Adrenal function in patients with active tuberculosis

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ABSTRACT Although tuberculosis is a recognised cause of adrenal insufficiency, little is known about adrenal function in patients with active tuberculosis. Ninety Melanesian adults with active tuberculosis (30 pulmonary, 30 miliary, 30 extrapulmonary) had adrenal function assessed prospectively before and three to four weeks after starting antituberculous chemotherapy. Basal serum cortisol concentrations were normal in 55 (61%) and raised in 35 (39%) of the subjects. No patient had a low basal cortisol concentration. After Synacthen stimulation, cortisol responses were normal in 81 (92%) of the patients and subnormal in seven (8%). After antituberculous chemotherapy the response to Synacthen stimulation was normal in all but one patient. It is concluded that adrenal dysfunction is an uncommon problem in patients with active tuberculosis, and that, contrary to recent reports, antituberculous chemotherapy regimens that include rifampicin do not have an adverse effect on adrenal function.

Introduction

Tuberculosis is a recognised cause of adrenal failure. In a review of necropsy findings in 403 patients with Addison's disease from 1900 to 1929 tuberculosis of the adrenals is said to have been found in 69.7% of cases.1 As the incidence of tuberculosis in developed countries has declined, its importance in the aetiology of Addison's disease has diminished.2,4 Far less is known, however, about adrenal function in patients with active tuberculosis nor is it known whether adrenal function varies in these patients according to the extent of their disease.

We sought therefore to determine the state of adrenal function in a prospective study of patients with active tuberculosis. The effects of disease extent and antituberculous chemotherapy were investigated.

Methods

Ninety Melanesian adults admitted with active tuberculosis to the university hospital in Port Moresby, Papua New Guinea, were studied prospectively. They were divided into three groups according to the extent of their disease. Each group consisted of 30 consecutive patients who fulfilled the criteria for that group:

- **Pulmonary** These patients had radiographic evidence of either a pulmonary infiltrate (not a miliary pattern) or a pleural effusion, sputum positive for acid fast bacilli (direct smear or culture) or histological evidence of tuberculous pleuritis from pleural biopsy, and no evidence of extrapulmonary spread.

- **Miliary** All patients had a typical miliary pattern on their chest radiographs. The presence or absence of extrapulmonary spread did not affect the classification of a patient as having miliary disease. Histological or microbiological confirmation (or both) of tuberculosis was made in 25 cases; in the remaining five the diagnosis was made from typical radiographic and clinical features, and from the response to antituberculous chemotherapy.

- **Extrapulmonary** This group includes patients with lymph node (12), peritoneal (11), bone (6), and genitourinary (1) tuberculosis. The diagnosis was confirmed in 23 cases, either histologically or by demonstration of acid fast bacilli by direct smear or culture. The other seven patients had clinical features consistent with tuberculosis and improved with antituberculous treatment.

On entry into the study all patients had the following investigations: (1) serum sodium (Na+) and potassium (K+) concentrations; (2) basal serum cortisol concentration, measured at 7.30 and 8.00 am (the basal concentration was taken as the mean of these...
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two measurements); (3) a standard Synacthen stimulation
after the intravenous injection of 0.25 mg
Synacthen (synthetic adrenocorticotropic hormone)
at 8.00 am, serial serum samples for measurement
and a Synacthen stimulation test were repeated 20–30
days after the start of treatment.
The mean serum sodium and potassium concentrations
for each group of patients were compared by a
one way analysis of variance.

Results

SERUM ELECTROLYTES
The serum Na concentration was normal (135–145
mmol/l) in 53 and below normal in 37 patients. Most
cases of hyponatraemia were mild, the lowest value
being 124 mmol/l. There was no significant difference
between the three groups with respect to the
prevalence of hyponatraemia. Serum K concentration
was normal (3.5–4.9 mmol/l) in 63 and below
normal in 27 patients. None of the patients was
hyperkalaemic. There was no significant difference in
serum K concentration between the three groups.

INITIAL BASAL SERUM CORTISOL
CONCENTRATIONS
Basal serum cortisol concentrations were normal in 55
patients at the time of diagnosis and raised in 35. No
patient had a low basal concentration. Patients with
miliary tuberculosis had the highest basal serum
cortisol concentrations, 18 of 30 patients having raised
concentrations (table 1).

INITIAL SYNACTHEN STIMULATION
After the parenteral administration of Synacthen, 74
of the 90 patients had a normal cortisol response (that
is, an increment of over 200 nmol/l above the basal
centration). Of the remaining 16 patients with a

Table 1 Basal serum cortisol concentrations before
treatment

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mean (SD) basal concentration</th>
<th>Normal values</th>
<th>Raised values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>600 (206)</td>
<td>22 (73)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Miliary</td>
<td>855 (351)</td>
<td>12 (40)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>572 (161)</td>
<td>21 (70)</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

*Normal range 150–650 nmol/l.

subnormal response, nine started with a raised basal
serum cortisol concentration. There were therefore
only seven patients with normal basal cortisol concentra-
tions who had a subnormal response to Synacthen
stimulation. These seven patients consisted of four
with extrapulmonary tuberculosis, two with pul-
monary tuberculosis, and one with miliary tuberculosis.

CORTISOLS AND SYNACTHEN STIMULATION
AFTER TREATMENT
Seventy seven patients were restudied 20–30 days after
starting antituberculous chemotherapy. The remain-
ing 13 patients were not restudied owing to transfer to
another health centre (5), self discharge from hospital
(5), or death (3). Of the 77 patients restudied, only five
had persistently raised basal serum cortisol concentra-
tions; the remainder had concentrations within the
normal range. All three groups had lower mean basal
serum concentrations than before treatment (table 2).

After Synacthen stimulation all subjects had a
normal cortisol response except for one subject, whose
increment in serum cortisol was 120 nmol/l.

Discussion

There is evidence that secretion of the major cortico-
steroid hormones is stimulated early in the course of
acute infectious illness.12-14 In contrast, adrenocortical
secretion is generally depressed during chronic infec-
tions, including tuberculosis.15-19 Few published
studies have examined adrenal function in patients
with active tuberculosis. A recent report from South
Africa15 described a suboptimal response to Synacthen
in 55% of African Zulus with acute pulmonary
tuberculosis. In these patients antituberculous
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 rifampicin. It was
postulated that rifampicin, by its effect on hepatic
enzyme induction and subsequent increased gluco-
corticoid metabolism, may disturb adrenal func-
tion.16-17 Our study, however, showed that a regimen
that included rifampicin for all patients had a
favourable effect on adrenal function, only one of 76 patients having a subnormal Synacthen response three to four weeks after starting treatment. The striking difference in results between our study and the African study may be explained by differences in the criteria used to assess abnormal adrenal function. In the study from Africa basal serum cortisol concentrations are not reported, the response to Synacthen was based on only one serum specimen taken one hour after Synacthen injection, and a normal cortisol response was defined as a rise of at least 300 nmol/l above the baseline value.

Serum Na⁺ concentration was a poor predictor of adrenal function in our study. Hyponatraemia was present in 41% of patients, yet there was no correlation between serum Na⁺ concentration and either the basal serum cortisol concentration or the response to Synacthen stimulation. We could not investigate the pathophysiology of hyponatraemia any further in these patients, but presumably most cases were due to causes other than hypoadrenalism (for example, salt depletion, inappropriate antidiuretic hormone secretion).

None of our 90 patients had depressed basal serum cortisol concentrations; indeed, 39% had a raised basal serum concentration, suggesting an appropriate adrenal response to the "stress" of active infection. The nine patients with raised basal concentrations who did not achieve an increment greater than 200 nmol/l after Synacthen stimulation could not be considered to show evidence of significant adrenal insufficiency. The seven with normal basal serum cortisol concentrations who did not achieve the required increment with Synacthen must, however, be considered as having some degree of adrenal dysfunction. Although the numbers are small, it is worth noting that most (4/7) of these patients had extrapulmonary tuberculosis—Pott's disease of the spine (2) and peritoneal (1) and lymph node (1) tuberculosis. The pathogenesis of depressed adrenal function in tuberculosis is not clear, but it is probably related to the chronicity of infection rather than any specific characteristics of mycobacterial infections. Although evidence of tuberculosis affecting the adrenal glands was found in most of the Addisonian patients in the necropsy study quoted above,1 most cases of hypoadrenalism are likely to be due to a functional disorder of the adrenal glands as after antituberculous treatment (and clinical improvement) the Synacthen response returned to normal in all but one patient. This concept of functional hypoadrenalism (or even hypopituitarism) is supported by the results of other studies.12-14

We conclude that there is a low but definite incidence of adrenal dysfunction in patients with active tuberculosis. Antituberculous chemotherapy regimens that include rifampicin have a favourable effect on adrenal function.

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References