

Original Article

Evaluation of Subclinical Adrenal Insufficiency in Patients with Active Tuberculosis

AA Abdullah¹, SM Arafat², MM Sabeka³, M Asaduzzaman⁴, MAB Siddque⁵

Abstract:

The existence of subclinical adrenal insufficiency in active tuberculosis is a matter of debate and little is known in this regard. This analytical cross-sectional study is contemplated to find out the association between active tuberculosis and subclinical adrenocortical insufficiency. Where 77 active tubercular patients have been included consecutively in the study along with 30 age and sex matched healthy controls for comparison. Nearly two-thirds (64.9%) of the cases were diagnosed as pulmonary tuberculosis and rest 35.1% as extra pulmonary tuberculosis. In pulmonary tuberculosis 68.8% had subclinical adrenal insufficiency but 31.2% in extra pulmonary tuberculosis. It shows that 62.3% of the cases had sub-clinical adrenocortical insufficiency as opposed to none in the control group ($p < 0.001$). Adrenal insufficiency appeared to be significantly associated with smear positivity, X-ray evidence of severe disease and multi-drug resistance. Therefore, physician ought to look for subclinical adrenal insufficiency among patients with active tuberculosis specially if they are sputum positive, X-ray evidence of severe disease and multidrug resistant TB.

Key words: Sub-clinical adrenal insufficiency, Active tuberculosis.

Introduction:

Tuberculosis is a global public health problem, causing significant morbidity, mortality and economic burden. Adrenal insufficiency may co-exist in many patients with tuberculosis, resulting in treatment failure and adding further to economic loss. Moreover, adrenal insufficiency is manifested in illusive way with unexplained fatigue or no symptoms at all. Therefore, high index of suspicion may save life. Treatment with glucocorticoid should be started along with treatment for tuberculosis. However, the existence of subclinical

insufficiency in active tuberculosis patients is a matter of debate and little is known about adrenal function in this situation^{1,2}. Lack of consensus on the status of adrenal reserve in patients with active tuberculosis preclude the physician initiating therapy.

Therefore, it is necessary to address the problem of adrenal insufficiency in patients with tuberculosis. The present study is contemplated to find out the association between active tuberculosis and subclinical adreno-cortical insufficiency. This study is expected to contribute to the knowledge of the physicians of Bangladesh and will help the policy makers to take necessary decisions in managing tuberculosis more efficiently in our country.

Materials and Methods:

The study has been conducted from January 2010 to December 2011, in the department of medicine and gastroenterology of Bangabandhu Sheikh Mujib Medical University (BSMMU) and in National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka. The laboratory support has been contributed by the department of Bio-chemistry, BSMMU, Dhaka. This is an analytical cross-sectional study where 77 patients with active tuberculosis have been included consecutively in the study along with 30 age

1. Dr. Abu Ahmed Abdullah, MBBS, MD (Internal Medicine), Senior consultant (Medicine), General Hospital, Faridpur.

2. Dr. Shohael Mahmud Arafat, MBBS, FCPS (Medicine), MRCP (UK), Professor, Department of Internal Medicine, BSMMU, Shahbag, Dhaka.

3. Dr. Meera Momtaz Sabeka, MBBS, MD (Neurology), MRCP(UK), MPH(Melbourne), Fellow in Epilepsy and EEG (Malaysia), Consultant Neurologist, William Harvey Hospital, Kent, England.

4. Dr. Md. Asaduzzaman, MBBS, MD (Internal Medicine), Senior consultant (Medicine), General Hospital, Satkhira.

5. Dr. Mohammad Abu Bakar Siddque, MBBS, MD (Internal Medicine), Assistant Professor, Department of Medicine, Faridpur Medical College.

Address of correspondence :

Dr. Abu Ahmed Abdullah, MBBS, MD (Internal Medicine), Senior consultant (Medicine), General Hospital, Faridpur.
Phone: +88 01911008674, E-mail: abdullahmasud72@gmail.com

and sex matched healthy controls for comparison. The diagnosis of active tuberculosis was made from clinical feature (with improvement of clinical condition following anti-tubercular chemotherapy), positive smear, positive culture, chest X-ray, high ESR, high ADA, positive pleural or ascitic fluid study, Biopsy/FNAC and PCR. Patients with overt clinical features of adrenal insufficiency, pregnancy, using hormonal contraception, chronic steroid therapy, chronic kidney disease, chronic liver disease, HIV seropositivity, chronic alcohol abuse, diabetes mellitus, hypertension, connective tissue disease, and patients on anti-tubercular chemotherapy for >24 hours were excluded from the study. All the subjects consented to participate after being informed about the nature and aim of the study. Ethical clearance was obtained from the Departmental Technical Committee, Department of Medicine, BSMMU and Institutional Review Board, BSMMU with due procedures.

Data were collected by semi-structured questionnaire that includes complete history with physical examination and blood samples were collected from each patient for basal serum cortisol level and serum cortisol level 45 minutes after intravenous injection of 1 μ gm ACTH. Subclinical adrenal insufficiency was diagnosed in patients whose basal cortisol level was low, normal or increased but post ACTH stimulation test showed <250nmol/l rise of serum cortisol than basal level.

Statistical analysis was done using SPSS(11.5). Unpaired t-test was carried out to compare between mean cortisol level (both basal and post ACTH) in cases and controls. Chi-square test was used to see the association between subclinical adrenal insufficiency and socio-demographic characteristics like age groups, gender, education, occupation, income groups, BMI, disease duration, smoking. Spearman correlation was done to show the relationship between increased cortisol level following ACTH stimulation and BMI.

Results:

The study enrolled total 77 untreated active tuberculosis patients as cases and 30 healthy subjects as controls to depict the association between subclinical adrenal insufficiency and active tuberculosis. Proportions of male patients were higher in both groups, with different representation from urban and rural area. Nearly 40% of the cases and 20% of the controls were smoker and about two-thirds (66.2%) of the cases were underweight as opposed to only 13.3% of the control group.

The median duration of illness was 12 weeks with cough (58.4%) (with sputum 27.3% and without sputum 21.3%), fever (98.7%), anorexia (84.4%),

significant weight loss (83.7%), night-sweating (75.3%), pleural effusion (35.5%), haemoptysis (24.7%), lymphadenopathy (16.9%), ascites (7.8%) and abdominal mass (5.2%) (Table I).

Table I: Distribution of patients according to demographic profile

Clinical features	Median (range)	Frequency (%)
Duration of illness (wks)	12(4 – 150)	----
Cough	----	45 (58.4)
With sputum		21(27.3)
Without sputum		11(14.3)
Fever	----	76(98.7)
Anorexia	----	65(84.4)
Significant weight loss	----	64(83.7)
Night sweating	----	58(75.3)
Pleural effusion	----	27(35.5)
Haemoptysis	----	19(24.7)
Characteristic lymphadenopathy	----	13(16.9)
Ascites	----	6(7.8)
Abdominal mass	----	4(5.2)

Nearly two-thirds (64.9%) of the cases were diagnosed as pulmonary tuberculosis and rest 35.1% as extrapulmonary tuberculosis. About two-thirds (66%) of the pulmonary tuberculosis patients had sputum smear positive for AFB and 34% negative. Pulmonary lesion was minimal in 5(10%), moderately advanced in 12(24%) and far advanced in 33(66%) patients (Table II).

Table II: Distribution of patients according to diagnosis (n=77)

Diagnosis	Frequency (%)
Type of tuberculosis (n = 77)	
Pulmonary	50(64.9)
Extrapulmonary	27(35.1)
AFB(n = 50)	
Positive	33(66.0)
Negative	13(26.0)
Not done	04(8.0)
Extent of pulmonary lesion (n = 50)	
Minimal	05(10.0)
Moderately advanced	12(24.0)
Far advanced	33(66.0)

Table III shows that 62.3% of the cases had < 250 nmol/L increase of serum cortisol from their basal cortisol level (sub-clinical adrenocortical insufficiency) as opposed to none in the control group (p < 0.001).

Table III: Comparison of subclinical adrenal insufficiency between cases and controls

Increase serum cortisol after ACTH stimulation (nmol/L)	Group		p-value
	Case (n = 77)	Control (n = 30)	
< 250	48(62.3)	0(0.0)	<0.001
≥250	29(37.7)	30(100.0)	

Figures in the parentheses denote corresponding percentage.

Data were analyzed using Chi-square test.

Table IV shows that the basal cortisol was significantly higher in the case group than that in the control group ($p < 0.001$). No significant difference was observed between the groups in terms of post ACTH cortisol level ($p = 0.202$).

Table IV: Comparison of serum cortisol level between case and control

Serum cortisol (nmol/L)	Group		p-value
	Case (n = 77)	Control (n = 30)	
Basal	429.3 ± 227.1	196.1 ± 78.5	< 0.001
Post ACTH	646.2 ± 242.8	587.2 ± 102.2	0.202

Figures in the parentheses denote corresponding percentage.

Data were analyzed using Student's t-Test and were presented as mean ± SD

Certain demographic and TB-related factors or variables were supposed to be associated with subclinical adrenocortical insufficiency and such they were tested using Chi-square Test (Table V). None of these variables (BMI, smoking habit, duration of disease, type of TB and MDR TB) except radiological extent of PTB was found to be associated with subclinical adrenocortical insufficiency ($p = 0.007$). Smear positive PTB was significantly higher in subclinical adrenocortical insufficiency ($p = 0.027$).

Table V: Association between certain demographic and TB-related factors and subclinical adrenocortical insufficiency

Factors/variables	Serum cortisol increase after ACTH stimulation (nmol/L)		p-value
	< 250 (n = 48)	≥250 (n = 29)	
BMI (kg/m ²)			
< 18.5 (Underweight)	32(66.7)	19(65.5)	0.918
≥18.5 (Normal)	16(33.3)	10(34.5)	
Smoking status			
Smoker	11(22.9)	8(27.6)	0.714
Non-smoker	66(77.1)	22(72.4)	
Duration of disease (weeks)			
< 12	22(45.8)	13(44.8)	0.932
≥12	26(54.2)	16(55.2)	
Type of TB			
Pulmonary	33(68.8)	17(58.6)	0.372
Extrapulmonary	15(31.2)	12(41.4)	
MDR TB			
Yes	4(8.3)	3(10.3)	0.007
No	44(91.7)	26(89.7)	
Extent of TB (X-ray evidence)			
Minimal/moderately advanced	6(18.2)	10(62.5)	0.007
Far advanced	27(81.8)	6(37.5)	
Smear positive PTB	26(78.8)	7(41.2)	0.027
Smear negative PTB	5(21.2)	8(57.8)	

Figures in the parentheses denote corresponding percentage.

Data were analyzed using Chi-square (X^2) test.

Discussion:

Existence of functional hypoadrenalism with anatomically normal adrenal glands has been reported in patients with untreated active tuberculosis by Sharma et al³, Prasad et al⁴ and Zargar et al⁵. In the present study, active tuberculosis was diagnosed on the basis of criteria described by Zargar et al⁵ and Gordon et al⁶.

Nearly two-thirds (64.9%) of the cases were diagnosed as pulmonary tuberculosis and rest 35.1% as extra pulmonary tuberculosis. Adrenocortical insufficiency was found in 66% patients with pulmonary tuberculosis as opposed to 34% with extra pulmonary tuberculosis. This result of current study is higher than the result revealed by Zargar et al⁵.

The current study shows that 62.3% of the cases had <250 nmol/L increase of serum cortisol from their basal cortisol level (sub-clinical adrenocortical insufficiency) as opposed to none in the control group ($p < 0.001$). Zargar et al⁵ revealed that 35% patients had suboptimal response and 65% had normal response to ACTH stimulation. Chan et al⁷ showed 41%, Ellis et al⁸ showed 55% and Mugusi et al⁹ showed 32%. In their study, 32.14% patients with PTB had suboptimal response and 41.67% with extra pulmonary tuberculosis had suboptimal response. Sharma et al³ demonstrated evidence of compromised adrenal reserve in 49.5% active tuberculosis patients, 50% of PTB patients, 51.6% of disseminated tuberculosis patients and 48% of MDR TB patients. Result of this study is much higher than the others that is more patients are having adrenocortical insufficiency, probably due to higher proportion of patient had extensive pulmonary disease, low BMI and use of physiological dose of ACTH.

Basal cortisol was significantly higher in the case group than that in the control group ($p < 0.001$). No significant difference was observed between the groups in terms of post ACTH cortisol level ($p = 0.202$). These findings are in agreement with few earlier studies by Zargar et al⁵, Mugusi et al⁹, Kaplan et al¹⁰, Behera et al¹¹, Frenkel et al¹², Levi et al¹³ but contrary to Prasad et al⁴ and Sharma et al³.

Radiological extent of PTB was found to be associated with subclinical adrenocortical insufficiency ($p=0.007$). Disease severity (PTB) was obtained by CXR and was staged as mild/moderate and severe. Cortisol level was suboptimal (<250 nmol) in 6(18.2%) of minimal/moderately advanced cases, whereas adrenal insufficiency was found among 27 (81.8%) far advanced cases. Zargar et al⁵ revealed in their study that suboptimal cortisol response to ACTH was more frequently observed in patients with far advanced tuberculosis (66.7%) than those with minimal lesion tuberculosis (11.11%). York et al¹⁴ also revealed significant diurnal variation of cortisol level among those with more extensive disease roentgen graphically.

Conclusion:

Subclinical adrenal insufficiency may increase the sufferings of patients with active tuberculosis and this hidden condition needs steroid replacement therapy. This study is expected to shed light in the existing knowledge base and help the physician to manage their patients with greater efficiency. Physician ought to look for subclinical insufficiency among patients with active tuberculosis especially if they are sputum positive, X-ray evidence of severe disease and multidrug resistant TB. Future study ought to be done in this area with larger sample size and better study design.

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