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Evaluation of Pseudoadrenal Insufficiency in Tuberculosis Patients

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ABSTRACT

Background: *Adrenal insufficiency following initial treatment of active tuberculosis (TB) is a rare phenomenon. It is also one of the most important causes of mortality within the first few days of TB treatment. The present study evaluated this adverse effect of anti-tuberculous treatment.*

Materials and Methods: *A prospective study was performed on TB patients hospitalized in Masih Daneshvari Hospital between 2004 and 2005. All patients had received standard anti-TB drug regimen. We evaluated pseudo-adrenal insufficiency in these patients.*

Results: *The study group included 429 patients out of which 6(1.4%) developed adrenal insufficiency following anti-TB treatment. In all 6 patients, basal serum cortisol levels were measured which were below the normal range after treatment. No patient had clinical findings of adrenal insufficiency before initiation of anti-TB therapy. After treatment with dexamethasone, the general condition of patients improved. (The average response to treatment was 3.1±1.7 days). No mortality was reported during the treatment course or follow-up period.*

Conclusion: *In TB patients, the adrenal reserve/ serum cortisol reserve level is low. Standard anti-TB drug regimen including rifampicin causes rapid catabolism of cortisol in tissues specially in the liver and lungs; therefore, serum cortisol level will be more decreased and consequently the patient develops adrenal insufficiency. As a whole, despite of the low incidence rate of this adverse effect, early diagnosis and treatment is essential to save the patient's life.* ***(Tanaffos 2007; 6(1): 67-70)***

Key words: *Pseudo-adrenal insufficiency, Active tuberculosis, Rifampicin*

INTRODUCTION

Tuberculosis (TB) is associated with a relatively high mortality rate within the first days of diagnosis inspite of receiving a standard anti-TB drug regimen (1). Among known causes of death due to TB, delay in immune inflammatory response, pulmonary embolism due to induced hypercoagulability, super imposed bacterial infection on damaged lungs and with a lower probability adrenal involvement causing secondary hypoadrenalism can be mentioned (2).

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The presence of subclinical pseudo-adrenal insufficiency in active tuberculosis has been disputable and studies have shown variable results/ reports of adrenal insufficiency (3-5). In one study, low adrenal response was reported in 49.5% of 97 patients with active tuberculosis (6).

Anti-TB standard regimen including rifampicin, (a liver enzyme inducing antibiotic) may be responsible for adrenal insufficiency by accelerating cortisol catabolism resulting in low level in the tissues (7).

The aim of this study was to demonstrate the importance of early diagnosis of pseudo-adrenal insufficiency following rifampicin-based antituberculous regimen to save the patient's life.

MATERIALS AND METHODS

Between 2004 and 2005 all hospitalized TB patients in Masih Daneshvari hospital who had a positive sputum smear or culture for Mycobacterium tuberculosis or confirmed extrapulmonary TB (an accessible pathologic report) and had undergone WHO standard anti-TB treatment (isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, isoniazid and rifampicin for 4 months), were evaluated for adrenal insufficiency due to rifampicin. Patients with a history of exogenous corticosteroid use or kidney, liver and adrenal disorders were excluded from the study.

At initiation of treatment, no patient had signs and symptoms of adrenal insufficiency like nausea, vomiting, hypotension, low consciousness level and abdominal pain. Furthermore, the level of liver enzymes and paraclinical tests were all normal. When all the above-mentioned findings were detected, liver enzymes (ALT, AST and ALK-P) and serum Na, K, Urea, BUN, Creat, and blood sugar were measured. Basal serum cortisol level at 8 a.m was also measured. Our diagnostic criteria included clinical findings (malaise, decreased appetite, nausea, vomiting, hypotension, abdominal pain, etc), decreased basal serum cortisol level and dramatic response to corticosteroid use.

Intravenous dexamethasone (stress dose) was given to patients with high suspicion of adrenal insufficiency. After improvement of the general condition of the patients, intravenous corticosteroid was changed to oral corticosteroid and continued for one month and then tapered. The duration of follow-up period was one year after completion of treatment.

RESULTS

Between 2004 and 2005, 429 patients with tuberculosis were admitted to Masih Daneshvari Hospital, out of which, 6 were diagnosed with adrenal insufficiency due to rifampicin. Demographic characteristics included age, sex, nationality, accompanying disease, sputum smear and human immunodeficiency virus (HIV) test. All patients were female and Iranian with a mean age of 69.33±12.12 yrs (range, 54-82 yrs). Three patients had diabetes mellitus and one had hypothyroidism. Smear-positive pulmonary tuberculosis and culture positive (smear negative) pulmonary tuberculosis were detected in 4 and 2 patients, respectively. The mean duration between initiation of 4-drug anti-TB regimen and manifestation of symptoms was 7.33±4.8 days (range, 1-14 days). The mean interval between initiation of symptoms and diagnosis of adrenal insufficiency was also 3.66±4.6 days (range, 1-13 days). Clinical and para clinical findings were demonstrated in tables 1 and 2, respectively.

The most common symptom of the patients was malaise (100%) followed by hypotension, nausea and vomiting, respectively. Decreased level of consciousness and abdominal pain were detected in 50% of patients. Paraclinically, basal serum cortisol level decreased in all 6 patients. Hypoglycemia (66.7%), hyponatremia (50%) and hyperkalemia (33.3%) were the most common findings, respectively. The general condition of patients improved after initiation of intravenous

dexamethsone (stress dose). The mean duration of therapeutic response was 3.1±1.7 days. Paraclinical abnormalities reversed to normal range gradually. All patients improved completely and no mortality was reported during the treatment course and in the follow-up of patients.

Table 1. Symptoms and signs in TB patients suspected to have adrenal insufficiency after anti-TB treatment.

Clinical findings	Malaise	Nausea	Vomiting	Diarrhea	Abdominal pain	Hypotension	Fever	Low consciouness level	Skin color change
Patients									
Number	6	4	4	0	3	5	2	3	0
percent	100	66.7	66.7	0	50	83.3	33.3	50	0

Table 2. Biochemical indicies in TB patients suspected to have adrenal insufficiency after anti-TB treatment.

Biochemical indices	Serum cortisol		Blood sugar		Blood sodium		Blood potassium	
Patients	Normal	Low	Normal	Hypoglycemia	Normal	Hyponatremia	Normal	Hyperkalemia
No	0	6	2	4	3	3	4	2
%	0	100	33.3	66.7	50	50	66.7	33.3

Table 3. Laboratory parameters in TB patients with/ suspected to have pseudo-adrenal insufficiency after anti-TB treatment.

Laboratory parameter	Cortisol	Blood sugar	Sodium	Potassium
Patients				
First patient	55	92	148	3.3
Second patient	170	128	136	3.2
Third patient	60	75	130	4.2
Forth patient	60	94	128	5.6
Fifth patient	180	65	122	5.9
Sixth patient	50	117	121	4.3

DISCUSSION

Early diagnosis of complications related to anti-TB drugs has a major role in control and treatment of tuberculosis and can save the patient's life. However, some studies showed tuberculosis concomitant with adrenal insufficiency in 6% of cases (8). Pseudo-adrenal insufficiency following treatment of TB patients is rare (9) and also one of the important complications of using anti-TB drugs. In recent years, some studies have shown decreased adrenal reserve in patients with active pulmonary TB and decreased serum level of basal cortisol following treatment with anti-TB drugs which can be an important factor in mortality rate (10).

In a study conducted by Prasad et al. in New Delhi, subclinical adrenal insufficiency was significantly observed in a large number of patients without sensitivity or resistance to anti-TB drugs. Additionally, adrenal gland enlargement was detected in some of them (6) which decreased in size following appropriate treatment (11). However, abnormal function of the adrenal glands has not been observed in patients with pleural tuberculosis (12).

Sharma et al. showed that in half of the understudy patients with active pulmonary TB, a subclincial adrenal insufficiency was detected and no appropriate response to adrenocorticotropin hormone stimulation test was reported but it returned to normal after completion of treatment (3).

It is noticeable that our patients had no signs of adrenal insufficiency before initiation of anti-TB treatment but developed pseudo- adrenal insufficiency following treatment. Thus, the serum level of basal cortisol was not measured in any patient before anti-TB treatment and only by manifestation of clinical signs and symptoms and presence of paraclinical findings following treatment it was measured which was decreased in all 6 patients. It seems that the cause of this complication is rifampicin which causes acceleration of cortisol catabolism by inducing liver enzymes resulting in

low serum levels of cortisol in patients. Consequently, the function of cortisol will be decreased and its effect will be diminished in tissues especially in the liver and lungs. This theory may be confirmed by the remarkable response to dexamethasone therapy. Although rifampicin does not affect adrenocortical function in the initation of treatment, it can lower basal serum cortisol level on the 5th day (2). Furthermore, it may have a remarkable effect on metabolism of steroids (13).

It is suggested that stress dose of steroid can save the lives patients who have suspected signs and symptoms and tuberculosis accompanied by pseudo adrenal insufficiency has been diagnosed in them (14).

No mortality was reported during the hospitalization and one year follow-up period. This type of adrenal insufficiency is reversible by appropriate treatment.

CONCLUSION

In TB patients, basal serum cortisol level is low. In our study, it seems that this level has been much lowered in tissues especially in the liver and lungs by initiation of treatment with standard drug regimens including rifampicin causing enzyme induction and rapid catabolism of cortisol; consequently, our patients developed adrenal insufficiency. Therefore, we should be aware of this complication (despite its low frequency) in TB patients.

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