SERUM CORTISOL LEVELS IN PATIENTS WITH UNCOMPLICATED AND CEREBRAL MALARIA

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Abstract. Ten patients with uncomplicated malaria, ten with cerebral malaria and 37 controls (blood donors from blood bank) were included in the study. The serum cortisol levels of the patients were determined daily for 7 days while they were at the hospital. A radio-immunoassay method was used for quantitative measurement of cortisol in human serum. The mean serum cortisol level of patients with uncomplicated malaria was 528.2 ± 123.9 nmol/l, with cerebral malaria was 516.0 ± 80.5 nmol/l, and in controls was 393.8 ± 141.0 nmol/l.

There was a significant rise of serum cortisol levels in patients with malaria when compared to controls at the day of admission to hospital. There was no significant difference between uncomplicated malaria patients and those with cerebral malaria. There was also no significant difference between the different days of treatment up till day 7. We found no cortisol insufficiency in cases with falciparum malaria during acute and convalescent stages of illness.

INTRODUCTION

Dexamethasone and other corticosteroids had been recommended for patients with cerebral malaria for their anti-inflammatary effect, but clinical studies failed to confirm the value of using corticosteroids. A recent study reported that patients with some infectious diseases can have low serum cortisol levels (Lim *et al*, 1986), for example, cortisol insufficiency in hemorrhagic fever with renal syndrome cases with or without pituitary atrophy has been reported. Hence the serum cortisol level of malaria patients needs to be estimated this has not been reported in the literature before.

PATIENTS AND METHODS

Ten consecutive patients with uncomplicated malaria and another 10 patients with cerebral malaria who were admitted to the North Okkalapa General Hospital during the 1995 malaria season were studied. Adult patients of both sexes and ages between 12 and 60 years were included in the study. Patients with other complications other than cerebral malaria, such as those with jaundice, acute renal failure, anemia, were not included in the study. Cerebral malaria is defined as the patient with unrousable coma not attributable to other cause in the presence of falciparum malaria. For the diagnosis of cerebral malaria, coma should persit for at least 30 minutes after a generalized convulsion. The patients with uncomplicated malaria were treated with mefloquine 750 mg single dose. The patients with cerebral malaria were treated with injection Artemether 160 mg intially followed by 80 mg twice a day for another two days, with mefloquine 750 mg given via nasogastric tube as a single dose. The sera of patients were collected daily for 7 days and were stored at -4°C, before the estimation of serum cortisol level. 37 sera samples collected from blood donors, of the Blood Bank, Yangon General Hospital were included in the study as controls.

We determined the serum cortisol levels of the selected cases using commercially available RIA Kits (Double Antibody Cortisol kits, Diagnostic Products Corporation, Los Angeles, CA, USA). It is a competitive radio-immunoassay in which ^{125}I-labeled cortisol competes with cortisol in the patient sample for antibody sites. The lower detection limit is 8.28 nmol/l and both intra-assay and interassay error is less than 10%. We performed all analyses in duplicate; a Packard Auto-Gamma Scintillation Spectrometer, Model 5230 was used for radioactive measurements.

Statistical analysis

Data analysis was performed with SPSS (Ver 3.0; SPSS Corporation, Chicago, IL, USA) on an IBM PC computer. Data are expressed as mean ± (SD). Comparisons between serum cortisol levels among groups (uncomplicated malaria, cerebral malaria, controls) were made using Student's *t* test for unpaired samples (two tailed). Differences in serum cortisol levels in relation to days of admission were assessed using Student's *t* test for paired data (two tailed). Differences were considered significant if $p < 0.05$.

RESULTS

All the patients responded well to treatment. Uncomplicated malaria patients were treated with mefloquine. Cerebral malaria patients were treated with artemether and mefloquine standard dose. The average duration of stay in hospital for uncomplicated and cerebral malaria patients were 7 days and 10 days respectively.

The mean serum cortisol level of patients with uncomplicated malaria on the day of admission to hospital was 528.2 ± 123.9 nmol/l. The mean cortisol level of patients with cerebral malaria at the day of admission to hospital was 516.0 ± 80.5 nmol/l, and among controls, the mean level was 393.8 ± 141.0 nmol/l.

There was a significant rise of cortisol levels in patients with malaria when compared to controls at the day of admission to the hospital. There was no significant difference between uncomplicated malaria patients and those with cerebral malaria. There were also no singificant difference between different days of treatment in the two groups of malaria patients up till day 7 (Table 1, Fig 1).

But in one patient with cerebral malaria the initial cortisol level was 3,640 nmol/l and 2,086, 1,019, 560 nmol/l at days 0, 1, 2, 4. Because of the exceptionaly high level of cortisol this patient was not included in the calculation.

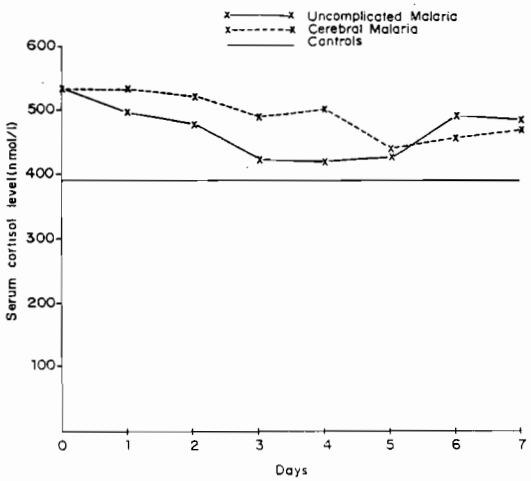

Fig 1–Serum cortisol levels in patients with uncomplicated and cerebral malaria.

Table 1

Mean serum contisol level (mean ± SD nmol/l) in patients with falciparum malaria.

Days of admission to the hospital	Patients with uncomplicated falciparum malaria (10)	Patients with cerebreal malaria (10)	Control (37)
Day 0	528.2 ± 123.9**	516.0 ± 80.5**	393.8 ± 141.0*
Day 1	498.0 ± 115.8	534.9 ± 97.3	-
Day 2	480.2 ± 135.9	520.9 ± 105.5	-
Day 3	425.9 ± 107.2	489.0 ±126.4	-
Day 4	416.9 ± 83.0	505.6 ± 147.7	-
Day 5	433.8 ± 86.3	443.6 ± 169.7	-
Day 6	494.7 ± 122.4	457.0 ± 184.1	-
Day 7	488.3 ± 52.4	474.0 ± 146.4	-

( ) = No. of patients studied
*-** = difference between two groups significant $p < 0.001$
- = difference between two groups not significant

DISCUSSION

In this study, there was significant rise in serum cortisol level of malaria patients compared to controls on admission. There was no significant difference between uncomplicated malaria patients and those with cerebral malaria. Moreover, there was not a single patient with cortisol level less than the mean level of controls during the 7 days period of treatment. Hence we may conclude that there was no cortisol insufficiency in cases of falciparum malaria during acute and convalescent stages of illness.

Dexamethasone in a dose of 0.5 mg/kg, 10 mg every 6 hours for 48 hours by slow intravenous injection has been tested in a double-blind placebo-controlled trial involving 100 patients with strictly defined cerebral malaria in eastern Thailand (Warrell *et al*, 1980). Dexamethasone did not decrease mortality ($p = 0.8$) but significantly prolonged unconsciousness and led to an increased incidence of steroid-related side-effects including infections and gastrointestinal bleeding. Similar problems have been encountered in patients with septic shock treated with dexamethasone (Sprung *et al*, 1984) and methylprednisolone (Bone *et al*, 1987), in patients with cerebral hemorrhage treated with dexamethasone (Poungvarin *et al*, 1987), and in patients with respiratory failure treated with methylprednisolone (Weigelt *et al*, 1985). The study of cerebral malaria in Thailand was criticized on the grounds that the dose of dexamethasone was much too low (Hoffman, 1982) or too high but given for too short a time (Rees, 1982, 1983). Hoffman *et al*, 1988) carried out a double-blind trial of 11.4 mg of dexamethasone/kg over 48 hours in 10 stuporose and 28 comatose patients with falciparum malaria in Irian Jaya, Indonesia. The mortality was 21% in each group. Three out of 19 dexamethasone-treated patients and none of the placebo group developed gross gastrointestinal bleeding.

Evidence from clinical studies in man also does not support the hypothesis that cerebral malaria results from an inflammatory breakdown in permeability of the blood- brain barrier resulting in cerebral edema (Looareesuwan *et al*, 1983; Warrell *et al*, 1986). Thus Wyler (1988) reviewed the literature and concluded that corticosteroids should not be used in cerebral malaria as this treatment lacks a theoretical basis and clinical evidence of efficacy, and carries a risk of side effects.

In this present study on patients with falciparum malaria a two-fold increase in serum cortisol level was observed.

During illness, a direct relationship between the release of cortisol and disease severity had been documented (Baxter and Tyrrell, 1981). The present study demonstrates higher serum cortisol levels in acute stages of illness than their corresponding convalescent levels. This is in agreement with the study by Inamo *et al* (1991) where a two-fold increase in cortisol levels during febrile illnesses was reported. Although increments up to 5-fold have been reported in patients with pneumonia, bacterial meningitis and fever of unknown origin (Nickels and More, 1989), we observed only a two-fold increment in cases of falciparum malaria.

In one particular patient with cerebral malaria, the serum cortisol level increased to 9 times that of controls. Apart from cerebral signs and symptoms he had no other complications and responded well to the artemether-mefloquine regimen. Further studies are needed on such patients may contribute to our knowledge on pathogenesis of cerebral malaria.

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