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Full Length Research Paper

Assessment of adrenal cortex function in a group of HIV infected patients in sub-Saharan-Africa

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The relationship between adrenal insufficiency and the HIV infection have been less investigated. The aim of this study was to assess the adrenal cortex function according to the stage of infection in a group of HIV-infected patients in sub-Saharan Africa. We conducted a cross-sectional study in 60 consenting subjects consisted of 20 healthy controls and 40 HIV-infected patients divided equally into 4 groups according to the stage of the infection. Plasma cortisol levels were measured at baseline and after synacthen stimulation by ELISA test. Basal and post-synacthen cortisol levels were comparable between healthy controls and HIV infected patients. Overall, the majority of HIV-infected subjects and healthy controls had normal cortisol levels at baseline. Only 5% of the HIV-infected patients in stage 4 had absolute adrenal insufficiency. The majority of HIV-infected subjects and healthy controls doubled their cortisol levels after synacthen stimulation. They were considered as having normal adrenal function. Adrenal function seems to be preserved in the majority of HIV-infected patients. However, patients at the late stage of the disease could have an impairment of adrenal function and therefore should be placed on cortisol supplementation.

Key words: Adrenal function, cortisol, synacthen, HIV-infected patients, sub-Saharan Africa.

INTRODUCTION

Nearly three decades after its discovery, the HIV/AIDS pandemic remains an actual threat worldwide. According to UNAIDS report, about 38.4 million people lived with HIV globally in 2021 and AIDS-related deaths were

reported in 650000 people. This pandemic affects people irrespective of age, race or gender. In sub-Sahara Africa (SSA) for example, 5 million people were concerned with HIV infection in 2021 (UNAIDS Global AIDS Update, 2022).As observed with many other systemic diseases, endocrine abnormality is common in HIV-infected patients (Cardoso et al., 2007; Lo and Grinspoon, 2010). In fact, HIV can affect the endocrine system at several levels: adrenal and gonadal dysfunction, osteoporosis with increased fracture risk, dyslipidemia with increased cardiovascular risk, are some of the endocrine disorders mostly observed in HIV-infected patients that may negatively influence quality of life, and increase morbidity and mortality. These endocrine disorders could be due to HIV itself, related opportunistic infections, cytokines, immune activation, or antiretroviral therapy (ART) (Zaid and Greenman, 2019; Girei and Fatima, 2013).

Although adrenal insufficiency is often subclinical and consequently under-diagnosed, its prevalence appears to be greater in HIV-infected patients than in the general population (Bons et al., 2013). Several hypotheses were formulated in order to explain the etiology of adrenal insufficiency in HIV-infected patients. Direct destruction of adrenal gland by the virus itself or by invasive infection with opportunistic organisms such as cytomegalovirus, *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Pneumocystis carinii, Cryptococcus* and toxoplasmosis as well as side effects of the various medications used by these patients have been reported as possible etiology (Afreen et al., 2017; Brockmeyer et al., 2000).

Biochemical evidence of adrenal insufficiency was also reported in HIV infected patients with some controversy. In early studies, only 4 of 74 AIDS patients had evidence of adrenal insufficiency when screened with a cosyntropin stimulation test (Membreno et al., 1987), while 14 of the 49 HIV infected patients experienced adrenal insufficiency in a study performed by Abbott et al. (1995). Moreover, in recent studies, high frequency of adreno-cortical insufficiency was reported in HIV infected patients (Afreen et al., 2017; Ibrahim and Yahaya, 2017). However, these studies did not consider the involvement of HIV itself or the related opportunistic diseases in the adrenal dysfunction found in HIV-infected patients. Furthermore, to the best of our knowledge, the potential relationships between adrenal insufficiency and the stage of HIV infection has been less investigated, mainly in sub-Saharan Africa (SSA) populations where the burden of HIV infection is remarkably high. Therefore, this study was undertaken in order to assess the adrenal cortex function according to the stage of infection in a group of HIV-infected patients in SSA.

MATERIALS AND METHODS

Study design, setting and population

This was a cross-sectional study that took place from October 2010 to February 2011 at the Yaoundé Central Hospital, a tertiary hospital in Yaoundé, Cameroon. HIV infected patients attending the HIV care unit of this hospital for their outpatient consultations were consecutively enrolled in this study. The matched healthy controls recruited among medical staff and students served as control group. HIV infected patients were classified according to the clinical stage of the disease, using WHO criteria. A total of 40 HIV infected patients and 20 healthy matched controls were enrolled in this study.

Clinical parameters and physical examination

The aim of the study was explained to the patients and those who gave written informed consent were interviewed. Sociodemographic and clinical characteristics were recorded using a standard questionnaire. Medical history of each patient enrolled in the study was obtained from their medical files. All eligible patients underwent complete physical examination, which involved collecting hemodynamic parameters, researching for melanoderma and the evaluation of each system.

Assessment of corticotrophic function

The assessment of corticotrophic function was performed at the endocrinology unit of the Yaoundé Central Hospital, using synacthen® test. Eligible patients presented themselves at the endocrinology unit at 7H30' after a 12-h overnight fast. A basal venous blood sample was collected at 08H00 in two dry tubes and immediately followed by the injection of 250 µg synacthen® (beta 1-24 corticotropin or tetracosactid), a synthetic analogue of corticotropin (ACTH) given intramuscularly. Sixty minutes after the injection, a second venous blood sample was collected. Serum samples were stored at -20°C for cortisol assay.

Cortisol assay

Basal and post-stimulation cortisol levels were measured at the Biochemistry laboratory of the Yaoundé Teaching University Hospital, by Enzyme Linked Immunosorbent Assay (ELISA), using IBL Cortisol Elisa Kit (IBL, International GMBH). Absolute adrenal insufficiency was defined for a basal cortisol level <50 ng/ml (138 nmol/l) while any patients who did not double its cortisol levels after ACTH stimulation was considered as having low functional adrenal reserve.

$$\text{Delta cortisol (\%)} = \frac{post-synacthen\ cortisolemia - basal\ cortisolemia}{basal\ cortisolemia} \times 100$$

Ethical considerations

Ethical clearance was obtained from the National Ethics Committee

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at the Ministry of Public Health, Cameroon (N°241/CNE/SE/2010). Before enrollment in the study, each participant provided a written informed consent.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) version 16.0 (SPSS Inc, Chicago, IL, USA). The results were presented as means ± Standard Deviation. Categorical variables were presented in proportions. Comparison of the means between groups was performed using ANOVA test. Significance was set at 5%.

RESULTS

Characteristics of study subjects

Overall, we included in this study 60 subjects, consisted of 40 HIV infected patients (mean age: 40.6±11.7 years) and 20 healthy matched controls (mean age: 34.8±9.7 years). The mean weight, body mass index (BMI) and blood pressure were comparable between the two groups (Table 1). The common symptoms and signs found in HIV infected patients enrolled in this study were Asthenia (22.5%, 9 patients), Amenorrhea (22.5%, 9 patients) and melanodermia (20%, 8 patients). Concerning the opportunistic and others associated diseases, dermatosis, Kaposi sarcoma and tuberculosis were reported in the majority of HIV infected patients while mouth candidosis, gastroenteritis, toxoplasmosis, pneumonia and cryptococcosis were found in a few numbers of these patients (Table 2).

Adrenal function of the study subjects

Basal cortisolemia

As shown in Table 3, mean basal cortisol levels were comparable in HIV negative and HIV infected subjects at each stage of the infection. Overall, 67.5% (27 patients) of HIV infected subjects had normal basal cortisol levels compared to 75% (15 patients) of healthy matched controls while high baseline cortisol levels (defined as a basal cortisol levels > 230 ng/ml) was reported in 27.5% (11 patients) and 25% (5 patients) of HIV infected and HIV negative subjects, respectively. Absolute adrenal insufficiency (defined as basal cortisol levels < 50 ng/ml) was found in 5% (2 patients) of HIV infected patients (Figure 1A). When investigating the basal cortisol levels in HIV infected subjects at each stage of the infection, we found that all the cases of absolute adrenal insufficiency were reported in stage 4 HIV infected patients (Figure 2).

Post synacthen stimulated cortisol levels

Sixty minutes after the injection of synacthen, the mean cortisol levels were comparable (P = 0.37) between healthy controls and HIV infected subjects at each stage of the infection (Table 3). The majority of the patients in HIV negative group (78.3%) and HIV positive group (82.5%, 33 patients) irrespective of infection stage had normal adrenal function (defined as doubled cortisol levels after synacthen stimulation) (Figure 1B). Reserve adrenal insufficiency (patients who did not double cortisol levels after synacthen stimulation) was reported in 17.5% (7 patients) of the HIV infected subjects compared to 21.7% of the healthy controls (Figure 1B).

We compared anthropometric characteristics of HIV infected patients with normal adrenal function and reserve adrenal insufficiency at each stage of the infection as shown in Table 4. The mean age and blood pressure were comparable in HIV infected patients with normal adrenal function and reserve adrenal insufficiency at different stage of the infection. In stage 3 HIV infected patients, the mean weight and BMI were significantly higher in patient with reserve adrenal insufficiency compared to patients with normal adrenal function. Contrary to this finding, BMI was significantly lower in stage 4 HIV infected patient with reserve adrenal insufficiency (17.01 Kg/m^2) compared to patients with normal adrenal function (24.69±5.86 kg/m^2).

DISCUSSION

The aim of this study was to assess the adrenal cortex function according to the stage of infection in a group of HIV-infected patients in sub-Saharan Africa. We conducted a cross-sectional study from October 2010 to February 2011 at the Yaoundé Central Hospital, a tertiary hospital in Yaoundé, Cameroon. HIV infected patients attending the HIV care unit of this hospital were consecutively enrolled in this study and matched to healthy controls recruited among medical staff and students to serve as control group. HIV infected patients were further classified according to the clinical stage of the disease, using WHO criteria. A total of 40 HIV infected patients and 20 healthy matched controls were enrolled in this study.

Overall, HIV-infected patients had a mean age of 40.6±11.7 years whereas the 20 healthy matched controls had a mean age of 34.8±9.7 years.

The mean weight, body mass index (BMI), and blood pressure were comparable between the two groups. Mean basal cortisol levels were comparable in HIV-negative subjects and HIV-infected subjects at each stage of the infection. Overall, 67.5% (27 patients) of HIV-infected subjects had normal basal cortisol levels compared to 75% (15 patients) of healthy matched controls. This is similar to the prevalence of normal basal cortisol obtained in Northern Nigeria and in a South African study, irrespective of the WHO stage. Akase et al. (2019) reported a prevalence of hypocortisolism at 30.9% while Ekpebegh et al. (2011) found a prevalence of hypocortisolism at 27%.

Table 1. Sociodemographic and clinical characteristics of study subjects.

Characteristics	HIV (+) subject N=40	HIV (-) subject N=20
Age* (year)	40.6±11.7	34.8±9.7
Sex n (%)		
Male	14(56)	11(44)
Female	26(74.3)	9(25.7)
Weight* (kg)	69.13±22.68	72.65±20.44
BMI* (kg/m^2)	24,67±7,66	24,94±12
SBP* (mmHg)	116,10±24,06	111,45±17,52
DBP* (mmHg)	69,90±17,58	69,90±17,58

*Data are mean± standard deviation; BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Source: Author

Table 2. Symptoms, signs and associated diseases in HIV (+) subjects.

Variable	HIV (+) subject N=40
Symptoms and signs, n (%)	
Asthenia	9 (22.5)
Anorexia	2 (5)
Weight loss	4 (10)
Salt appetence	37 (92.5)
Amenorrhea	9 (22.5)
Melanodermia	8 (20)
Associated diseases, n (%)	
Dermatosis	15 (37.5)
Kaposi sarcoma	7 (17.5)
Zona	7 (17.5)
Tuberculosis	7 (17.5)
Fever	6 (15)
Mouth candidosis	4 (10)
Gastroenteritis	3 (7.5)
Toxoplasmosis	3 (7.5)
Pneumonia	2 (5)
ENT infection	1 (2.5)
Cryptococcosis	1 (2.5)

Source: Author

High baseline serum cortisol (defined as a basal cortisol levels > 230 ng/ml) was observed in 27.5% (11 patients) and 25% (5 patients) of HIV infected and HIV negative subjects, respectively. This result is similar to that of Sharma et al. (2018) who observed high basal cortisol levels in 21.17% of their HIV positive study population. As reported by some studies, this finding is related to the increased systemic inflammatory response triggered by HIV infection which stimulates the hypothalamo-pituitary axis (Membreno et al., 1987). Moreover, Costa et al. (2000) reported a link between the HIV envelope protein GP 120 and the stimulation of the hypothalamo-pituitary axis in this group of patients.

When investigating the basal cortisol levels in HIV infected subjects at each stage of the infection, we found that all the cases of absolute adrenal insufficiency were

Table 3. Basal and post-synacthen cortisol levels in HIV (+) and HIV (-) subjects.

Parameter	HIV (-) N=20	HIV(+)				Anova	P-value
		Stage 1 N=10	Stage 2 N=10	Stage 3 N=10	Stage 4 N=10		
Basal cortisol levels (ng/ml)*	182.6±183.8	172.0±169.7	252.80±454.6	197.0±154.9	202.6±357.0	0.47	0.70
Post-synachten cortisol level (ng/ml)*	415.50±413.1	451.40±306.2	525.20±518.8	565.20±291.2	447.2±217.6	1.07	0.37
Delta cortisol (%)*	169.19±227.7	215±321.8	150±168.6	226±256.4	109±93.2	2.02	0.12
Normal adrenal function, n (%)	14 (70)	8 (80)	7 (70)	9 (90)	9 (90)		
Reserve adrenal insufficiency, n (%)	6 (30)	2 (20)	3 (30)	1 (10)	1 (10)		
Absolute adrenal insufficiency, n (%)	0	0	0	0	2(20)		

*****Data are mean±standard deviation.
Source: Author

Table 4. Anthropometric characteristics of HIV(+) patients according to adrenal function at each stage of infection.

Characteristic	HIV stage 1 N=10			HIV stage 2 N=10			HIV stage 3 N=10			HIV stage 4 N=10		
	Normal adrenal function N=8	Reserve adrenal insufficiency N=2	P-value	Normal adrenal function N=7	Reserve adrenal insufficiency N=3	P-value	Normal adrenal function N=9	Reserve adrenal insufficiency N=1	P-value	Normal adrenal function N=9	Reserve adrenal insufficiency N=1	P-value
Age (year)*	36.12±17.44	41±5.08	0.62	38.14±18.52	32.33±12.85	0.35	41.0±16.96	34.0±0.0	0.45	47.88±3.02	55.0±0.0	0.66
Weight (kg)*	66.38±17.14	81.50±12.72	0.05	71.29±25.12	75.33±15.14	0.62	59.33±15.87	95.0±0.0	<0.001	72.44±19.12	65.0±0.0	0.48
BMI (kg/m^2)*	24.79±7.57	25.54±0.36	0.79	27.32±8.38	25.76±3.86	0.56	22.07±6.22	31.04±0,0	0.02	24.69±5.86	17.01±0.0	0.03
SBP (mmHg)*	113.75±28.14	130±28.28	0.18	115.71±15.73	116.67±30.54	0.89	114.89±27.56	12.0±0.0	0.73	115.56±24.72	120.0±0.0	0.74
DBP (mmHg)*	71.25±16.69	60±0.00	0.10	68.57±13.80	70.00±20.00	0.79	67.33±13.26	80±0.0	0.10	73.33±24.48	70.0±0.0	0.80

*Data are mean±standard deviation. BMI: Body mass index; SBP: systolic blood pressure, DBP: diastolic blood pressure.
Source: Author

reported in stage 4 HIV infected patients. Absolute adrenal insufficiency (defined as basal cortisol levels < 50 ng/ml) was found in 5% (2 patients) of HIV infected patients at stage WHO stage 4 of the disease. As described in other studies, absolute adrenal insufficiency is common with advanced HIV disease, when over 80 to 90% of the adrenal glands have been destroyed (Bhatia, 2018). In addition, the likelihood of having several comorbidities also comes as the disease progresses.

The majority of the patients in HIV negative group (78.3%) and HIV-positive (82.5%, 33 patients) irrespective of infection stage had normal adrenal function (defined as doubled cortisol levels after synacthen stimulation). This may be related to the fact that a majority of our participants were clinically stable and presented with a few symptoms.

In stage 3 HIV infected patients, the mean weight and BMI were significantly higher in patient

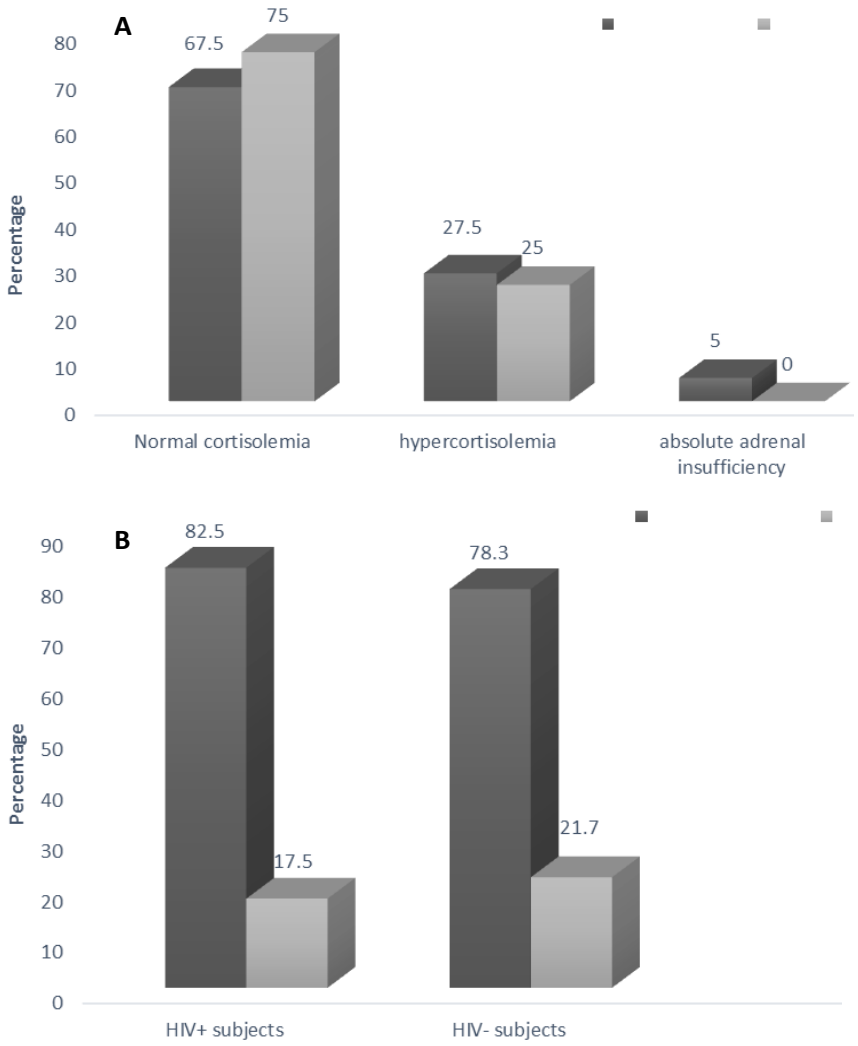


Figure 1. Basal (A) and post-synacthen (B) cortisolemia in HIV (+) and HIV(-) subjects.
Source: Author

with reserve adrenal insufficiency compared to patients with normal adrenal function. Contrary to this finding, BMI was significantly lower in stage 4 HIV infected patient with reserve adrenal insufficiency (17.01 kg/m^2) compared to patients with normal adrenal function (24.69±5.86 kg/m^2).

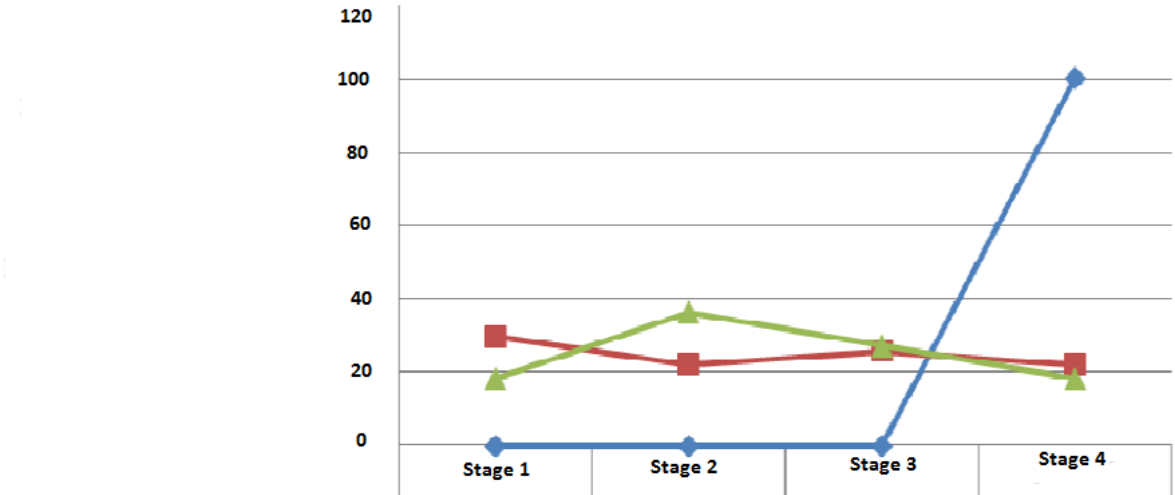
Reserve adrenal insufficiency (patients who did not double cortisol levels after synacthen stimulation) was reported in 17.5% (7 patients) of the HIV-infected participants compared to 21.7% of the healthy controls. After cortisol stimulation with a threshold of 180 ug/l. Akase et al. (2019) reported a prevalence of hypocortisolism at 16.3% among HIV-infected patients. Furthermore, they did not report any significant difference with respect to WHO clinical classification nor CD4 count (Akase et al., 2019).

As limits to this study, we did not assess CD4 count and viral load to check association with the adrenal insufficiency. Nevertheless, our study gives an idea of the spectrum of adrenal function impairment within the HIV-positive population. It also highlights the need to have a high index of suspicion of adrenal insufficiency in these patients as a direct association between clinical symptoms and adrenal insufficiency has not been shown.

Conclusion

It was concluded that the adrenal function is preserved during HIV infection except in patients at the late stage of the disease.

It was recommeneded that cortisol supplementation should be considered at the terminal stage of HIV infection.



	Stage 1	Stage 2	Stage 3	Stage 4
Absolute adrenal insufficiency (%)	0	0	0	100
Normal cortisolemia (%)	29.6	22.2	25.9	22.2
Hypercortisolemia (%)	18.2	36.4	27.3	18.2

Figure 2. Basal cortisolemia in HIV(+) subjects by stage of the infection.
Source: Author

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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