which is mainly due to the selective depletion of CD4 lymphocytes. In our practice, in a resource-poor setting, Synacthen® is not readily available and when available, the cost is out of reach of the patients. The cost of cortisol assay is also expensive. However, CD4 count is done as part of the evaluation of persons with HIV infection to monitor the extent and progression of the disease. Whether CD4 count can be used to predict the presence or absence of AI in patients with HIV infection, has not been firmly established.

The main objective of this study was to determine the usefulness of CD4 count in predicting AI in persons with HIV infection. Other aims included documentation of the clinical and biochemical correlates of adrenal insufficiency in this group of patients.

Materials and Methods

Consecutively presenting treatment naive persons with HIV infection who met the inclusion criteria were selected. The estimated sample size was 42. The sample size of 42 was arrived at by using the formula: $n = Z^2$ pq/d^2.[15] For determination of sample size; P is the prevalence; the proportion of the target population estimated to have a particular characteristic. Estimated prevalence of HIV infection in Nigeria in 18-60 years age range is 5%.[16] However, the prevalence of AI in persons with HIV infection was taken to be 50% since prevalence is not known in Nigeria.[16] Z is the standard normal deviate which is 1.96. This corresponds to the 95% confidence interval. q is (1- p) and d which is the precision, is 0.15. Forty-two apparently, healthy non-HIV infected age and sex matched controls were selected. Making allowance for dropouts, (those who do not complete the study), 50 HIV infected patients were recruited for the study groups and 100 patients were recruited for the control group to increase the power of the study.

Persons who are pregnant, diabetic, and on drugs (e.g., steroid, cotrimoxazole, etc.) known to affect adrenocortical function were excluded from the study. Persons with HIV infection with concomitant pulmonary tuberculosis were excluded from the study. Persons with HIV infection who has had recent treatment with ketoconazole were excluded from the study. Children were also excluded from the study. Healthy volunteers, HIV negative, aged between 18 and 60 years who met the above criteria and consented to taking part in the study were recruited as control.

Of the 100 healthy volunteers (HIV negative) recruited as control for the determination of adrenocortical response to 1 μg of ACTH, 70 persons (35 males and 35 females) completed the exercise. Thirty persons declined further testing. The study group and the controls were recruited from the Lagos University Teaching Hospital (LUTH). Informed consent was obtained from all subjects and the study was approved by the LUTH Ethics and Research Committee.

The study groups were divided into batches of 10 subjects each. A data collection sheet, filled by the investigator, was used to obtain information from the subjects and controls. Information obtained from each participant included the biodata, presence of weakness, fatigue, cough, hemoptysis fever, weight loss, anorexia, nausea, vomiting, diarrhea, a history of glucocorticoid and/or antiretroviral drug use.

The subjects arrived on the assigned day at the laboratory, 60 min before the ACTH testing, after an overnight fast of 8-10 h. Physical examination including pulse rate and blood pressure in supine and erect position was performed. The anthropometric measurements (weight, height, and waist and hip circumference) were also taken. A 21-G canulla was inserted into a cubital vein and kept patent with heparinized saline. The subject then rested for 30 min after securing the venous access before samples were collected.

Low dose short Synacthen® test was performed as follows: A baseline blood sample for cortisol, fasting plasma glucose (FPG), full blood count (FBC), erythrocyte sedimentation rate (ESR), CD4 count, and electrolytes were collected immediately before administration of ACTH. ACTH testing was conducted between 08.00 and 9.00 hour. After the samples had been taken, the subject received an intravenous bolus injection of 1 μg ACTH (Alliance Pharmaceuticals Ltd., Chippenham, Wiltshire SN15 2BB).

To prepare 1 μg of ACTH solution, 1 mL of ACTH solution was drawn from an ampule containing 250 μg/mL of ACTH. This was diluted with 249 mL of normal saline to yield a concentration of 1 μg/mL; 1 mL of this solution, containing 1 μg ACTH, was administered using 1 mL syringe, as bolus low dose injection. The remainder of the diluted ACTH solution was stored at 4°C in a refrigerator for subsequent use. After the bolus was administered, blood sample was drawn for cortisol level at 30 min. The samples were separated and transported on an ice slab to the laboratory where the plasma were stored at −20°C until assayed.

A normal basal cortisol, derived from 70 controls, was defined as a 0 min cortisol level of ≥145.1 nmol/L (mean-3SD). A normal response to 1 μg ACTH stimulation was defined as a 30 min cortisol level of ≥380.2 nmol/L (mean-3SD) and an increment from basal to stimulated cortisol level of ≥158.5nmol/L (mean -3SD). This was derived from 70 non-HIV infected controls. Using these values, AI in this study

was defined as 30 min cortisol level <380.2 nmol/L and increment from basal to stimulated cortisol level <158.5 nmol/L. HIV infection was diagnosed if screened positive by enzyme-linked immunosorbent assay (ELISA method) and confirmed by immunoelectrotransference (Western blot).[17] Postural hypotension was defined as difference between supine systolic blood pressure and erect systolic blood pressure >20 mmHg.[18] A diagnosis of hypoglycemia was made at plasma glucose level <2.3 mmol/L.[19] A diagnosis of hyponatremia was made at plasma sodium level <135 mmol/L.[20] A diagnosis of hyperkalemia was made at plasma potassium level >5.0 mmol/L.[20] A diagnosis of anemia was made at hemoglobin level <12.0 g/dL.[21] Low CD4 count refers to CD4 cells <200/mm^3.[17]

Assay

Serum cortisol levels were determined by an ELISA technique using the Diagnostic Automation Inc. cortisol assay method. It is a competitive immunoenzymatic colorimetric method for quantitative determination of cortisol concentration in serum. The respective intra assay and interassay coefficients of variation percentage (CV%) of 4.5 and 3.1% for serum cortisol were within the acceptable range of variation.

Statistical analysis

Calculations and analysis were done using the SPSS 19.0 software. Continuous variables were expressed as means ± standard deviation (SD). Student's *t*-test was used for the comparison of means between two groups. Chi-square was used for comparison of proportions between two groups. Pearson's correlation coefficient analysis was used to determine associations between continuous data. The level of statistical significance was taken as $P < 0.05$.

Results

A summary of the demographic and biochemical parameters are as shown in Tables 1 and 2. The mean basal cortisol (0-min) was 154.9 ± 27.2 nmol/L while the 30-min post ACTH stimulation cortisol level was 354.8 ± 19.9 nmol/L in HIV group. Using the normal cortisol values derived from healthy subjects, 15 (34.8%) persons with HIV infection had AI. Comparison of the standard recommended cutoff value (cortisol < 500 nmol/L) with that used in this study showed that a higher proportion of person with HIV infection 38 out of 45 (83.4%) have AI [Table 3]. Of the patients with AI, seven (46.7%) had low CD4 count, while the remaining eight had CD4 count > 200 cells/mm^3 ($\chi^2 = 1.246$; $P = 0.264$). Of the 38 persons with AI using the standard recommended cutoff value, 21 (55.3%) had low CD4 count while 17 (44.7%) had CD4 count > 200 cells/mm^3 ($\chi^2 = 1.111$; $P = 0.292$). Low CD4 counts (CD4 < 200 cells/mm^3) was present in 25 (58.1%) of the patients with HIV infection. There was no significant correlation between basal cortisol levels and CD4 count in patients with HIV infection (r = -0.2, P = 0.198). There was no significant correlation between stimulated cortisol level and CD4 count in patients with HIV infection (r = -0.09, $P = 0.516$). In HIV patients with AI (15/43), negative correlation also exists between basal cortisol levels, stimulated cortisol level, and CD4 count however, this was not significant (r = -0.008, $P = 0.976$ and r = -0.039, $P = 0.89$, respectively). The risk of AI and CD4 count level is shown in Table 4. The proportion of persons with HIV infection with clinical features of AI is shown in Table 5. None of the patients with HIV had hyperpigmentation, postural hypotension, or hypoglycemia.

Discussion

Many investigators have evaluated adrenal function in critically ill patients by employing several approaches. Basal serum cortisol levels have been found to be elevated in patients with HIV, and therefore, are not reliable to exclude AI.[3] The gold standard for the assessment of adrenal function is insulin tolerance test (ITT).[22] The drawback in employing ITT to evaluate adrenal function is that it requires some degree of expertise and it is also unsafe in the setting of critical illness.[22] Adrenocortical function is thus assessed using ACTH to stimulate the adrenal gland in the setting of critical illness. The standard

dose (250 μg) of ACTH have been used to assess adrenocortical function.[22] This however has been found to be the supraphysiological dose capable of inducing or mobilizing cortisol from other sources, thus giving a falsely normal test.[22] This has led to investigators using 1 μg of ACTH to stimulate the adrenal gland. The 1 μg ACTH stimulation of the adrenal gland has been found to elicit maximal cortisol response comparable to the 250 μg ACTH test.[23,24] The 1 μg of synthetic ACTH has been suggested and used as a replacement for the standard 250 μg test.[22,25]

In this study, the mean basal cortisol value (154.9 nmol/L) and 30 min stimulated cortisol value (354.8 nmol/L) in persons with HIV was significantly lower than mean basal and 30 min stimulated cortisol levels in the healthy controls. The mean incremental rise (100 nmol/L) was also significantly lower in persons with HIV. Some investigators have used different diagnostic criteria for the diagnosis of AI as it relates to the population under study.[26,27,28,29] We also chose to define a diagnostic criteria for the population we studied. Using the diagnostic criteria for AI in this study, (peak cortisol <380 nmol/L and increment <158.5 nmol/L), we found that 15 (34.8%) persons out of 43 with HIV had AI. However, using serum cortisol level of 500 nmol/L suggested as the cutoff point for 30 min cortisol response,[30] 38 (88.4%) out of 43 persons with HIV had subnormal response to ACTH test in this study [Table 3]. This might be an over estimation of the prevalence of adrenocortical failure in persons with HIV infection in the study, hence the use of a stringent diagnostic criteria in this study.

Our finding in this study is similar to the findings in previous studies.[7,8,10,13] The prevalence of 34.8% for AI is higher than 19% reported in a recent Ugandan study[31] and 19% in a Brazilian study.[32] In the Ugandan study, the basal cortisol level was used to diagnose AI. A higher prevalence in this study could be explained by the fact that stimulated cortisol value was used, whereas basal cortisol level was used in the Ugandan study. However, patients with HIV infection have been found to have normal basal cortisol level as demonstrated in this study.[7,8,13] The abnormal response may be attributable to minimal degree of adrenal damage recognized in cases from autopsy studies.[1,33] The amount of adrenal gland tissue remaining functional, however, is apparently enough to provide a satisfactory glucocorticoid production in the basal state. In times of stress, adrenocortical response may not be adequate. AI might have been underdiagnosed in the Ugandan study.

The progression of HIV infection is accompanied by immunodepression which is mainly due to the selective depletion of CD4 lymphocytes. In a resource poor setting, ACTH stimulation of the adrenal gland poses a great challenge in terms of cost and availability of ACTH. One would have thought a measure of the HIV infection severity and progression (CD4 count) may be useful to predict AI. There exists a weak negative but not significant correlation between cortisol levels (basal and stimulated) and CD4 counts. This is similar to findings in other studies.[34,35,36] In the subgroup of patient with AI, seven out of 15 (46.7%) have CD4 count below 200 cells/mm^3 while the remaining eight (53.3%) have CD4 count above 200 cells/mm^3. There is no significant difference between the two groups. The number of people with AI was lower in those with CD4 count < 200 cells/mm^3 than in those whose CD4 count was > 200 cells/mm^3. This, however, was not significant [Table 4].

The decrease in the number of CD4 lymphocytes is accompanied by an increase in serum cortisol. The associations between cortisol and a fall in the number of CD4 cells suggest that this steroid plays an important role in the normal function of the immune system through its effects on cytokine secretion and lymphocyte proliferation and activity.[35,36,37] The increased serum cortisol concentration observed in people with HIV infection, most often without concomitant increase in circulating ACTH, suggests that the adrenal cortex is directly stimulated by other factors. Cytokines, such as interleukin-1 (IL-1) and interferon alpha (IFNα), acting indirectly or directly, could well modulate adrenal steroid production via their influence on the hypothalamic-pituitary-adrenal (HPA) axis.[35,36,37] The increase in cortisol level while CD4 count is falling could also be explained by the fact that there is decreased cortisol catabolism caused by an abnormal fatty acid profile[38] and alterations in the concentrations and binding properties of corticosteroid-binding globulin in HIV-infected patients.[39]

None of the patients with HIV infection and impaired adrenal response to ACTH test (AI) had hyperpigmentation or postural drop in blood pressure. This was similar to the finding in a previous study.[40] None of the person with HIV infection and AI had the classical hyperkalemia seen in adrenal insufficiency. This is similar to findings in other studies in other parts of Africa.[40,41] The mineralocorticoids are under the control of the renin-angiotensin system. This system is probably intact in people with HIV infection.

In conclusion, a CD4 count does not predict the presence or absence of AI. It cannot be used to diagnose adrenocortical function. A dynamic test using ACTH to stimulate the adrenal gland remains the acceptable standard.

Limitations

The preparation of 1μg ACTH could be affected by dilution error. It would have been ideal if there is commercially prepared 1 μg ACTH for stimulation of the adrenal glands. The use of lower cutoff value for the diagnosis of AI could have underestimated the proportion of persons with HIV infection with AI. These are possible limitations to our study.

Footnotes

Source of Support: Nil

Conflict of Interest: No

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Figures and Tables

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Table 1

Demographic data in subjects with HIV and healthy subjects

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Table 2

Comparison of plasma biochemical variables in persons with HIV and healthy subjects

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Table 3

Comparison of a higher recommended cutoff value with that used in this study

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Table 4

Risk of AI and CD4 count

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Table 5

Clinical features of AI in HIV patients

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