Afr. J. Med. med. Sci. (2011) **40**, 33-38

Adrenocortical function in Nigerian patients with Pulmonary Tuberculosis (PTB)

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Summary

Addison's disease was frequently consequent upon affectation of the glands by tuberculosis. Pulmonary Tuberculosis (PTB) is still very common in Nigeria but no report on the functional status of the adrenal cortex in patients with PTB in Nigeria exists. It is very important to note that subclinical adrenocortical failure in tuberculosis is an entity that should be considered as cortisol deficiency could be responsible for unexpected sudden death in this category of patients. This study sets out to determine the prevalence of subclinical adrenocortical failure in persons with PTB by determining the response to low-dose (1ìg) ACTH stimulation. Forty four persons with newly diagnosed sputum-positive PTB and treatment naive, (23 males and 21 females, mean age 34.4±11.3 years, and mean Body Mass Index (BMI) of 18.9±2.9 kg/m^2) completed the study. Of the one hundred healthy volunteers recruited as control subjects, 70 persons (35 males and 35 females, mean age 38.1±12.5 years, BMI 24.1±3.7kg/m^2) completed the exercise. There was no statistically significant difference in the basal cortisol of healthy subjects and persons with PTB (239.9 vs 229.1nmol/L, p=0.661). The thirty minute response to ACTH stimulation test and increment were significantly lower in persons with PTB than in healthy subjects. Adrenocortical insufficiency, mostly at the subclinical level, is common in persons with PTB infection, occurring in about 23% of patients. We therefore recommend that basal cortisol levels should not be used to detect adrenocortical insufficiency; rather stimulation tests should be used to exclude or confirm suspected adrenocortical insufficiency in patients with PTB.

Keywords: *Cortisol; adrenocorticotropic hormone (ACTH); hypothalamo-pituitary-adrenal (HPA); pulmonary tuberculosis; Nigerians.*

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Résumé

La maladie d'Addison était fréquemment la conséquence de l'infection des glandes par la tuberculose. La tuberculose pulmonaire (TP) est encore très commune au Nigeria mais pas le rapport dans le statut fonctionnel des glandes surrénales chez les patients ayant la tuberculose pulmonaire ; il est important de noter que le défaillance adrenocorticales subclinique chez les tuberculeux est une entité qui doit être considérée comme une déficience des cortisols et pourrait être responsable d'une mort subite chez cette catégorie de patients. Cette étude est menée pour déterminer la prévalence des défaillances adrenocorticales subcliniques chez des personnes soufrant de tuberculose pulmonaire en déterminant les réactions aux faibles doses (1ìg) ACTH de stimulation. Quarante quatre personnes avec des nouveaux diagnostics positifs au PTB, (23 males and 21 femelles, une moyenne d'âge de 34.4±11.3 ans, and la moyennes d'indice de masse corporelle (IMC) de 18.9±2.9 kg/m^2) complétait l'étude. Des 100 volontaires en bonne santé recrutés comme sujets control, 70 personnes (35 males and 35 femelles, moyenne d'âge 38.1±12.5 ans, BMI 24.1±3.7kg/m^2) complétait l'exercice. Il n'y avait statistiquement pas de différence significative sur le cortisol de base des sujets en bonne santé et ceux des personnes atteint de tuberculose pulmonaire (239.9 vs 229.1nmol/L, p=0.661). Les trente minutes de réaction au test de stimulation d'ACTH et de l'incrément étaient significativement plus bas chez les personnes atteint de tuberculose pulmonaire que chez ceux en bonne santé. L'insuffisance adrenocorticale, le plus souvent à un stade Clinique, est fréquente chez les personnes atteintes de tuberculose pulmonaire, survenant chez environs 23% des patients. Nous recommandons cependant que le niveau du cortisol de base ne soit pas utilisé pour détecter l'insuffisance adrenocorticale. Les tests de stimulation devraient plutôt être utilisés pour exclure ou confirmer l'insuffisance adrenocorticale chez les patients atteint de tuberculose pulmonaire.

Introduction

Addison's disease was frequently consequent upon affectation of the glands by tuberculosis. Pulmonary Tuberculosis (PTB) is still very common in Nigeria but no report on the functional status of the adrenal cortex

in patients with PTB in Nigeria exists. It is very important to note that subclinical adrenocortical failure in tuberculosis is an entity that should be considered as cortisol deficiency could be responsible for unexpected sudden death in this category of patients [1]. In South Africa, TB mortality increased by 44% from 1994 to 1995[2]. Subclinical adrenocortical failure in tuberculosis have been assessed by various workers and the prevalence in these studies varies (0-55%) [3-6]. Assessment of the adrenal gland functional reserve with the short synacthen (synthetic adrenocorticotrophic hormone (ACTH)) test has long been accepted as the most reliable diagnostic screening procedure in patients with a clinical picture suggestive of adrenocortical hypofunction or in high-risk populations [7]. Classically, the recommended test is carried out with 250μg synthetic ACTH 1–24, taking blood samples for serum cortisol at baseline, 30 and 60 min after intravenous (i.v) or intramuscular (i.m) stimulation. Recent evidences, however, suggests that i.v. administration of 250μg ACTH 1–24 could be a provocative pharmacological rather than a physiological stimulus [8, 9, 10]. Trials with a reduced number of healthy individuals have shown that 1, 5, 10 and 250 μg ACTH 1–24 i.v. are also able to produce similar serum cortisol peaks [8-13]. In addition, Dickstein *et al.*[8], evaluating patients on long-term glucocorticoid therapy, found low sensitivity of the standard ACTH testing at identifying secondary adrenal failure when contrasting it to 1 μg ACTH. It was thus proposed that low-dose (1ìg) ACTH stimulation may be a more sensitive method of assessing adrenocortical function. Subtle changes in cortisol secretion may also be revealed.

This study sets out to determine the prevalence of subclinical adrenocortical failure in persons with PTB by determining the response to low-dose (1ìg) ACTH stimulation.

Materials and methods

Forty four persons out of 50 newly diagnosed, consecutively presenting, sputum-positive PTB and treatment naive, (23 males and 21 females, mean age 34.4±11.3 years, and mean Body mass index (BMI) of 18.9±2.9 kg/m^2) completed the study. Persons who were pregnant, diabetic and on drugs (e.g. steroid) known to affect adrenocortical function were excluded from the study. Of the one hundred healthy volunteers recruited as control for the determination of adrenocortical response to 1ìg of ACTH, 70 persons (35 males and 35 females, mean age 38.1±12.5 years, BMI 24.1±3.7kg/m^2) completed the exercise. There was no significant difference between those that completed the study and those that dropped out. The study groups were recruited from the respiratory clinic in Lagos University Teaching Hospital (LUTH), while the controls were recruited from the student and staffs of College of Medicine, University of Lagos and Lagos University Teaching Hospital (LUTH) respectively. 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 pre-tested questionnaire 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, haemoptysis fever, weight loss, anorexia, nausea, vomiting, diarrhea, a history of glucocorticoid and/or antituberculosis drug use. Persons with PTB also had abdominal ultrasound scan to determine adrenal gland involvement. All of them have normal adrenal glands.

The subjects arrived on the assigned day at the laboratory, 60 minutes before the ACTH testing, after an overnight fast of 8-10 hours. Physical examination including pulse rate and blood pressure in supine and erect position was performed. The anthropometric measurements (weight, height, waist circumference 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 at least 30 minutes after securing the venous assess before basal sample for cortisol, fasting plasma glucose and electrolytes was obtained.

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

To prepare 1ìg of ACTH solution, 1mL of ACTH solution was drawn from an ampoule containing 250ìg/mL of ACTH. This was diluted with 249mL of normal saline to yield a concentration of 1ìg/mL. 1mL of this solution, containing 1ìg ACTH, was used as bolus low-dose injection. The remainder of the diluted ACTH solution was stored at 4^{0}C in a refrigerator for subsequent use. After the bolus was administered, blood

sample was drawn for cortisol level at 30 minutes. 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 response to 1ìg ACTH stimulation was defined as a 30 minute cortisol ≥380.2 nmol/L and increment from basal to stimulated level ≥158.5nmol/L. This was derived from 70 controls in whom the minimum serum cortisol at 30 minute post ACTH stimulation was 380.2 nmol/L and increment from basal to stimulated level was 158.5nmol/L. Using these values, adrenal insufficiency in this study was defined as 30 minute cortisol <380.2nmol/L and increment from basal to stimulated level <158.5nmol/L. Pulmonary tuberculosis was diagnosed using sputum positive for acid and alcohol fast bacilli (AAFB) using ZN stain.

Statistical analysis

Average values were expressed as means ± standard deviation (SD). Calculations and analysis were done using the SPSS 15.0 software. Statistical comparisons were made using the Student's t test for quantitative variables. Chi squared test was used for the comparison of proportions. The level of statistical significance was taken as $p<0.05$.

Results

Demographic data

Forty-four persons with PTB, (23 males and 21 females), completed the study. There was significant difference in the weight between subjects with PTB and healthy subjects. The characteristics of persons with PTB are compared with those of healthy participants in table 1.

Table 1: Demographic data in subjects with PTB vs healthy subjects

	Pulmonary Tuberculosis(n= 44)	Healthy Control(n= 70)
Age (years)	34.4±11.3	38.1±12.5
Weight (kg)	52.9±10.0*	65.9±11.1
BMI (kg/m^2)	18.9±2.9*	24.1±3.7
Supine systolic BP (mmHg)	110.5±13.1*	119.4±12.9
Supine diastolic BP (mmHg)	70.0±08.1*	76.2±10.4
Erect systolic BP (mmHg)	111.5±13.8*	119.4±12.2
Erect diastolic BP (mmHg)	70.8±7.9*	76.2±9.6

*Wt, Weight; BMI, Body Mass Index; SSBP, Supine Systolic Blood Pressure; SDBP, Supine Diastolic Blood Pressure; ESBP, Erect Systolic Blood Pressure; EDBP, Erect Diastolic Blood Pressure. *p<0.05 (Control vs PTB).*

Postural hypotension was defined as difference between supine systolic blood pressure and erect systolic blood pressure >20mmHg [14]. A diagnosis of hypoglycaemia was made at plasma glucose level <2.3mmol/L [15]. A diagnosis of hyponatraemia was made at plasma sodium level <135mmol/L [16]. A diagnosis of hyperkalaemia was made at plasma potassium level >5.0mmol/L [16].

Assay

Serum cortisol levels were determined by an Enzyme Linked Immunosorbent Assay (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 inter-assay CV% of 4.5% and 3.1% for serum cortisol were within the acceptable range of variation.

Adrenal response to ACTH test in persons with pulmonary tuberculosis and healthy subjects

The adrenal response to 1ìg ACTH stimulation in persons with pulmonary tuberculosis and healthy subjects are as shown in Table 2. There was no statistically significant difference in the basal cortisol of healthy subjects and persons with PTB (239.9 vs 229.1 nmol/L, p=0.661). The thirty minute response to ACTH stimulation test and increment were significantly lower in persons with PTB than in healthy subjects (524.8 vs 870.9nmol/L, p<0.001 and 190.5 vs 588.8nmol/L, p<0.001 respectively).

The basal cortisol and 30-minute cortisol were higher in females with PTB compared with males with PTB. This, however, was not statistically significant (p=0.096 and 0.277 respectively). The increment was not significantly different in both males and females (p= 0.600).

One person (2.3%) had abnormal basal cortisol <74.1nmol/L (1[4.3%] males) while 43 (97.7%) persons had normal basal cortisol >74.1nmol/L (22 [95.7%] males and 21 [100%] females; X^2=0.934, p=0.334). The person with low basal cortisol had lost weight but had no other symptoms or signs of adrenocortical dysfunction. He had post ACTH stimulation serum cortisol >380.2nmol/L. However, after stimulation with 1ìg ACTH, 10 (22.7%) persons, (5 [21.7%] males and 5 [28.8%] females) had adrenocortical insufficiency using the criteria defined previously.

Table 2: Comparison of serum cortisol levels in response to ACTH test in healthy subjects and persons with PTB

	Cortisol Level Mean ± SD nmol/L		P-value
	Healthy subjects	Persons with PTB	
0 minute	239.9 ± 31.6	229.1 ± 50.1	0.661
30 minutes	870.9 ± 19.9	524.8 ± 63.1	<0.001
Increment	588.8 ± 31.6	190.5 ± 79.4	<0.001

Table 3: Comparison of biochemical parameters in persons with PTB and healthy subjects

Plasma Analyte	Mean ± SD		P-value
	Persons with PTB	Healthy subjects	
FPG(mmol/L)	5.7±1.3	4.9±0.6	<0.001
Na^+(mmol/L)	136.7±2.8	138.1±1.5	0.096
K^+(mmol/L)	3.7±0.5	3.8±0.3	0.278
Urea(mmol/L)	3.1±0.9	3.2±0.5	0.154

FPG, Fasting Plasma Glucose; Na^+, Sodium; K^+, Potassium.

Comparison of biochemical parameters in persons with PTB and healthy subjects

Table 3 shows some biochemical parameters in persons with pulmonary tuberculosis compared with healthy subjects. The FPG, though within acceptable limit, was significantly higher in persons with PTB than in healthy subjects. The plasma sodium concentration and potassium concentration were higher in the healthy control subjects. However this was not statistically significant. Five (11.4%) of persons with PTB had hyponatraemia. None of them however had symptoms or signs of adrenocortical failure. They had normal basal and 30 minutes post ACTH test serum cortisol level.

Discussion

The adrenal glands play an important role in the body's ability to cope with stresses such as infections, hypotension and trauma including surgery [17, 18]. The most common cause of primary adrenal insufficiency is tuberculous adrenalitis. Tuberculous adrenalitis is believed to be a major factor in development of primary adrenal insufficiency in the developing world [19]. Detection of impaired adrenocortical function is of potential relevance as cortisol deficiency could account for unexpected deaths seen occasionally in patients with tuberculosis [1].

The basal cortisol value was comparable in both the control group and persons with PTB. The 30 minute cortisol value was however significantly lower in persons with PTB. This is similar to the finding of Sharma *et al* and Zargar et al in their studies of persons with tuberculosis [20, 21]. Ten (22.7%) of our forty-four persons with PTB had adrenocortical insufficiency (using the peak cortisol <380nmol/L and increment <158nmol/L to define adrenocortical insufficiency). This percentage is lower than that reported by Zargar *et al* [21] who found adrenocortical insufficiency in 35% of patients studied.

The number of patients with adrenocortical insufficiency in this study was also less than that reported in a large study from South Africa where suboptimal responses to ACTH stimulation was found in 55% of persons with PTB [4]. Using the serum cortisol level of 500nmol/L suggested as cutoff point [22], 54.5% of PTB patients in this study would be classified as having adrenocortical insufficiency. This is regarded as an overestimate hence the use of the stringent diagnostic criteria in this study.

The abnormal response may be attributable to minimal degree of adrenal damage recognised in cases from autopsy studies [23, 24]. 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.

One (10.0%) person out of the ten with adrenocortical insufficiency had hyponatraemia which could have been due to other causes. None of the persons with PTB had hyperpigmentation or postural hypotension. This was similar to the finding in a previous study [25]. The significant difference in the weight between persons with PTB and the healthy controls is most likely due to weight loss due to the chronic nature of PTB. These groups of people (persons with PTB)

have normal basal cortisol level. Weight, however, have no effect on their (persons with PTB) adrenal response to ACTH stimulation [13].

The mean fasting plasma glucose is significantly different in persons with PTB and healthy control. However it is within the acceptable normal range. None of the subjects had hypoglycaemia. Those with impaired cortisol response had no record of hypoglycaemia. This is similar to the findings in previous studies [19,25]. Each of these studies found glucose concentration to be similar in those with an impaired cortisol response and those with normal response. The normoglycaemia seen in them is explained by their normal basal cortisol level.

The peak cortisol response to ACTH stimulation have been shown to be more reliable in the diagnosis of adrenocortical insufficiency as reported in other studies [6,25,26,27]. However, combining the peak cortisol response to ACTH stimulation and serum cortisol increment to diagnose adrenocortical insufficiency will reduce overestimation.

Clinically evident adrenocortical insufficiency is uncommon in persons with PTB infection. Adrenocortical reserve may be impaired as shown by the subnormal response to ACTH stimulation test by persons with PTB infection.

Adrenocortical dysfunction is a potentially life-threatening condition that may affect about 23% of persons with PTB infection. This diagnosis should be considered whenever this group of people undergoes stressful conditions such as trauma and infection. It is important to establish that the adrenocortical reserve is intact in this group of people to prevent adrenal crisis when they are subjected to stressful conditions.

Measurement of plasma ACTH would have been of value in the diagnosis of primary adrenal failure. This, however, was not employed in this study. It would have been ideal to screen the healthy volunteers for PTB but for financial reasons, it was not done. It is thus possible to have recruited some healthy subjects that have PTB into the study. However, they appear reasonably healthy. Magnetic resonance imaging of the abdomen for adrenal gland pathology would have been helpful in the diagnosis of tuberculosis of the adrenal gland. This was not done due to financial reason.

Conclusion

Basal serum cortisol levels are within the normal range in many persons with PTB infection even in the presence of reduced adrenocortical function. Adrenocortical insufficiency, mostly at the subclinical level, is common in persons with PTB infection, occurring in about 23% of patients. We therefore recommend that basal cortisol levels should not be used to detect adrenocortical insufficiency; rather stimulation tests should be used to exclude or confirm suspected adrenocortical insufficiency in patients with PTB. We also recommend that routine use of corticosteroids is not recommended in persons with PTB. However, corticosteroid use may be indicated when these persons with biochemical evidence of subclinical adrenocortical insufficiency are exposed to stressful conditions like surgery, infections or trauma.

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Received: 19/05/10
Accepted: 08/11/10