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Reversal of subclinical adrenal insufficiency through antituberculosis treatment in TB patients: a longitudinal follow up

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***Background & objectives*: Subclinical adrenal insufficiency has been shown to occur in patients with tuberculosis. Whether this insufficiency can be reversed with therapy and on long-term follow up, is not known. We studied the effect of antituberculosis treatment (ATT) with respect to reversal of the adrenal insufficiency, as assessed by response to standard dose adrenocorticotropin (ACTH) stimulation test in TB patients.**

***Methods*: One hundred and five HIV-negative tuberculosis patients were studied. Of these, 72 patients had pulmonary and 33 had extrapulmonary forms of the disease. Baseline (pre-treatment) standard-dose ACTH stimulation test was done on all the subjects, following which, they were put on standard antituberculosis therapy, depending on the type of disease and were followed up for a period of 30 months. ACTH stimulation tests were performed at follow up, every 6 months.**

***Results*: Baseline (pre-treatment) standard-dose ACTH stimulation test revealed an impaired response in 52 of 105 patients (49.5%). At 6 months, the percentage of responders had increased to 71 per cent with a gradual increasing trend noted thereafter. At 24 months, 31 of the 32 patients (97%) who were followed up demonstrated a normal response to ACTH stimulation. The percentage of responders was comparable in both pulmonary [21 of 22 patients (95%)] and extrapulmonary TB [10 of 10 patients (100%)] groups at follow up.**

***Interpretation & conclusion*: Our study shows that nearly half of patients with active tuberculosis had a subclinical adrenal insufficiency indicated by an impaired response to ACTH stimulation test. This insufficiency reverse with therapy in most patients on long-term follow up.**

Key words ACTH stimulation test - antituberculosis treatment - subclinical adrenal insufficiency - tuberculosis

Tuberculosis (TB) affects about 7-8 million people globally every year[1]. With the advent of the human immunodeficiency virus (HIV) infection epidemic the global incidence is growing at the rate of 0.4 per cent per year. One-third of the global burden is shared by India alone[1]. Worldwide, the disease stakes nearly two million lives each year; thus underscoring its importance as a major public health issue.

The existence of a subclinical adrenal deficiency in active TB has been a matter of debate in the past[2,3]. Previous studies that have addressed the issue have reported variable results ranging from the presence of an adrenal insufficiency in 0-50 per cent of the cases[2-4] to an actual state of hypersecretion of cortisol[5]. We have earlier reported an incidence of adrenal hyporesponsiness in 49.5 per cent cases in a cohort of 97 patients with active TB[4]. The discrepancy in the data is probably accounted for by the high prevalence of malnutrition in the Indian population of patients. This insufficiency exists in active stage of the disease and may be present with or without evidence of physical involvement or destruction of the glands[4], and may become important only in a stressful situation.

Few follow up studies have been done, a limitation with these studies was the short period of follow up, ranging from two weeks to two months[5-9]. The present study was done to determine the reversibility of the subclinical adrenal insufficiency using standard antituberculosis therapy and to identify a temporal correlate, if any, with duration of therapy and reversal of adrenal compromise.

Material & Methods

Study subjects: A total of 105 HIV-negative patients having various forms of TB that included pulmonary (PTB) (n=32), disseminated or miliary TB (DTB/MTB) (n=33) and multi-drug resistant TB (MDR-TB) (n=40) were recruited from the outpatient clinics and wards at the All India Institute of Medical Sciences, New Delhi during 1995-1998. The criteria applied for diagnosing these patients were the same as those in our previous study[4]. Of this cohort of 105, patients results of cross-sectional study (n=97) have been reported previously[4]. Eight new patients were recruited. The present study describes results of longitudinal follow up of adrenocortical function in these 105 subjects. Written informed consent was obtained from all the patients participating in the study. The Institutional Ethics Committee approved the study.

Healthy controls: A group of 27 age-matched healthy controls were also subjected to a baseline ACTH stimulation test. The controls were selected from the medical outpatient department based on normal haemogram, normal liver and renal function tests, a normal chest radiograph and a negative Mantoux test.

Adrenocortical reserve estimation: A standard (250 μg) dose ACTH stimulation test was performed for estimation of the adrenal reserve. Based on the criteria defined by Tyrell *et al*[10], a normal response was defined as a peak cortisol value >410 nmol/l with an increment of >137 nmol/l. If a peak value >550 nmol/l was obtained, the response was considered normal regardless of the increment. The subjects were then classified as responders and non-responders based on the presence or absence of a normal response as described previously[4].

Treatment and follow up: All patients with PTB and DTB/MTB received standard 4-drug anti-TB treatment for a period of 6 months and 6-9 months respectively. Patients with MDR-TB received second-line anti-TB drugs for duration of 18-24 months.

All patient groups were followed up for a period of 30 months with the ACTH stimulation test being performed at intervals of six months during follow up.

Statistical analysis: Data were analysed using STATA Inc. Corp software package, College station, Texas, USA. Paired and unpaired t-test was used for analysis.

Results & Discussion

When compared to a group of age-matched healthy controls, the study population showed significantly (P<0.001) lower values for body mass index, serum albumin and mid-arm circumference (Table I).

Prior to initiation of anti-TB treatment, 52 (49.5%) of the 105 patients showed evidence of compromised adrenal reserve. Of these, 16 had PTB, 17 had DTB and 19 had MDR-TB. The percentages of non-responders were comparable in the three groups: 50 per cent PTB, 51.6 per cent DTB and 48 per cent MDR TB.

Thirty two patients of the initial 105 were followed up to 24 months. With 31 of these 32 patients demonstrating a responsive adrenocortical axis, the percentage of responders at this stage of the follow up had escalated to 96.87 per cent from the initial 50.5 per cent (P<0.05) (Fig.). Table II compares the cortisol values to ACTH stimulation test across various subgroups.

Table I. Baseline demographic characteristics of tuberculosis patients and normal controls

	Healthy controls (n=27)	Tuberculosis group (n=105)
Age (yr)	26.9 ± 5.6	29 ± 10.2
Sex (M/F)	23/4	69/36
Duration of symptoms (wk)	-	8.3 ± 128.7
BMI (kg/m^2)	20.7 ± 2.5	17.6 ± 2.9*
MAC (cm)	26.3 ± 3.2	22 ± 3*
TSFT (mm)	10.3 ± 3.4	9.2 ± 3.3
ALC (mm^3)	2580 ± 546	2664 ± 1199
Total serum proteins (g/dl)	8.26 ± 0.40	8 ± 0.8
Albumin (g/dl)	5.16 ± 0.57	4.2 ± 0.74*

All values except sex are presented as mean ± SD
BMI, Body mass index; MAC, mid-arm circumference; TSFT, triceps skin fold thickness; ALC, absolute lymphocyte count
*P<0.001 compared to controls

Table II. Cortisol response to ACTH testing in various subgroups

II a. Comparison of cortisol values (n mol/l) at pre-treatment and 6 month follow up

		Controls (n=27)	DTB (n=33)	PTB (n=32)	MDR-TB (n=40)
0 min	Pre-treatment	395 ± 124	381 ± 215	392 ± 131	358 ± 138
	Post-treatment		385 ± 148	462 ± 162*	352 ± 137
30 min	Pre-treatment	499 ± 159	482 ± 229	455 ± 134	428 ± 178
	Post-treatment		533 ± 199	549 ± 202*	471 ± 125
60 min	Pre-treatment	530 ± 195	473 ± 196	477 ± 145	485 ± 172
	Post-treatment		573 ± 204	567 ± 203*	539 ± 198

II b. Comparison of cortisol values (n mol/l) for the cohort present at final follow up (24 months)

		DTB (n=10)	PTB (n=8)	MDR-TB (n=14)
0 min	Pre-treatment	293 ± 102	385 ± 146	334 ± 148
	Post-treatment	436 ± 253*	517 ± 333	442 ± 124
30 min	Pre-treatment	432 ± 163	477 ± 139	417 ± 194
	Post-treatment	653 ± 192**	807 ± 266**	693 ± 137**
60 min	Pre-treatment	452 ± 159	487 ± 140	378 ± 368
	Post-treatment	755 ± 198**	785 ± 252**	844 ± 214**

DTB, Disseminated TB; PTB, pulmonary TB; MDR-TB, multi-drug resistant TB
*P<0.05, **<0.01 compared to pre-treatment

An analysis of the subgroups was done based on the pulmonary, disseminated and MDR forms of the disease (Table II). In the pulmonary TB category the percentage of ACTH-responders increased from 50 per cent (16 of 32) at study initiation to 68.8 per cent (22 of 32) at treatment completion (6 months). Eight patients who were followed up to 24 months revealed an escalation of the responders to 87.5 per cent of 8 patients (P<0.05).

In the disseminated TB group, the ACTH responders increased from 48.4 per cent (16 of 33) at study initiation to 75 per cent at treatment completion (6-9 months). The ACTH-responders increased to 100 per cent at 24 months, with all 10 patients who followed up at this period demonstrating a responsive axis (P<0.05).

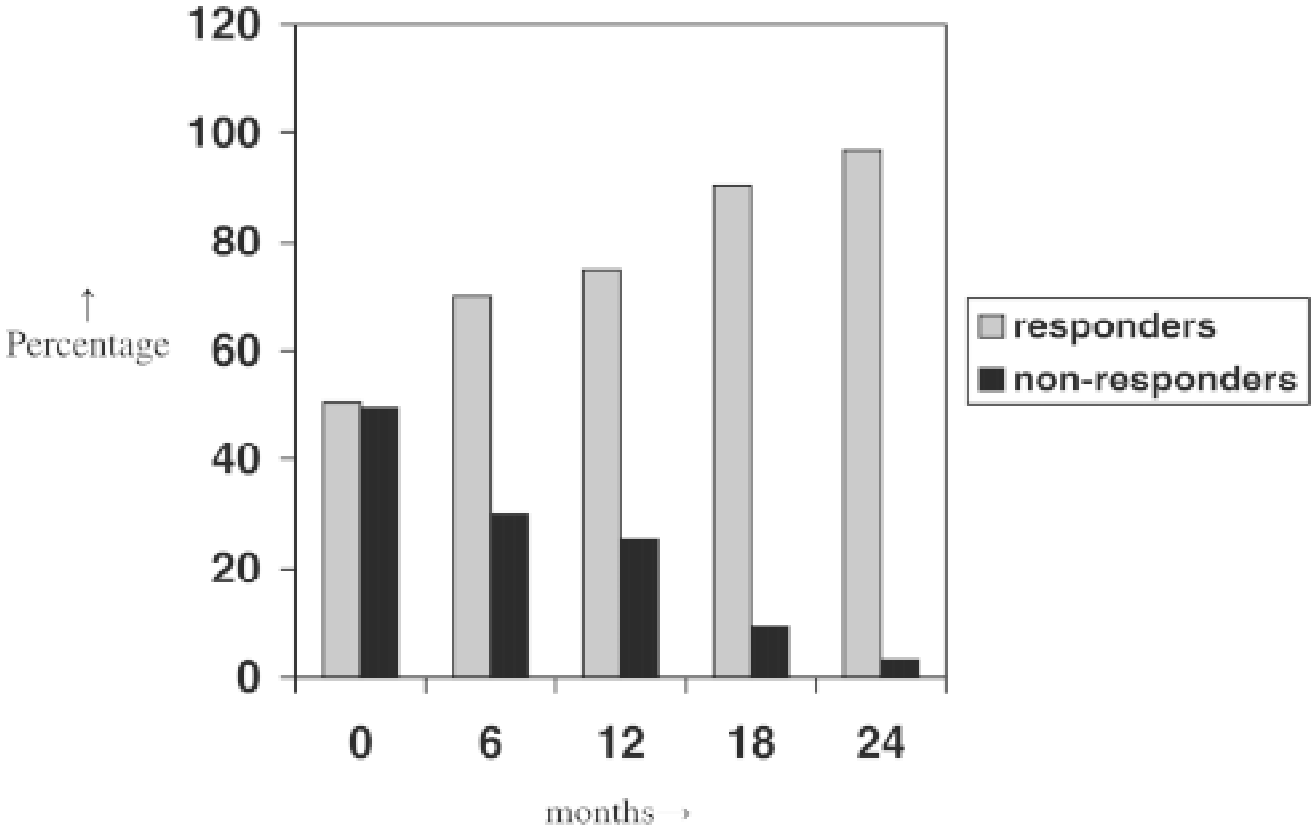

Fig. Responsiveness of the adrenocortical axis with respect to institution of chemotherapy in tuberculosis patients. The percentage of responders escalated from 49.5 per cent (0 months) to 96.87 per cent (24 months).

In the MDR-TB group (n=40), 52 per cent patients were ACTH responders at initiation, 20 patients followed up at treatment completion (18 months), of these 85 per cent (n=17) demonstrated a responsive axis. All 14 patients who were followed at 24 months demonstrated ACTH responsiveness *i.e.*, 100 per cent ($P<0.05$).

A standard dose (250 µg) ACTH stimulation test was conducted in all patients at the time of inclusion and 6 monthly thereafter for a period of 2.5 yr. The reason for selecting a standard 250 µg dose test as against a low dose was the lack of adequate evidence in support of the low dose test at the time we initiated our study, and the recent recommendations also suggested the need for cautious interpretation of the low dose test[11]. Using the criteria suggested by Tyrell *et al*[10], we classified patients into responders and non-responders and based our subsequent data analysis according to this stratification. This classification on the basis of ACTH responsiveness and adrenal reserve function appeared clinically more relevant than the actual levels of basal and peak serum cortisol. The longitudinal follow up enabled us to identify trends in the adrenal functional reserve with respect to therapy. However, owing to the large sample size (n=105) coupled with the long-term follow up, significant attrition was a problem (n=16 at 30 months). In order to eliminate attrition bias we interpreted results at 24 months (n=32).

We noted a near total reversal in our study group as the responders increased from 49.5 to nearly 97 per cent after a follow up of two years. Similar results have been described previously in studies with a small number of cohorts[7-9]. The study by Ellis and Tayoub in 41 subjects[7] noted a drop in the non-responders from 55 (pre-treatment) to 30 per cent after two weeks of therapy. Barnes *et al*[9] noted a decrease in the negative responders following one month of therapy, however, the incidence of adrenal compromise reported was very small (8% of the study population of 90 patients).

Chan *et al*[8] reported a reversal of all the 41 per cent ACTH non-responders (pre-treatment) in a group of 39 patients, when re-tested at 2 months of treatment. The limitation of these studies has been the short-term follow up. A study published in 1996 by Gulmez *et al*[12], in a group of 11 patients, showed a decrease in the size of the adrenals on CT scan after receiving 8 months of ATT. Though ACTH responsiveness was not tested at the 8 month follow up, a reduction in gland size on CT imaging suggested a reversal of adrenal pathology following appropriate chemotherapy, and thus supports our hypothesis.

It is thus evident that in comparison to the previous studies, a near-complete reversal of the adrenal hyporesponsiveness has been noted in our study. This may be attributable to the 24 month follow up period. This long-term follow up also enabled us to make an interesting observation. Maximal reversal of the non-responders was seen in the initial 6 months of therapy, which is the time for complete cure of active disease in majority of the patients with pulmonary TB. This might suggest that it was perhaps the impact of the active disease process (in the setting of a malnourished state) that induced the adrenal insufficiency.

Thus, it may be concluded that the subclinical adrenal compromise in patients with active tuberculosis affects a sizeable portion of the TB patients with active disease in India. The distribution of non-responders was found to be equal in various forms of the disease. This abnormality in adrenal function was reversible and appeared to resolve with chemotherapy, in all subsets of patients, affected with various forms of the disease. The reversal seen was maximal following six months of chemotherapy and correlated well with cure of disease in most patients. This subclinical insufficiency may become important and clinically significant in acute stressful situations.

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