

Evaluation of Adrenal Function in Long Standing Pulmonary Tuberculosis: A Study of 100 Cases

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Abstract

Tuberculosis is a major public health problem in Pakistan and adrenal involvement in long-standing tuberculosis has been found to be common. A multi-center study was conducted to assess the adrenal function using short Synacthen® test in one hundred patients with tuberculosis of more than 6 months duration at three hospitals of Rawalpindi and Islamabad. Forty patients demonstrated impaired response to Synacthen test. In 21(52.5%) the increment from basal level was less than 300 nmol/L with a peak level increasing to over 600nmol/L in 15 (37.5%) patients, the increment from basal level was less than 300 nmol/L as well as the peak level was also less than 600 nmol/L. In 4(10%) patients the increment was more than 300 nmol/L but they were not able to obtain a peak level of 600 nmol/L. No significant difference was found between the patients with normal response and the impaired response with regards to their clinical features, duration of illness, body mass index (BMI), blood pressure variation and routine biochemical profile. It is concluded that adrenal dysfunction is common in patients with long-standing tuberculosis. Diagnosis of hypoadrenalism is not possible on clinical grounds and routine biochemical examinations. Synacthen® stimulation test is necessary for its diagnosis (JPMA 47:132,1997).

Introduction

Tuberculosis is a common clinical problem in hospital practice in Pakistan. The figures for the patients admitted in 30 major hospitals during the year 1990-91 is 105,000, including 65,000 cases of pulmonary tuberculosis. Tuberculosis contributes to high morbidity and mortality in all age groups, particularly in the adult population. The prevalence of open pulmonary tuberculosis (sputum positive) is 0.17 percent¹. Mycobacterium tuberculosis can involve virtually any organ of the body, however, in majority of cases it presents as pulmonary tuberculosis. Involvement of adrenal cortex in long-standing and extensive pulmonary tuberculosis is a well recognized entity, that results in adrenal insufficiency². While in developing countries, adrenal destruction by tuberculosis is still considered to be common, in economically developed countries autoimmune disease has emerged as the most common cause of Addison's disease³. Early diagnosis of involvement of adrenal gland secondary to tuberculosis needs a high index of suspicion on part of the physician. It has been shown that there may be subclinical involvement of adrenal gland due to tuberculosis which can only be unmasked by specific Synacthen (Tetracosactin) induced stimulation of the gland^{4,5}. This may well have a bearing on the eventual outcome of patients treated for tuberculosis. In addition treatment of tuberculosis with rifampicin, an enzyme inducer may result in enhanced cortisol metabolism and aggravate an already compromised adrenal function^{6,7}. The aim of this study was to determine the prevalence of sub-clinical hypofunction of adrenal gland in patients with long standing than six months duration) pulmonary tuberculosis.

Patients and Methods

A multi-center study was carried out over a period of two months in one hundred adult patients with long-standing pulmonary tuberculosis to evaluate the status of adrenal function. Long standing pulmonary tuberculosis was defined as a case of pulmonary tuberculosis of over 6 months duration, irrespective of anti-tuberculous chemotherapy. (The patients included in the study were taken from Pakistan Institute of Medical Sciences, Islamabad (PIMS), Samly Tuberculosis Sanitorium, Murree and Federal Government Tuberculosis Center, Rawalpindi). Excluded from the study were patients with previously diagnosed cases of Addison's disease, hypopituitarism, diabetes mellitus, those on steroid therapy and those suffering from concomitant autoimmune disease. Demographic, clinical and biochemical profile of each patient was recorded on a questionnaire. Blood pressure was measured using mercury sphygmomanometer in sitting and standing postures, in addition to examination of skin and mucus membranes and the respiratory system.

Blood samples were collected between 8 am to 12 noon. Five milliliters of venous blood was drawn for the measurement of basal serum cortisol level. Adrenal function was evaluated by short Synacthen test using 250 micrograms of tetracosactrin (Synacthen). Five minutes later the patient was given 250 micrograms of tetracosactrin intramuscularly and further venous blood samples were taken at 30 and 60 minutes intervals. The serum cortisol measurement was done by radioimmunoassay using Amerlex cortisol RIA kit. Blood was also drawn for complete blood picture, erythrocyte sedimentation rate, urea creatinine, electrolytes and blood glucose if they were not done initially. The adrenal response was considered to be impaired to Synacthen stimulation if the peak serum cortisol level achieved was less than 600 nmol/L one hour after Synacthen® injection and/or the increment in the plasma cortisol was less than 300 nmol/L between 0 and 60 minutes from the basal cortisol level, even in the presence of normal basal serum cortisol levels. Data was entered and analyzed on a microcomputer using EPIINFO version 5.0. Significance testing where required was done using the X² or Student's t-test.

Results

One hundred patients of long-standing pulmonary tuberculosis were studied (64 males, 36 females). Their mean age was 35.4 ± 13.6 years. More than 70% of the patients belonged to poor socio-economic class with no educational background. Eighty-four patients were sputum positive with the history and radiological findings suggestive of pulmonary tuberculosis. Sixteen patients had strong clinical and radiological evidence of pulmonary tuberculosis. On the basis of adrenal response the patients were categorized into two groups. Sixty patients had normal response to Synacthen® stimulation test, 40 patients had impaired response. Seventy-three patients were taking anti-tuberculous chemotherapy including rifampicin; among these 44 were in normal response group and 29 were in impaired response group ($p > 0.5$). The mean duration of illness was 29 ± 41 months (range from 6 months to 20 years). The mean duration of illness was 34 months in patients with impaired response and 26 months in patients with normal response ($P = 0.36$). There was no significant difference between the two groups in symptomatology (Table I).

Table I. Symptomatology of pulmonary tuberculosis patients with normal and impaired response.

Symptoms	Normal response (%)	Impaired response (%)
Mean duration of illness	26 months	34 months
Fever	100	100
Cough	98	98
Night sweats	96	97
Breathlessness	98	92
Weight loss	93	97
Anorexia	84	97
Syncope	61	66
Hemoptysis	60	57
Nausea	47	56
Vomiting	23	23
Pigmentation	29	24

The mean body mass index (BMI) was 16.88 kg/m² in the normal adrenal response group and in impaired adrenal response group it was 16.93 kg/m². The mean systolic and diastolic blood pressures in the two groups of patients were also similar in sitting and standing position. Although there was a postural drop of 10 mm Hg of diastolic blood pressure, it was present in both the groups. Routine laboratory investigations revealed no difference in the two groups (Table II).

Table II. Comparison of hematologic and biochemical profile of pulmonary tuberculosis patients with normal and impaired response.

Investigations	Normal response	Impaired response
Hemoglobin (g/dL)	11.13	11.14
Total leukocyte count (/mm ³)	9370	8740
Erythrocyte sedimentation rate (mm 1st hour)	79	72
Blood urea (mg/dL)	27	26
Random blood glucose (mg/dL)	90	89
Serum sodium (mEq/L)	137	136
Serum potassium (mEq/L)	5.0	5.2

The mean hemoglobin in our patients was 11.2 gm/dl with normal leukocytes and differential counts, the mean erythrocyte sedimentation rate (ESR) was 76 mm in first hour with no significant difference in the two groups. The renal functions, electrolytes and blood glucose levels were also similar in both the groups. Of the 40 patients who showed an impaired response to Synacthen in 21(52.5%), the peak level was more than 600 nmol/L, but the increment from basal level was less 300 nmol/TL. In 4 (10%) patients the increment was more than 300 nmol/L but the peak level was less than 600 nmol/L, while in 15 patients (37.5%), the increment was less than 300 nmol/L as well as the peak level was less than 600 nmol/L. Mean serum cortisol levels for the normal and impaired adrenal response groups are shown in Table III.

Table III. Comparison of mean and post-stimulation cortisol levels in pulmonary tuberculosis patients with normal and impaired response.

Adrenal response	No. of observations	Basal cortisol levels (nmols/L)	Post-30 minute cortisol levels (nmols/L)	Post-60 minute cortisol levels (nmols/L)
All patients	100	523.4±318.0	853.2±498.6	885.8±358.6
Normal response group	60	558.0±361.4	984.9±582.9*	1022.8±368.9**
Impaired response group	40	473.6±240.4	662.4±242.7*	688.6±231.3**

*p<0.001

**p<0.0001

Whereas there was no significant difference (p=0.16) among the mean basal cortisol level in patients with normal (558±361 nmol/L) and impaired response (474±240 nmol/L), there was a significant difference in cortisol levels after 30 and 60 minutes of Synacthen stimulation. The mean cortisol level 30 minutes post-stimulation in the normal adrenal response group was 1022±369 nmol/L as compared

to 689+231 nmol/L in the group with impaired adrenal response ($p < 0.0001$).

Discussion

Primary adrenocortical insufficiency due to any cause is a rare disease with an estimated incidence in western countries of around 50 per million population³. Prevalence in Pakistan is unknown and it is likely that most cases remain undiagnosed. In developed countries as the incidence of tuberculosis has fallen, the autoimmune destruction of the adrenal gland has become the most important cause of Addison's disease. Kasperlik et al⁹ found 69% cases of primary adrenocortical insufficiency due to autoimmune destruction of the adrenal gland. In Pakistan tuberculosis is still considered to be one of the most common causes of adrenocortical insufficiency. It has been suggested that patients of Addison's disease should always be given anti-tuberculosis chemotherapy even in the absence of clear evidence of active tuberculosis in Third World countries¹⁰. Many reports have pointed to a high incidence of adrenal involvement in patients with long-standing tuberculosis. Mugusi in Tanzania found that 32% of the patients with chronic pulmonary tuberculosis had an impaired response to Synacthen⁴. A similar study in South Africa suggested that adrenal function may be impaired in 55% of patients with acute pulmonary tuberculosis⁵. In our study 40% of patients with pulmonary tuberculosis showed an impaired adrenal response to Synacthen® stimulation, which seems comparable to other studies.

In another study by Barnes et al on ninety Melanesian patients with active tuberculosis, the cortisol responses were subnormal only 8%¹¹. The difference in result between our study and Melanesian study may be explained by differences in the criteria used to assess abnormal adrenal function. The criteria for normal cortisol response in Melanesian study was an increment of over 200 nmol/L above the basal cortisol level and nine of their patients who had an increment below 200 nmol/L but had high basal cortisol level were also considered as normal. Anti-tuberculous chemotherapy has a variable response on the outcome of patients with compromised adrenal function and active pulmonary tuberculosis. It has been shown that rifampicin being an enzyme inducer may occasionally precipitate the onset of adrenal crisis in patients with already compromised adrenocortical function and cause unexpected death⁷. Others found that anti-tuberculous chemotherapy had a favourable effect on adrenal function, though those who received rifampicin showed less improvement than those who were given regimens that did not, include rifampicin⁵. In another study, it was seen that anti-tuberculous chemotherapy including rifampicin had favourable effect on adrenal function¹¹. Although assessing the effect of anti-tuberculous therapy on the status of adrenal function was not an objective of our study, we also could not demonstrate any difference in adrenal function between the group who were and were not receiving anti-tuberculous drugs. The present and some of the above studies^{4,5} clearly suggest that sub-clinically impaired adrenal function of patients with active pulmonary tuberculosis cannot be differentiated on the basis of routine clinical examination and laboratory tests. Patients with impaired adrenal function

cannot be differentiated even on the basis of basal serum cortisol levels unless a Synacthen stimulation test is performed as has been shown in this study. Early diagnosis of adrenal involvement needs a high index of suspicion on the part of attending physician. Since pulmonary tuberculosis is an important clinical problem in this country, the possibility of sub-clinical impairment of adrenal function be actively considered and biochemical confirmation done by stimulation test with Synacthen (Tetracosactrin) unmasking the impaired adrenal response. Since Synacthen (Tetracosactrin) injection and cortisol evaluation are not easily available in Pakistan, it is equally essential to make these readily available.

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