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Adrenal cortical function and adrenal volume in leprosy: A study of 40 cases

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Summary

Background: Leprosy is a chronic infectious disease predominantly affecting peripheral nerves and skin. Whether *Mycobacterium leprae* infection affects adrenal structure and/or its function remains to be fully elucidated.

Methods: Forty untreated leprosy patients and 10 healthy controls were evaluated for adrenal function and morphology by measuring the basal and stimulated cortisol levels after a low dose adrenocorticotrophin stimulation test (LDT) and contrast enhanced computed tomography (CECT) respectively.

Results: The basal cortisol levels were in the normal range in leprosy patients and did not change significantly with the type of leprosy or presence of reaction ($P > 0{\cdot}05$). Peak cortisol response to LDT was < 550 nmol/L at 30 and 60 minutes in 21 (52·5%) leprosy cases [two (15·4%) paucibacillary (PB) cases and 19 (70·4%) multibacillary (MB) cases] indicating significant subclinical adrenal insufficiency in multibacillary cases ($P < 0{\cdot}001$). This depressed response was unrelated to the presence or type of reaction. The mean adrenal gland volume was found to be marginally larger in leprosy patients (both PB and MB) than the controls, although, not statistically significant ($P > 0{\cdot}05$). All the leprosy patients had normal morphology of the adrenal glands.

Conclusions: There is a relative adrenocortical hypofunction in patients with multibacillary leprosy without any dimensional or structural change in adrenal

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glands. Thus, these patients may have suboptimal responses during periods of stress from infection, surgery or otherwise.

Keywords: Leprosy, adrenal gland, low dose adrenocorticotrophin stimulation test

Introduction

The adrenal glands can be affected by various organisms either through direct infection or due to disturbance of the hypothalamic pituitary (HPA) axis from physiological stress or cytokine release.[1] Granulomas and amyloid infiltration have been documented in the adrenal cortex of lepromatous leprosy cases on autopsy.[2] The prolonged stress of *Mycobacterium leprae* infection results in the release of inflammatory cytokines, such as IL-1, IL-6 and TNF-α, which may alter adrenal gland function and glucocorticoid secretion.[3]

The results of investigation of adrenal function in leprosy have been found to range from low to normal.[4–7] Multibacillary (MB) leprosy cases have been noted to have lower basal and stimulated plasma cortisol levels.[8] However, studies based on basal plasma cortisol lack sensitivity.[9] Moreover, 80–90% of both adrenal glands must be destroyed before features of adrenal insufficiency appear.[10] Therefore, there is concern about unsuspected subclinical adrenocortical hypofunction in leprosy and leprosy reactions. Acute adrenal failure may occur in the wake of acute stress such as trauma, infection and leprosy reactions.[4]

Adrenal gland volume has been shown to increase in granulomatous infections like tuberculosis, fungal infections and stressful conditions such as depression, Cushing disease, and during septic shock.[11–13] Moreover, a study showed that patients with adrenal gland enlargement had lower basal and stimulated cortisol levels.[14] This suggests that morphological assessment of adrenal glands in illness may provide additional information on adrenal function and related corticosteroid insufficiency.

Recent studies highlight the importance of the more sensitive low dose adrenocorticotrophin (ACTH) stimulation test (LDT) in evaluating adrenal function, but there is a paucity of studies investigating adrenocortical function using LDT and adrenal morphology in leprosy patients. The latter has not been elucidated in leprosy. This study was thus conducted to evaluate adrenal gland function and morphology by LDT and contrast enhanced computed tomography (CECT) respectively.

Materials and Methods

A prospective case-control study was conducted in the department of Dermatology, Venereology and Leprosy at a tertiary care hospital after approval by the institutional ethics committee. Forty untreated cases of leprosy were recruited for the study. Patients who had received treatment for leprosy, and those with a history of oral or local steroid use were excluded from the study. Patients with any concurrent chronic infective or autoimmune illness were also excluded.

Ten age and sex-matched consenting healthy volunteers belonging to same geographic region were enrolled as controls. Prior to enrolment, written informed consent was taken from

every patient and control. A detailed clinical examination, slit skin smears for bacillary index and skin biopsy were performed in all leprosy patients. The type of lepra reaction was noted, if present. They were classified as per the WHO classification.[15]

After overnight fasting, blood was collected from leprosy patients and controls at 8 a.m. for serum electrolytes and basal cortisol level estimation. The low dose ACTH stimulation test (LDT) was performed using 1 μg synthetic ACTH (1–24 amino acids of ACTH) prepared by diluting a vial of 250 μg ACTH in 250 mL of normal saline. One millilitre of the prepared ACTH solution was then injected intravenously. Thereafter, blood was collected at 30 minutes and 60 minutes for estimating the stimulated serum cortisol levels. The levels of cortisol hormone were measured using the competitive immunoassay technique on Vitros ECIQ Immunodiagnostic System. Basal serum cortisol of <138 nmol/L was suggestive of adrenal insufficiency whereas a basal cortisol value of ≥ 415 nmol/L indicated this as unlikely. The normal response at 30 or 60 minutes after ACTH stimulation was defined by a peak serum cortisol level greater than 550 nmol/L (>20 ug/dl).[16]

Adrenal imaging was performed in all cases and controls using Siemens emotion 16 slice CT scanner after contrast injection; 3 mm axial sections were obtained of both the adrenal glands. The presence, size and morphology of both adrenal glands were evaluated. The length of the gland was taken as its cephalocaudal dimension and the width as the greatest linear dimension seen on any single tomographic section. The thickness of the adrenal gland was taken as its dimension perpendicular to the long axis of the gland or one of its limbs. The measurements were made to the nearest millimetre and then multiplied by the appropriate factor to obtain the adrenal volume. Normal mean adrenal gland volume has been reported as $8{\cdot}50 \pm 1{\cdot}40\,cm^3$.[17]

Statistical analysis was done using Student's T test, chi square test, Pearson correlation coefficient and analysis of variance (ANOVA) test. P value of 0·05 or less was considered as significant in all statistical tests.

Results

The study group consisted of 40 leprosy patients, 29 (72·5%) males and 11 (27·5%) females; and 10 controls, seven (70%) males and three (30%) females. The mean age of the patients was $33{\cdot}05 \pm 12{\cdot}7$ years and that of the controls was $31{\cdot}5 \pm 12{\cdot}8$ years. Twenty seven (67·5%) of the patients had multibacillary leprosy (MB) and 13 (32·5%) had paucibacillary leprosy (PB). Seven (17·5%) had Type 1 downgrading reaction and four (10%) had Type 2 reaction. The mean duration of disease in PB cases was $4{\cdot}5 \pm 1{\cdot}9$ months ranging from 2 months to 8 months. The mean duration of disease in MB cases was $7{\cdot}6 \pm 3{\cdot}1$ months ranging from 4 months to 15 months. The mean duration of Type 1 and Type 2 reactions were 3·2 weeks and 3·0 weeks respectively. No patient with Type 1 reaction could recall a history of a similar episode in the past, while in two patients with Type 2 reaction, there was a history of 2–3 similar episodes previously. Addisonian pigmentation was not present in any of the leprosy patients. The serum electrolyte levels were in the normal range in all leprosy patients and the controls.

The mean serum basal cortisol was lower in MB leprosy patients ($449{\cdot}30 \pm 85{\cdot}26$ nmol/L) than controls ($479{\cdot}60 \pm 53{\cdot}06$ nmol/L) and PB cases ($482{\cdot}46 \pm 59{\cdot}86$ nmol/L), but the difference was not statistically significant ($P > 0{\cdot}05$) (Table 1).

The mean levels of basal cortisol were lower in cases with Type 1 reaction (442 ± 83·66 nmol/L) than cases with no reaction (457 ± 79·74 nmol/L) and both were less than the controls; they were higher in cases with Type 2 reaction (514 ± 49·77 nmol/L) but the difference was not statistically significant ($P > 0{\cdot}05$) (Table 1).

The basal serum cortisol was < 415 nmol/L in 2 (15·38%) cases with PB leprosy, 11 (40·7%) cases with MB leprosy, 10 (34·48%) cases with no reaction and 3 (42·85%) cases with Type 1 reaction, suggestive of likely adrenal insufficiency. Of the four cases with Type 2 reaction none had a basal serum cortisol of < 415 nmol/L ($P > 0{\cdot}05$) (Table 2).

As compared to the mean serum cortisol levels in the controls (585·00 ± 68·53 nmol/L) after injection ACTH at 30 minutes, the level was higher (597·08 ± 65·54 nmol/L) in PB cases while lower in MB cases (498·07 ± 98·54 nmol/L) and the difference between PB and MB cases was statistically significant ($P < 0{\cdot}001$) (Table 1).

Also, at 60 minutes the mean serum cortisol levels was significantly higher ($P < 0{\cdot}001$) in PB cases (516·92 ± 68·26 nmol/L) than in MB cases (416·74 ± 120·91 nmol/L) while in controls it was (516·50 ± 62·48 nmol/L).

No significant difference was observed in the mean serum cortisol levels at 30 minutes and 60 minutes after the injection of ACTH in cases with T1R and T2R.

Serum cortisol at 30 minutes and 60 minutes after the injection of ACTH was <550 nmol/L in two (15·38%) PB cases and 19 (70·37%) MB cases ($P < 0{\cdot}001$); and eight (61·53%) PB cases and 23 (85·18%) MB cases respectively ($P > 0{\cdot}05$) (Table 3).

In four (57·14%) cases with Type 1 reaction and one (25·0%) case with Type 2 reaction the serum cortisol at 30 minutes after the injection of ACTH was <550 nmol/L. ($P > 0{\cdot}05$) (Table 1) while at 60 minutes, four (57·14%) cases with Type 1 reaction and two (50·0%) cases with Type 2 reaction had serum cortisol response levels of <550 nmol/L ($P > 0{\cdot}05$) (Table 2).

Adrenal gland volume on CECT ranged between 6·77 cm^3 and 13 cm^3 in the patients and between 7·06 and 12·3 cm^3 in controls. The mean adrenal gland volume was 9·29 ± 1·01 cm^3 and 9·05 ± 1·70 cm^3 in the cases and the controls respectively; the mean volume was 9·34 ± 1·04 cm^3 in MB cases and 9·18 ± 0·97 cm^3 in PB cases. None of these differences are significant ($P > 0{\cdot}05$) (Table 3).

The mean volume of the adrenal glands for the 29 cases without reaction was 9·31 ± 1·01 cm^3, but 9·14 ± 0·33 cm^3 and 9·33 ± 1·31 cm^3 in the seven cases with Type 1 and four cases with Type 2 reaction, respectively ($P > 0{\cdot}05$) (Table 3).

CECT of the adrenal glands revealed normal morphology without gland oedema, haemorrhage or necrosis in either of the glands, in cases as well as controls (Figure 1).

Using Pearson's correlation, a positive and statistically significant correlation ($P < 0{\cdot}05$) was found between the basal serum cortisol, serum cortisol at 30 minutes (+0·88) and 60 minutes (+0·74) after injection ACTH in the leprosy cases and also between serum cortisol levels at 30 minutes and 60 minutes (+0·88) ($P < 0{\cdot}05$). There was a positive but weak (<0·1) correlation between serum cortisol levels (basal, 30 minutes and 60 minutes) and the total adrenal volume ($P > 0{\cdot}05$).

Discussion

The definitive diagnosis of adrenal insufficiency involves the demonstration of inadequate cortisol secretion. Most of the studies evaluating adrenal function in leprosy are based upon

Table 1. Relationship between the type of leprosy, type of reaction and mean cortisol level

Cortisol (nmol/L)	Controls ($n = 10$) Mean ± SD	PB ($n = 13$) Mean ± SD	MB ($n = 27$) Mean ± SD	No reaction ($n = 29$) Mean ± SD	Type 1 reaction ($n = 7$) Mean ± SD	Type 2 reaction ($n = 4$) Mean ± SD
Basal	479·60 ± 53·06	482·46 ± 59·86*	449·30 ± 85·26*	457 ± 79·74	442 ± 83·66*	514 ± 49·77*
30 minutes	585·00 ± 68·53	597·08 ± 65·54**	498·07 ± 98·54**	526·45 ± 101·19	518·43 ± 116·67*	578·25 ± 60·66*
60 minutes	516·50 ± 62·48	516·92 ± 68·26**	416·74 ± 120·91**	445·9 ± 112·01	431 ± 145·01*	506 ± 101·75*

*indicates P value $>0{\cdot}05$. **indicates P value $<0{\cdot}05$.

Table 2. Serum cortisol levels, basal and after 1 μg injection adrenocorticotrophin (ACTH)

	Serum Cortisol (nmol/L)								
	Basal			After 1 μg Injection adrenocorticotrophin (ACTH)					
				At 30 mins			At 60 mins		
							<550		
	<415	≥ 415 but <479	Mean controls ≥479·0	<550	≥ 550 but <585·0	(Mean controls) ≥585·0	<516·5 (Mean controls)	≥516·5 (Mean controls)	≥550
Total no. of cases ($n = 40$)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
PB ($n = 13$)	2 (15·38)	4 (30·76)	7 (53·85)	2* (15·38)	2 (15·38)	9 (69·23)	3 (23·08)	5 (38·46)	5 (38·46)
MB ($n = 27$)	11 (40·7)	9 (33·33)	7 (25·92)	19* (70·37)	3 (11·11)	5 (18·52)	23 (85·18)	0 (0)	4 (14·82)
T1R ($n = 7$)	3 (42·85)	2 (28·57)	2 (28·57)	4 (57·14)	0 (0)	3 (42·85)	4 (57·14)	0 (0)	3 (42·85)
T2R ($n = 4$)	0 (0)	1 (25·0)	3 (75·00)	1 (25·0)	2 (50·0)	1 (25·0)	2 (50·0)	0 (0)	2 (50·0)
No reaction ($n = 29$)	10 (34·48)	10 (34·48)	9 (31·03)	16 (55·17)	3 (10·34)	10 (34·48)	20 (69·0)	5 (17·24)	4 (13·79)

T1R: Type 1 reaction.
T2R: Type 2 reaction.
*indicates P value $< 0·05$.

Table 3. Total adrenal gland volumes in cases and controls

Normal adrenal gland volumes (cm^3)	Controls ($n = 10$) (Mean ± SD)	Cases ($n = 40$) (Mean ± SD)	PB ($n = 13$) (Mean ± SD)	MB ($n = 27$) (Mean ± SD)	No reaction ($n = 29$) (Mean ± SD)	Type 1 reaction ($n = 7$) (Mean ± SD)	Type 2 reaction ($n = 4$) (Mean ± SD)
8·50 ± 1·40	9·05 ± 1·70	9·29 ± 1·01*	9·18 ± 0·97*	9·34 ± 1·04*	9·31 ± 1·01	9·14 ± 0·33*	9·33 ± 1·31*

*indicates P value $> 0{\cdot}05$.

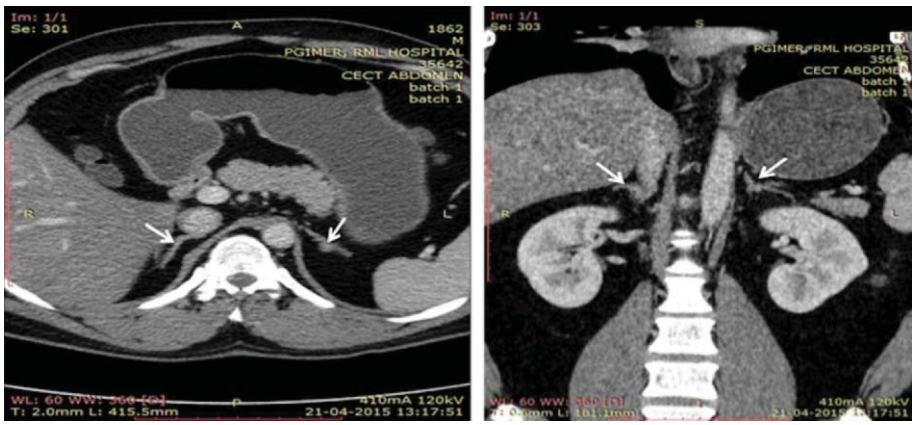

Figure 1. A. CECT showing right and left adrenal glands in cross section, in a patient with lepromatous leprosy. Normal morphology is seen. B. CECT showing right and left adrenal glands in coronal view, in a patient with lepromatous leprosy. Normal morphology is seen.

basal cortisol levels. Basal morning plasma cortisol of less than 138 nmol/l (or 5 μg/dl) is highly suggestive of adrenocortical insufficiency but lacks sensitivity. The standard test for adrenal function is the adrenocorticotrophin (ACTH) stimulation test (SDT) using 250 μg of synthetic ACTH hormone injected intravenously and measuring the plasma cortisol response.[9,18] However, 250 μg of ACTH is a pharmacological dosage and only useful in evaluating maximal secretion capacity of the adrenal glands.[17] In order to evaluate subclinical adrenal failure, a more sensitive low dose ACTH stimulation test using a physiological dose (1 μg of ACTH) was developed.[19–21] We evaluated adrenal function and its morphology in leprosy patients by measuring the basal and stimulated values of serum cortisol by LDT and CECT respectively.

Earlier studies on the basal serum cortisol levels in leprosy patients have shown results varying from low (Bansal *et al.*), no change (Garg *et al.*) to mildly raised (Saha *et al.*).[7,8,22] Moreover, low basal cortisol levels have been observed in MB leprosy, in both reactional and non-reactional leprosy patients.[22,23] In our study, the mean level of basal cortisol for the cases and the controls was in the normal range, although 13 (32·5%) leprosy cases had levels of <415 nmol/L, suggesting likely adrenal insufficiency. No significant difference ($P > 0{\cdot}05$) in the basal cortisol was present between leprosy patients (PB and MB) and the healthy controls. This suggests that the basal adrenal cortical function remained normal in leprosy, as has been reported in an earlier study by Dash *et al.*[24]

In patients who had Type 1 reaction, the mean basal cortisol was lower than in cases with no reaction and both of these, were less than the controls (479 nmol/L). But the cases with Type 2 reaction had mean basal cortisol higher than the controls though this was not statistically significant ($P > 0{\cdot}05$). Saha *et al.* had reported similar observations in Type 2 lepra reaction.[22]

On comparing the values of serum cortisol at 30 minutes and 60 minutes after LDT we found that they were lower in multibacillary leprosy patients than in paucibacillary cases and the difference was statistically significant ($P < 0{\cdot}001$). 21 (52·5%) of the leprosy cases (two (15·38%) PB and 19 (70·37%) MB) had serum cortisol levels of <550 nmol/L at both 30 minutes and 60 minutes after LDT, indicating subclinical adrenal insufficiency. There was a statistically significant decrease in adrenal function in multibacillary cases of leprosy versus

paucibacillary cases at 30 minutes after LDT ($P < 0{\cdot}001$). The PB cases with adrenal hyporesponse on LDT may be subclinically downgrading towards the lepromatous pole or foretelling a future downgradation. Colak *et al.* also reported low mean value peak cortisol response with both LDT and SDT in the lepromatous leprosy group.[4]

Five (45·45%) of the 11 cases with reaction (Type 1 reaction, four (57·14%) and Type 2 reaction, one (25%)) had a subnormal response to LDT (serum cortisol <550 nmol/L at 30 minutes and 60 minutes) indicating adrenal insufficiency in these cases as well though the difference was not statistically significant when compared to those with no reaction. However, the number of cases having Type 2 reaction was too small to conclusively elucidate the effect of this reactional state on the adrenal function. These findings are similar to those reported by Durairaj *et al.* who measured basal serum cortisol and values after SDT in non-reactional and reactional lepromatous leprosy patients.[23]

Our study thus shows a decrease in adrenocortical functional capacity in patients with multibacillary leprosy which could be either innate or due to minimal *M. leprae* invasion of the adrenal cortex, or the suppressive effect of various cytokines such as IL-5, IL-10, TGF-β, TNF-α and IFN-γ released as a result of tissue infiltration by *M. leprae*.[25–27] These factors may be preventing the adrenals from stepping up the cortisol release. It is important to note that this decreased reserve is found in non-reactional states also, which is a salient feature of our study. As the ACTH level was not done in our study, we cannot comment on whether there was a coexisting secondary adrenal insufficiency state in our patients.

The mean adrenal gland volume in leprosy patients (both PB and MB) was marginally more than the controls, although not statistically significant ($P > 0{\cdot}05$). There appears to be no direct involvement of adrenal glands as evident from their normal morphology on CECT. Thus, this marginal increase in the adrenal gland volume could perhaps be due to prolonged physiological or biological stress due to the *Mycobacterium leprae* infection, rather than due to direct invasion of the adrenals. A similar increase in adrenal gland volume has been recorded in diseases like tuberculosis and granulomatous fungal infections.[14,28] Further, no correlation between adrenal gland volume and serum cortisol levels, either basal or on stimulation with ACTH injection was found in our study.

In conclusion, our study shows that adrenal glands in leprosy patients maintain a normal basal cortisol secretion, but have a diminished functional capacity particularly in multibacillary leprosy patients without any dimensional or structural change in adrenal glands. Thus these patients may have a suboptimal response during the period of stress from infection, surgery or otherwise.

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