Abstract. Adrenal glands may be involved during both acute and chronic tuberculosis. They are enlarged in acute pulmonary tuberculosis. We aimed to investigate the changes in adrenal size in acute pulmonary tuberculosis before and after therapy in a prospective study. Eleven hospitalized patients with newly diagnosed sputum positive pulmonary tuberculosis were studied. Basal cortisol levels were measured in the patients before and after the therapy. Cortisol levels were also measured 30 and 60 min after Synacthen (250 µg i.v.) injection in the patients before the therapy. The size of the adrenal glands was measured by computerized tomography. The maximum width perpendicular to the long axis of the body of the gland, maximum width of the medial and lateral limbs and the length of the adrenals were measured. All measurements were done before and after the eight-month anti-tuberculosis therapy. All 11 patients had an intact adrenal cortisol reserve. Both the width and length of the right and left adrenal glands were significantly greater before the therapy than after the therapy. We conclude that adrenal enlargement demonstrated by computerized tomography in acute pulmonary tuberculosis is reduced after appropriate therapy.

Key words: Adrenal gland, Tuberculosis, Anti-tuberculous therapy

(TUBERCULOSIS is a well known cause of primary adrenocortical failure. The appearance of the adrenal gland in tuberculosis varies with the stage of infection. Involvement is usually bilateral and, with active infection, the glands are enlarged and inhomogenous in density, but longstanding tuberculous infection results in an atrophic gland [1]. It has been suggested that bilateral adrenal glands were enlarged in 75% of patients who had tuberculous Addison’s disease during the first two years, and at least one gland was enlarged during the initial four years following disease onset [2]. We have previously reported a patient characterized by adrenal failure and adrenal tuberculoma developed during acute pulmonary tuberculosis [3]. Adrenal failure may therefore be developed during acute pulmonary tuberculosis as a result of involvement of the adrenal gland by tuberculosis, or as seen more commonly, following haematogenous dissemination which is often not apparent for as many as 10 years after infection [4].

We have recently demonstrated that the adrenal glands are enlarged and cortisol reserve is normal in patients with acute pulmonary tuberculosis [5]. We think that adrenal enlargement during acute pulmonary tuberculosis is due to a stressful condition caused by acute tuberculosis. If this is true, the adrenal glands must be diminished in size after acute pulmonary tuberculosis has been appropriately treated. In this study we aimed to answer this question.
**Materials and Methods**

Eleven patients with acute pulmonary tuberculosis aged 18-55 (mean ± SD, 29.5 ± 1.7) years, 8 males and 3 females, were studied prospectively. All patients had typical chest radiographic changes and were positive for tubercle bacilli on direct microscopy or culture. Patients with acute pulmonary tuberculosis together with another disease were not included in the study. The present study did not include a control group.

Samples of blood were collected between 0800 and 0900 h from all patients for determination of basal plasma cortisol levels before and after the eight-month therapy. ACTH stimulation test was performed with Synacthen (Ciba Geigy Ltd, Germany) before the therapy. Thirty and 60 min after the intravenous administration of 250 µg Synacthen further blood specimens were taken. A plasma cortisol value of 550 nmol/l or more at any time during the test, including before injection, was taken as indicative of normal adrenal function [6]. Plasma cortisol concentrations were determined by a radioimmunoassay with a commercially available kit (Amerlex, Kodak Clinical Diagnostics Ltd, Amersham, UK). Intra and interassay coefficients of variation were 3.5 and 5.2%, respectively.

CT scanning of the adrenals was carried out in 11 patients with tuberculosis. CT examinations of 2 mm sections were done with a third generation Toshiba XT scanner. All CT examinations were performed by the same investigator (ACD). Sufficient images were obtained to ensure that the entire gland was imaged. The maximum width of the gland (defined as the maximum width perpendicular to the long axis of the body of the gland, at the junction of the adrenal limbs and the body) and width of the adrenal limbs (defined as the maximum thickness of the medial and lateral limbs of the gland perpendicular to the long axis of the limb) were measured as previously described [7]. We also measured the length (the anterior diameter or the greatest dimension) of the adrenal glands. The measurements were carried out both before and after the therapy.

The patients were given an anti-tuberculosis therapy consisting of isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamid 3 g/day and streptomycin for 2 months. Then isoniazid 300 mg/day and rifampicin 600 mg/day were given twice a week for 6 months. At the eighth month of the anti-tuberculosis therapy, the medications were stopped. For statistical evaluation Wilcoxon test was used.

**Results**

Although basal plasma cortisol levels were higher before the therapy (mean ± SD, 480.6 ± 169.0; range 283.5-780.3 nmol/L) than after the therapy (mean ± SD, 423.9 ± 76.4; range 350.0-554.4), the difference was not statistically significant (P>0.05). Cortisol response to Synacthen was normal in the patients. The mean of peak cortisol values was 951.2 ± 172.1 (range 753.2-1316.0) nmol/l.

The maximum width of the adrenal glands, width of the adrenal limbs and the length of the adrenal glands were significantly greater before the therapy than after the therapy (P<0.05). The findings are shown in Table 1. CT demonstrated no calcification either before or after the therapy.

**Discussion**

The adrenal glands may be involved during both acute and chronic tuberculosis [2, 3, 8]. Tuberculosis may directly involve the adrenal glands as seen in Addison's disease and tuberculoma of the gland or they may be enlarged as a result of increased cortisol requirement due to infection. We have previously studied 20 patients with acute pulmonary tuberculosis, 41 patients with chronic pulmonary tuberculosis and 20 healthy subjects. We found that adrenal glands were enlarged in patients with acute pulmonary tuberculosis, but became smaller in chronic tuberculosis. We did not find adrenocortical insufficiency in these patients, in contrast to previous suggestions [5]. Post et al. also reported intact adrenal reserve in active pulmonary tuberculosis [9].

In this study, we investigated adrenal size by CT scanning before and after the eight-month anti-tuberculosis therapy. We saw an early increase (during acute pulmonary tuberculosis) followed by a later decrease in the size of the adrenals after the therapy had been stopped.

Adrenal enlargement in active tuberculosis may
ADRENAL SIZE IN TUBERCULOSIS

Table 1. Average measurements of the adrenal glands (mm)

<table>
<thead>
<tr>
<th></th>
<th>Before therapy</th>
<th>After therapy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Maximum width</td>
<td>6.48 ± 0.33</td>
<td>7.27 ± 1.15</td>
</tr>
<tr>
<td></td>
<td>(5.8–7.0)</td>
<td>(5.3–9.8</td>
</tr>
<tr>
<td>Width of lateral limb</td>
<td>3.80 ± 0.38</td>
<td>3.95 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>(3.4–4.4)</td>
<td>(2.9–5.2)</td>
</tr>
<tr>
<td>Width of medial limb</td>
<td>3.65 ± 0.52</td>
<td>4.25 ± 0.59</td>
</tr>
<tr>
<td></td>
<td>(2.8–4.5)</td>
<td>(3.2–5.0)</td>
</tr>
<tr>
<td>Length</td>
<td>33.16 ± 5.50</td>
<td>30.23 ± 7.92</td>
</tr>
<tr>
<td></td>
<td>(22.3–39.4)</td>
<td>(17.6–39.3)</td>
</tr>
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* The maximum width perpendicular to the long axis of the body of the gland, at the junction of the adrenal limbs and the body. b The maximum thickness of the medial and lateral limbs of the gland perpendicular to the long axis of the limb. c The anterior diameter or the greatest dimension of the adrenal glands. d Mean ± SD. * Range. *P<0.05 vs. corresponding side of before therapy.

develop as a result of inflammation including granulomatous changes or the activation of the hypothalamus-pituitary-adrenal (HPA) axis. The adrenals are under stress in active pulmonary tuberculosis and secrete more cortisol as a result of increased ACTH secretion by the pituitary gland. The adrenals therefore become larger during active infection. The HPA axis is activated in stressful conditions such as infection [10]. It has long been known that adrenocortical secretion is increased during bacterial infections and that lipopolysaccharide (LPS) released from bacterial cell walls accounts for the effects of bacterial challenge on the HPA axis [11, 12]. It is widely accepted that LPS activates the HPA axis by increasing production of the cytokines, primarily IL-1 and IL-6 [13]. TNF-α also activates the HPA axis [14]. Perlstein et al. demonstrated that IL-6, IL-1 and TNF-α all play a role in the stimulation of corticotropin secretion induced by LPS [15].

It has been demonstrated that Mycobacterium tuberculosis cell-wall component lipoarabinomannan (LAM), mycobacterial heat shock protein-65 KD, and Mycobacterium tuberculosis culture filtrate stimulate the production of TNFα and IL-1β proteins and mRNA from mononuclear phagocytes [16]. M. tuberculosis cell wall component LAM acts similarly to LPS in activating mononuclear phagocyte cytokine TNFα and IL-1β release [16].

In conclusion, we think that the HPA axis is activated by cytokines including TNFα and IL-1β in acute pulmonary tuberculosis. The activation of the HPA axis results in more cortisol secretion from the adrenal glands which become enlarged. As the disease is treated, the enlarged adrenal glands are reduced in size. To make the relationship between the cytokines-HPA axis and tuberculosis more clear, more extensive studies are needed.

References