Functional Adrenal Insufficiency among Tuberculosis-Human Immunodeficiency Virus co-infected patients: A Cross-section study in Uganda

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Abstract

Objective Tuberculosis (TB) is the leading cause of adrenal insufficiency in resource-limited settings. The adrenal gland is the most commonly affected endocrine organ in TB infection. We assessed prevalence and factors associated with functional adrenal insufficiency (FAI) among human immunodeficiency virus (HIV)-infected patients with drug-resistant and drug-susceptible TB in Uganda. Patients with drug-sensitive and -resistant TB were enrolled, examined for clinical signs and symptoms of FAI with an early morning serum cortisol level obtained. FAI was defined as early morning serum cortisol <414 nmol//L. Associations with FAI were modeled using multivariable logistic regression.

Results : A total of 311 TB patients were screened, and 272 enrolled. Of these, 117 (43%) had drug-resistant TB. Median age was 32 years (IQR 18-66) and 66% were men. Prevalence of FAI was 59.8%. Mean cortisol levels were lower in participants with drug-resistant than susceptible TB (317.4 versus 488.5 nmol/L; p<0.001) . In multivariable analysis, drug-resistant TB (aOR 4.61; 95% CI: 2.3-9.1; p < 0.001), treatment duration > 1month (aOR 2.86 95% CI: 1.4- 5.5; p=0.002) and abdominal pain (aOR 2.06; 95% CI: 1.04-4.09; p=0.038) were significantly associated with FAI. Early morning serum cortisol levels should be quantified in TB-HIV co-infected patients.

Introduction

Functional adrenal insufficiency (FAI), subnormal corticosteroid production during acute illness, results in high morbidity and mortality in critically ill patients [1, 2]. FAI is common among HIV-infected patients, with incidence rates up to 75% [3]. *Mycobacteria tuberculosis* and cytomegalovirus (CMV) infection [4] are the commonest etiologies of FAI, also it has been described with *Cryptococcus neoformans*, *Toxoplasma gondii*, *Pneumocystis jiroveci*, non-Hodgkin's lymphoma and Kaposi's sarcoma [5, 6]. Adrenal dysfunction results from infectious infiltration of adrenal gland, inhibition of steroid synthesis by drugs used for opportunistic infections (e.g., ketoconazole), and stimulation of cytochrome P450 enzyme by rifampicin resulting in increased metabolism of cortisol, and cytokine abnormalities associated with HV infection [7-9]. Adrenal tuberculosis leads to adrenal insufficiency through direct glandular involvement, extra-adrenal infection or as a result of anti-tuberculous therapy [10]. Patients with drug resistant tuberculosis (DR-TB) have significantly longer duration of disease than those with drug sensitive (DS) TB [11], remain sputum positive for longer and have higher bacteriologic loads which increases risk of disseminated TB [11]. Subclinical FAI occurs in 23% of persons with pulmonary TB (PTB) infection [12], and is prevalent among patients with both DS and DR TB [11]. HIV and TB co-infection may compromise adrenocortical function and produce significant adrenocortical insufficiency [13].Globally, MDR-TB occurred in 3.5% of new and 18% of previously treated cases in 2017 [14]. In Uganda, a high TB-HIV burden country, prevalence of MDR-TB was 1.6% among newly diagnosed patients and 12.0% among previously treated patients [15]. Among ill HIV-infected adults in Uganda, FAI occurred in 19%, and those receiving rifampicin were 11 times as likely to have FAI [16]. A retrospective analysis of 13,762 patients (13,492 autopsies and 270 adrenalectomies) in Hong Kong found that active TB was present in 871 patients (6.5%) of 13,492 autopsies performed [17].

FAI is often missed or delayed [18]. Delayed diagnosis causes adrenal crisis, which is associated with increased morbidity and mortality [19]. Adrenocortical dysfunction is a known MDR-TB comorbidity [20]. One study found low prevalence of FAI among HIV-negative MDR-TB patients in Mexico, a low TB burden country [20]. We assessed the prevalence of FAI among TB patients in Uganda, a high TB burden country; hypothesizing that those with drug-resistant disease may be at higher risk for FAI.

Materials And Methods

Study design and setting

From September 2015 to February 2016, a cross-sectional study conducted at Mulago National TB Treatment Centre, in Kampala, Uganda, which has 60 and 40 beds for patients with DS-TB and DR-TB, respectively.

Participants

Out and in-patients diagnosed with TB and seeking treatment at Mulago National TB Treatment Centre were screened. We consecutively sampled in-patients and used convenience sampling for out-patients. Participants were referred by clinical staff. A research assistant stationed at the Center from Monday to Saturday provided Study information and obtained written informed consent prior to enrollment.

We verified drug resistance and HIV status by reviewing medical files. We excluded patients without Xpert® MTB/RIF or drug susceptibility testing (DST) results, those with history of steroid use in the prior 5 days, fluconazole use, pregnancy, diabetes mellitus, extra pulmonary TB or inability to provide informed consent (refusal, language barrier or unconscious with no attendant).

Variables

We obtained HIV and treatment status, TB past and current treatment, drug-susceptibility test results and verified primary or secondary drug-resistance from the participant's treatment card. Clinical examination was performed to assess hyperpigmentation of buccal mucosa, palms, and scarred skin, postural hypotension to assess for signs of adrenocortical failure. Early morning blood draws for serum cortisol level, electrolytes and complete blood count were performed.

Data collection and outcome measures

Functional Adrenal Insufficiency, the main outcome variable was defined as early morning serum cortisol ≤ 414 nmol/L [2]. Blood was drawn between 0700 and 0930 hours for serum cortisol, potassium, sodium,

calcium, and complete blood count. Total serum cortisol was measured using Cortisol ELISA Test (Diagnostic Automation Inc., California) with detection range 1-100 ng/ml (0.32-31.45 nmol/L). Diagnosis of rifampicin resistant-TB was performed using the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). Drug susceptibility testing for multidrug resistance was performed using the BACTEC MGIT 960 system (Becton Dickinson Microbiology System, Sparks, NV, USA) and Löwenstein-Jensen (L-J) media. An interviewer-administered questionnaire used to collect data on HIV and treatment status, TB past and current treatment, drug-susceptibility test results, patient demographics, and medical history.

Sample size estimation was guided by the difference between 2 proportions formula, assuming a 5% standard error, previous prevalence of FAI of 46% in DR-TB and 36% in DS-TB [21], giving a size of 191 for each group.

Statistical Analysis

Data were entered into Epi-Data version 3.1 and exported to Stata version 13.0 (StataCorp, College Station, TX, USA). A Student t-test was used to assess differences in serum cortisol for DR-TB and DS-TB participants. Associations with FAI were modeled using logistic regression. All significant variables at bivariate analysis were used in multivariate logistic regression model. All analyses were performed using Stata. Two-sided p-values ≤0.05 were considered statistically significant.

Results

Participant characteristics

Of the 311 participants (213 in-patients and 98 out-patients) screened, 272 were enrolled. Of these, 155 (57%) had drug-susceptible TB (DS-TB) and 117 had DR-TB (Figure S1). A total of 154 (57%) were HIV co-infected of whom 85 (57%) had DS-TB and 69 had DR-TB. The median age was 32 years (interquartile range [IQR] 18-66) and 180 (66%) were men. Baseline characteristics were comparable between DR-TB and DS-TB participants (Table 1). A total of 20 (7.4%) participants were TB treatment naïve. The median duration of TB treatment at enrollment was 4.6 months (IQR 1-6), and similar proportions of primary and secondary DR-TB (51% versus 49%, respectively). Compared with DR-TB patients, a larger proportion of DS-TB patients had clinical features of weight loss, including prominent zygoma (72.5% versus 54.7%; p=0.002) and prominent supraclavicular fossa (82.3% versus 69.0%; p=0.01) (Table1).

Functional adrenal insufficiency

Overall prevalence of FAI was 59.8%. The median serum cortisol was 414.27nmol/L (IQR 65.68-1380.00). DR-TB participants were more likely to have low basal morning [AM] serum cortisol (≤414.0nmol/L) levels compared to DS-TB (82.9% versus 42.1%; p<0.001). Similarly, mean cortisol levels were

significantly lower in DR-TB participants than DS-TB (317.4 versus 488.5 nmol/L; p<0.001). Cortisol levels remained lower among DR-TB participants irrespective of month of treatment (Figure 1).

Associations with FAI

In multivariate logistic regression analysis, participants with DR-TB were 5 times as likely to have FAI (adjusted odds ratio [aOR] 4.61; 95% confidence interval [CI] 2.3-9.1; p<0.001) [Table S1]. Being male was not associated with FAI (aOR 0.81; 95% CI: 0.43-1.5; p=0.53). Participants with FAI were more likely to report a history of abdominal pain (aOR 2.06; 95% CI; 1.04-4.09; p = 0. 038), 56% less likely to have skin hyperpigmentation (darkened palms and buccal mucosa) (aOR 0.44; 95% CI: 0.23-0.87; p= 0.02). Analysis by subgroups DS and DR-TB showed DS-TB patients with FAI were more likely to have been on prolonged treatment and 70% less likely to have skin hyperpigmentation (Tables S2 and S3).

Discussion

This cross-sectional study of HIV-TB co-infected adults in Uganda, had a high prevalence of FAI. FAI was prevalent in 42% of DS-TB compared to 83% of DR-TB. Mean serum cortisol levels were significantly lower among DR-TB participants. FAI was more likely among DR-TB co-infection, those reporting history of abdominal pain and treatment duration >1month, but less likely among men and those with skin hyperpigmentation.

Prevalence of FAI observed is higher than previously reported in India [11], Nigeria [12] and Uganda [16, 22], perhaps due to inclusion of persons co-infected with HIV which causes infectious adrenalitis [16]. By contrast, a study in Mexico among HIV-uninfected DR-TB patients, with equal numbers of primary and secondary multi-drug resistant TB cases, found a baseline prevalence of 4.2% using a serum cortisol cutoff of 500 nmol/L, and a prevalence of 8.3% when the cutoff was 550 nmol/L [20]. Delayed diagnosis and initiation of TB treatment in our setting may have led to hematogenous spread to the adrenal glands. Additionally, previous use of rifampicin, which enhances cortisol metabolism [16, 23], may account for the high FAI prevalence observed. Our data suggest that clinical management of TB-HIV co-infected patients should include assessment of adrenal function because FAI increases morbidity and mortality [24].

DR-TB participants had lower mean cortisol levels and higher FAI prevalence than DS-TB. Prevalence of DR-TB is higher in previously treated TB patients [25], and the lower cortisol levels observed in DR-TB patients were likely due to delays in initiating TB treatment or to previous TB episodes increasing the likelihood of adrenal gland infiltration [26]. Additionally, standard TB treatment regimens include rifampicin which accelerates cortisol breakdown resulting in low cortisol levels. This explains our finding that treatment duration >1month was associated with FAI among DS-TB patients in subgroup analyses [27]. This agrees with prior studies suggesting an association of adrenal insufficiency with rifampicin which is among the drugs for DS-TB treatment category 1 and 2 [28]. Men were less likely to have

adrenal insufficiency. Although TB is more prevalent in males, estrogen increases hepatic cortisol-binding globulin which lowers active free cortisol [18, 29]. Our finding agrees with prior work that showed that males have significantly higher free cortisol levels than females [30].

Infectious adrenalitis can be difficult to recognize clinically [31]. In low-income settings, where synthetic ACTH is not readily available for the gold standard stimulation test, relying on symptoms and signs usually leads to misdiagnosis, under diagnosis or delayed diagnosis [18]. However, symptoms including weakness/fatigue, anorexia, nausea and vomiting, abdominal pain, myalgia or arthralgia, postural dizziness, craving for salt, headache, depression and memory impairment may be suggestive of FAI [21] [32, 33]. In our study, abdominal pain, treatment duration was associated with FAI, contrary to prior studies in which primary adrenal insufficiency was associated with hyperpigmentation of the buccal mucosa, palms and scarred areas of the skin [22, 34]. Darkening of the palms, persistent postural dizziness, fatigability, profound general body weakness, and syncope have been reported in a case of HIV-associated Addison's disease without symptoms of PTB [35]. Skin hyperpigmentation is a specific sign of adrenal insufficiency, due to stimulation of melanocortin-1 receptors by the high levels of corticotrophin hormone due to lack of feedback from reduced cortisol levels [36].

In agreement with prior work [22], we found that history of abdominal pain was more likely among participants with FAI. Abdominal, flank and back pain is a common presentation in acute adrenal crisis mainly due to increased adrenal blood flow induced by increased secretion of ACTH [37]. Clinical manifestations of adrenal insufficiency result from deficiency of adrenocortical hormones secondary to adrenal cortex destruction , in the subgroup analysis DS-TB patients with FAI were twice likely to report abdominal pain [36, 38]. Hypotension in adrenal insufficiency is caused by inappropriate increases in arginine vasopressin, reduced aldosterone and sodium wasting [37]. Prior work in Uganda, found 43% of patients with FAI had systolic hypotension and 19% demonstrated a postural drop in blood pressure. Other work in the same setting found that 50% participants with adrenal insufficiency had systolic hypotension, and 29.2% had mucosal hyperpigmentation [22].

Conclusions

We found high FAI prevalence as assessed by morning cortisol levels among adults co-infected with HIV and TB. Presence of DR-TB, abdominal pain and treatment duration were associated with FAI. These factors may help clinicians in HIV/TB burdened resource limited settings to identify FAI, and should be confirmed with early morning cortisol to guide management.

Limitations

The inability to determine temporal relationships of HIV and TB infection in dually infected limited analysis of clinical correlates of FAI. Failure to do sensitivity analysis to address the issue of rifampicin-induced adrenal insufficiency due to the small number of treatment naïve. Exclusion of patients without Xpert® MTB/RIF or DST results or unable to consent, probably excluded sicker participants with FAI.

Limitation to assess adrenal morphology by CT-Scan. Lack of gold standard ACTH stimulation test in our setting probably misclassified FAI status in some participants. A strength of our study is inclusion of HIV sero-positive and negative DR-TB and DS-TB participants, and the high prevalence of TB-HIV co-infection (50%).

Abbreviations

ACTH: Adreno corticotropic hormone

CMV: Cytomegalo Virus

CT: Computerized Tomography

DR-TB: Drug-Resistant tuberculosis

DST: Drug susceptibility Test

DS-TB: drug-sensitive Tuberculosis

ELISA: Enzyme Linked Immuno Sorbent Assay

FAI: Functional Adrenal Insufficiency

HIV: Human Immunodeficiency Virus

IQR: Inter Quartile range

TB: Tuberculosis

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Makerere University School of Medicine Research and Ethics Committee (Ref No.2015-067) and the Uganda National Council for Science and Technology (Ref HS 2290). All study participants gave written informed consent prior to study procedures.

Availability of data and material

All the data supporting the findings is submitted with the manuscript and in 2 additional supporting files.

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Consent for publication

Not applicable

Competing interests

Authors declare that they have no competing interests

Authors' contributions

ABN, YM conceived and designed the study and contributed to data collection, statistical analysis and manuscript preparation. EM performed the statistical analyses. IAB, DBM, WW, AM and YM contributed to interpretation of results and writing of the manuscript and all approved the final draft.

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Table

Table 1. Participant Characteristics (insert under results at end of line 135, on page 6)

Demographic Characteristics	**DS- TB** (n=155) N (%)	**DR-TB*** (n=117) N (%)	**P-value**
Age (years)			0.783
≤30	82 (55.0)	62 (53.5)	
31-45	50 (33.6)	43 (37.1)	
≥46	18 (11.4)	11 (9.5)	
Sex			0.355
Male	103 (66.7)	72 (62.2)	
Female	52 (33.3)	45 (38.8)	
HIV status			0.404
Positive	85 (54.8)	69 (59.0)	
Negative	70 (45.2)	48 (41.0)	
HIV treatment			<0.001
ART naïve	38 (47.5)	4 (6.1)	
TDF-based regimens	27 (33.8)	40 (60.6)	
Other regimens	15 (18.8)	22 (33.3)	
TB treatment history			<0.001
Category 1	117 (94.4)	52 (70.3)	
Category 2	7 (5.6)	22 (29.7)	
Current TB treatment duration			< 0.001
<1 month	102 (68)	32 (28)	
<1 month	49 (32)	84 (72)	
History of abdominal pain			0.784
No	64 (41.8)	47 (41.9)	
Yes	89 (58.5)	70 (58.1)	
History of weight loss			<0.001
No	13 (8.5)	30 (25.6)	
Yes	140 (91.5)	87 (74.4)	
Clinical Characteristics			
Weight loss-prominent zygoma			0.002

No	42 (27.5)	53 (45.3)	
Yes	111 (72.5)	64 (54.7)	
Weight loss-supraclavicular fossa			0.010
No	27 (17.7)	36 (31.0)	
Yes	126 (82.3)	80 (69.0)	
Serum cortisol (nmol/L)			<0.001
<414	64 (42.1)	97 (82.9)	
>414	88 (57.9)	20 (17.1)	
Sodium [Na] (mmol/L)			<0.001
Low (<135)	43 (27.7)	12 (10.3)	
Normal (≥135)	112 (72.3)	105 (89.7)	
Potassium [K] (mmol/L)			0.043
≤5.0	125 (80.7)	104 (89.7)	
>5.0	30 (19.3)	12 (10.3)	
Haemoglobin (g/dL)			<0.001
≤9	46 (29.7)	10 (8.6)	
>9	109 (70.3)	106 (91.4)	

Category 1 TB treatment for new smear positive pulmonary TB (6 months of Isoniazid, rifampicin, and initial 2 months of ethambutol, pyrazinamide).
Category 2 TB treatment Sputum smear positive who have relapsed or who have treatment failure or who are receiving treatment after treatment interruption (8 months of isoniazid, rifampicin and ethambutol supplemented by streptomycin for initial 2 months, and pyrazinamide for initial 3 months).

* 56 participants had primary DR-TB and 54 had secondary DR-TB. Data were missing for 7 participants

participants

[a] data of missing cases excluded from analysis

Figures

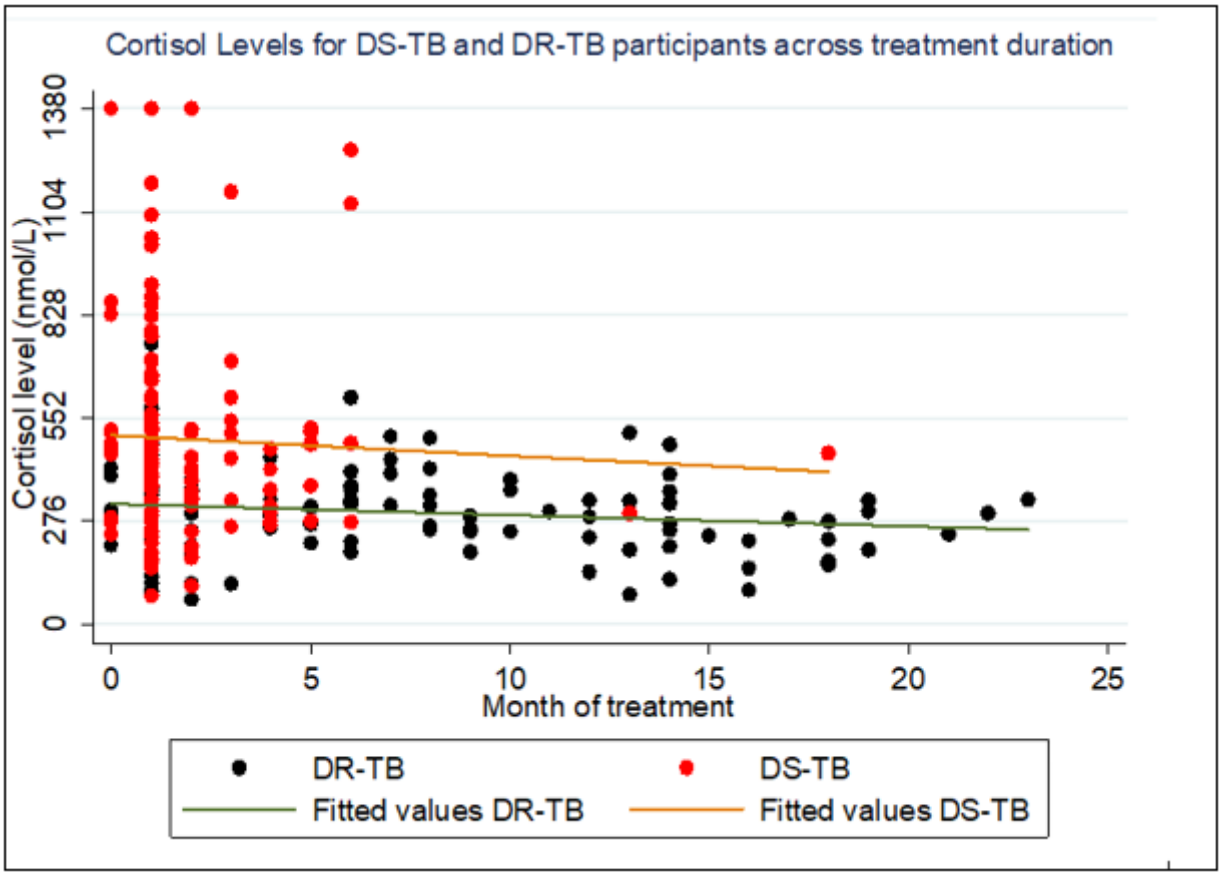

Figure 1

Cortisol Levels for DS-TB and DR-TB participants across treatment duration (insert under results section, at end of line 143, on page 7)

Supplementary Files

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