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

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Abstract

Objective:

Tuberculosis is the leading cause of adrenal insufficiency in resource-limited settings. The adrenal gland is the most commonly affected endocrine organ in tuberculosis infection. We assessed prevalence and factors associated with functional adrenal insufficiency among human immunodeficiency virus infected patients with multidrug-resistant and drug-susceptible tuberculosis in Uganda.

Patients with drug-sensitive and resistant tuberculosis were enrolled, examined for clinical signs and symptoms of adrenal insufficiency, an early morning serum cortisol level obtained. Functional adrenal insufficiency was defined as early morning serum cortisol below 414/nmol//L. Associations with functional adrenal insufficiency were estimated using multivariable logistic regression.

Results

A total of 311 tuberculosis patients were screened, and 272 enrolled. Of these, 117 (43%) had multi-drug resistant tuberculosis. Median age was 32 years (IQR 18-66) and 66% were men. Prevalence of functional adrenal insufficiency was 59.8%. Mean cortisol levels were lower in participants with multi-drug resistant than drug-susceptible tuberculosis (317.4 versus 488.5 nmol/L; p<0.001**)**. In multivariable analysis, multi-drug resistant tuberculosis (aOR 36.60; 95% CI 8.30-161.42; p**<**0.001) and skin hyperpigmentation (aOR 9.63; 95% CI: 2.83-32.8; p<0.001) were significantly associated with functional adrenal insufficiency. Early morning serum cortisol levels should be quantified in TB-HIV co-infected patients.

Introduction

Functional adrenal insufficiency, subnormal corticosteroid production during acute illness, results in high morbidity and mortality in critically ill patients [1, 2]. Infectious adrenalitis is the leading cause of adrenal insufficiency in resource-limited settings. Functional adrenal insufficiency (FAI) is common among severely ill HIV-infected patients, with incidence rates up to 75% [3]. *Mycobacteria tuberculosis* and cytomegalovirus (CMV) infection [4] are the most common etiologies of FAI, although it has also been described with *Cryptococcus neoformans, Toxoplasma gondii, Pneumocystis jiroveci,* non-Hodgkin's lymphoma and Kaposi's sarcoma [5, 6]. Adrenal dysfunction may result in infectious infiltration of the adrenal gland, inhibition of steroid synthesis by antifungal drugs used to treat opportunistic infections (e.g., ketoconazole), stimulation of cytochrome P450 enzyme activity by rifampicin resulting in increased metabolism of cortisol, and cytokine abnormalities associated with HV infection [7–9]. Subclinical FAI occurs in 23% of persons with pulmonary tuberculosis (PTB) infection [10], and is prevalent among patients with drug-sensitive and drug-resistant (DR) TB [11]. Human immunodeficiency virus (HIV) and TB co-infection may compromise adrenocortical function and produce significant adrenocortical insufficiency [12].

The World Health Organization (WHO) estimates that 190,000 people died of multi drug-resistant tuberculosis (MDR-TB) in 2017 [13]. Globally, MDR-TB occurred in 3.5% of new and 18% of previously treated cases in 2017 [13]. 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 in 2017 [14]. Among severely ill HIV-infected adults in Uganda, FAI occurred in 19% of cases, and those receiving rifampicin were 11 times as likely to have FAI [15]. Notably, 30% of TB/HIV co-infected patients who had FAI but did not receive corticosteroid therapy died. A large 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 [16]. Adrenal TB was observed at autopsy in 52 (6%) of 871 and in 3 patients at adrenalectomy. The adrenal gland was the only organ with active TB in 14 (25%) of 55 cases (52 autopsies and 3 adrenalectomies), suggesting that adrenal TB should be considered in the differential diagnosis of extra-pulmonary TB.

The diagnosis of FAI is often missed or delayed [17]. Delayed diagnosis is a frequent cause of adrenal crisis, which is associated with increased morbidity and mortality [18]. Adrenocortical dysfunction is a known comorbidity of MDR-TB [19]. One study found low prevalence of FAI among HIV-negative MDR-TB patients in Mexico, a low TB burden country [19]. We aimed to assess the prevalence of FAI among TB patients in Uganda, a high TB burden country; we hypothesized that those with drug-resistant disease experience treatment delays and may be at higher risk for FAI.

Materials And Methods

Subjects and setting

From September 2015 to February 2016, we conducted a cross-sectional study, screened 311 patients at Mulago National Tuberculosis Treatment Centre, in Kampala, Uganda. Patients were recruited from the 100-bed TB unit, which has 60 and 40 beds for patients with drug-susceptible and drug-resistant TB, respectively. We consecutively sampled in-patients and used convenience sampling for out-patients. Each participant received information about the study and provided written informed consent prior to enrollment. A medical history (including HIV diagnosis and treatment status and current and past TB treatment) was obtained, and clinical examination performed to assess darkening of buccal mucosa, palms, scarred skin, and postural hypotension, for all participants. Thereafter, we ascertained clinical signs of adrenocortical failure. 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, or inability to provide informed consent (refusal, language barrier or unconscious with no attendant).

Laboratory methods

Blood was drawn between 0700 and 0930 hours for serum cortisol, potassium, sodium, calcium, and complete blood count testing. 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); the gold standard ACTH stimulation test was not available in our setting. Diagnosis of rifampicin resistant-TB was performed using the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). DST for multidrug resistance was performed using the BACTEC MGIT 960 system (Becton Dickinson Microbiology System, Sparks, NV, USA) and Löwenstein-Jensen (L-J) media.

Statistical Analysis

The primary outcome was FAI, defined as a single early morning cortisol level ≤ 414nmo/L [2]. Data collected on structured questionnaires 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 between participants with MDR-TB and DS-TB. Associations with FAI were modeled using logistic regression. All the variables that were significant at the bivariate analysis were used in the multivariate 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 for the study, 272 were enrolled. Of these, 155 (57%) had drug-susceptible TB (DS-TB) and the remaining 117 had MDR-TB. A total of 154 participants (57%) were HIV co-infected of whom 85 (57%) had DS-TB and 69 had MDR-TB. The median age was 32 years (interquartile range [IQR] 18–66) and 180 (66%) were men. Baseline characteristics were comparable between MDR-TB and DS-TB participants (Table 1: Describing Participants Characteristics). A total of 20 (7.4%) participants were treatment naïve. The median duration of TB treatment at enrollment into the study was 4.6 months (IQR 1–6), and the proportion with primary and secondary MDR-TB was similar (51% versus 49%, respectively). Compared with MDR-TB patients, a larger proportion of DS-TB patients had clinical features of weight loss: prominent zygoma (72.5% versus 54.7%; p = 0.002) and prominent supraclavicular fossa (82.3% versus 69.0%; p = 0.01) (Table1*: Describes Participants' Characteristics).*

Functional adrenal insufficiency

The overall prevalence of FAI was 59.8%. The median serum cortisol was 414.27nmol/L (IQR 65.68–1380.00). Participants with MDR-TB were more likely to have low basal morning [AM] serum cortisol (≤414.0nmol/L) levels compared to those with DS-TB (82.9% versus 42.1%; p<0.001). Similarly, mean cortisol levels were significantly lower in participants with MDR-TB than DS-TB (317.4 versus 488.5 nmol/L; p<0.001). Cortisol levels remained persistently lower among MDR-TB participants irrespective of

the duration of treatment (Figure 1: Cortisol Levels for DS-TB and MDR-TB participants across treatment duration).

Associations with FAI

In the multivariate analysis, we found that participants with MDR-TB were 37 times as likely to have FAI (adjusted odds ratio [aOR] 36.60; 95% confidence interval [CI] 8.30–161.42; p<0.001). Male participants were 70% less likely to have FAI (aOR 0.30; 95% CI: 0.10–0.90; p = 0.032) (Table S1: Factors associated with FAI, see additional file 1). Participants with FAI were less likely to report a history of abdominal pain (aOR 0.21; 95% CI; 0.06–0.78; p = 0. 019) but more likely to have skin hyperpigmentation evidenced by darkened palms, and buccal mucosa (aOR 9.63; 95% CI: 2.83–32.0; p <0.001) (Table S1: Factors associated with FAI, see additional file 1).

Discussion

In this cross-sectional study of approximately 280 HIV-infected adults co-infected with TB in Uganda, we found a high prevalence of FAI. FAI was prevalent in 42% of those with drug susceptible TB compared to 83% with drug-resistant TB. Mean serum cortisol levels were significantly lower among participants with MDR-TB. FAI was more likely among those with MDR-TB co-infection and skin hyperpigmentation, but less likely among men and those reporting a history of abdominal pain.

The prevalence of FAI we observed is higher than that previously reported in India [11], Nigeria [10] and Uganda [15, 20], perhaps due to inclusion of persons co-infected with HIV which causes infectious adrenalitis [15]. By contrast, a study in Mexico among HIV-uninfected MDR-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 500nmol/L, and a prevalence of 8.3% when the cutoff was 550nmol/L [19]. These data suggest that the high FAI prevalence we report was due to TB co-infection in all study participants. Delayed diagnosis and initiation of TB treatment in our setting may have led to hematogenous spread to extra-pulmonary sites, including the adrenal glands. Additionally, previous use of rifampicin, which enhances cortisol metabolism [15, 21], may account for the high FAI prevalence we observed. Our data suggest that clinical management of HIV/TB co-infected patients should include assessment of adrenal function because FAI increases morbidity and mortality [22].

We found that participants with MDR-TB patients had lower mean cortisol levels and higher FAI prevalence than DS-TB patients. Prevalence of MDR is higher in previously treated TB patients [23], and the lower cortisol levels we observed in MDR-TB patients were likely due to delays in initiating TB treatment or to previous TB episodes which may have involved the adrenal glands and caused adrenal insufficiency [24]. Additionally, standard TB treatment regimens include rifampicin which may have accelerated cortisol breakdown resulting in low cortisol levels [25]. Men in our study 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 [17, 26]. Our finding is agreement with prior work that showed that males have significantly higher free cortisol levels than females [27].

Infectious adrenalitis can be difficult to recognize clinically. 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 [17]. 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[28] [29, 30]. In our study, skin hyperpigmentation was associated with FAI. This finding is in agreement with prior studies in which primary adrenal insufficiency was associated with hyperpigmentation of the buccal mucosa, palms and scarred areas of the skin [20, 31]. Progressive 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 [32]. 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 [33].

In contrast with prior work [20], we found that history of abdominal pain was less likely among participants with FAI, perhaps because of recall and social desirability bias. Abdominal, flank and back pain is a common presentation in acute adrenal crisis and is due to increased adrenal blood flow induced by increased secretion of ACTH [34]. Clinical manifestations of adrenal insufficiency result from deficiency of adrenocortical hormones secondary to adrenal cortex destruction [33, 35]. Hypotension in adrenal insufficiency is caused by inappropriate increases in arginine vasopressin, reduced aldosterone and sodium wasting [34]. 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% study participants with adrenal insufficiency had systolic hypotension, and 29.2% had mucosal hyperpigmentation [20].

Conclusions

In summary, we found high FAI prevalence as assessed by morning cortisol levels among African adults co-infected with HIV and TB. Presence of MDR-TB, weight loss and skin hyperpigmentation were associated with FAI. These factors may help clinicians in high HIV/TB burden resource limited settings to identify HIV/TB co-infected patients at risk for FAI, a diagnosis which should be confirmed with early morning cortisol to guide further treatment.

Limitations

A limitation of this cross-sectional study was the inability to determine temporal relationships of HIV and TB infection in dually infected individuals or the recency of TB infection thus limiting our analysis of clinical correlates of FAI. We were unable to do sensitivity analysis to address the issue of rifampicin-induced adrenal insufficiency due to the small number of TB treatment naïve participants. We excluded

patients without Xpert® MTB/RIF or DST results or those unable to provide consent and may have excluded sicker participants with FAI, thus limiting the precision of our point estimates. As a limitation of our setting, we did not have access to abdominal CT scan to assess adrenal morphology. Finally, the gold standard ACTH stimulation test was not available in our setting and we may have misclassified FAI status in some participants.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Makerere University School of Medicine Research and Ethics Committee (Rec 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 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 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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Tables

Table 1. Participant Characteristics (insert under "Results" at end of lines 126,132 on page 6)

Demographic Characteristics	**DS- TB** (n=155) N(%)	**MDR-TB*** (n=117) N 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
CAT 1	117 (94.4)	52 (70.3)	
CAT 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)	

CAT 1 = category 1 TB treatment; CAT 2 = category 2 TB treatment

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

participants

[a] data of missing cases excluded from analysis

Figures

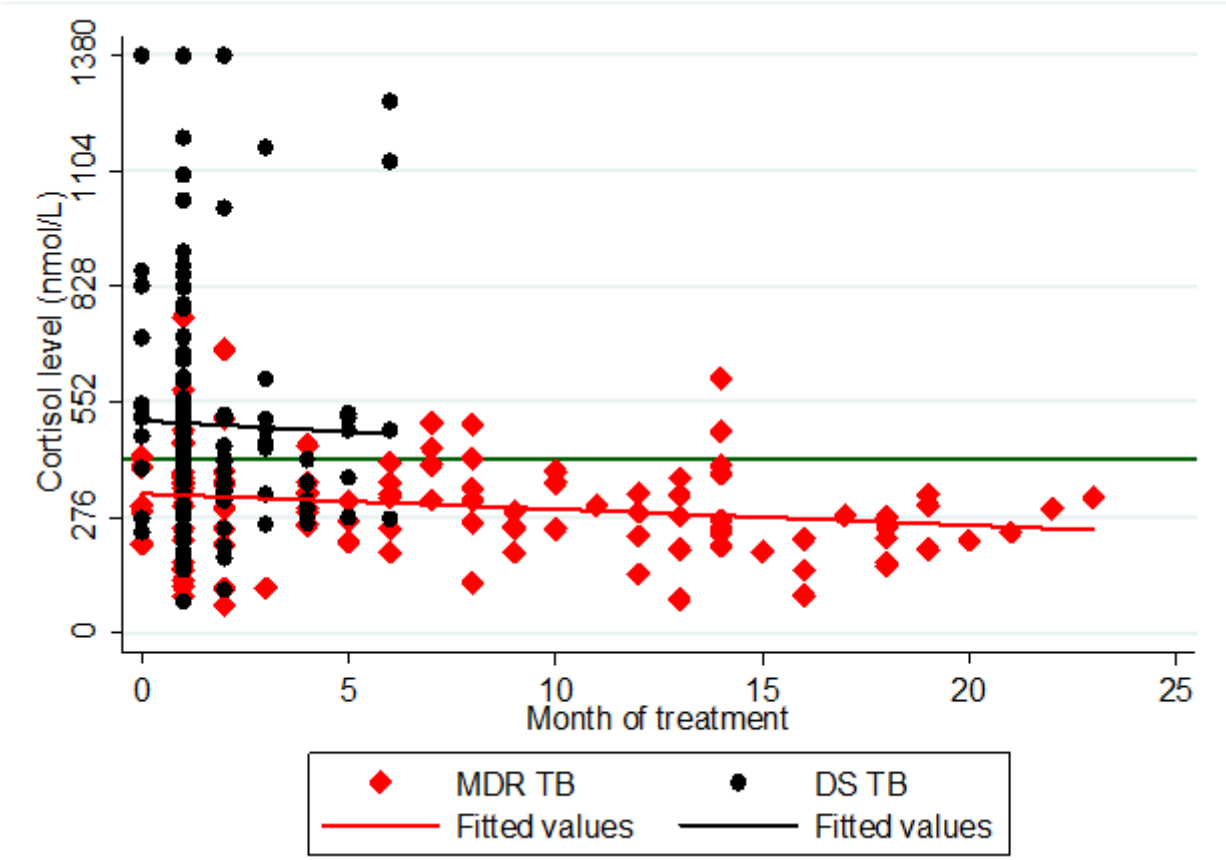

Figure 1

Cortisol Levels for DS-TB and MDR-TB participants across treatment duration (insert under results section, at end of line 140, on page 6)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx
- FigureS1.docx