

Title: Host Response (Renal) to Malaria.

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Introduction: Renal manifestations of malaria vary widely, from total renal failure to mild and non specific abnormalities of the urinary sediment and proteinuria. The cause of these latter abnormalities is not known. Previous studies used less sensitive indicators of renal damage such as blood urea nitrogen and therefore could not detect more subtle changes. The present study attempted to detect early or mild changes by Inulin-PAH clearance in naturally occurring falciparum malaria. Initially, renal function studies were performed on 2 patients. Significant hyponatremia was found in these patients, therefore detailed studies of salt and water metabolism were included in the later cases.

Material and Methods:

Twenty-five patients with clinical and laboratory evidence of malaria were studied. No specific selection criteria were used. With the exception of two patients, the patients were studied on a metabolic unit which was established at Sriracha Red Cross Hospital during Jan-Mar 1966.

Study Plan:

A history and physical examination was done upon admission, and repeated daily.

Initial and subsequent laboratory studies were obtained according to the general outline shown in table 1. Repeat clearances and body space measurements were usually performed after the patient had been afebrile for seven days. In addition, the patients had an admission and discharge electrocardiogram and chest X-ray. Between the second and the eighth day a percutaneous renal biopsy was performed.

Treatment was begun after the initial studies on the first day. The first 18 patients were treated with chloroquin. Because of relapses, failure to clear asexual parasites, and/or poor initial clinical response, 14 of these were subsequently treated with quinine. The last six patients and one with malaria with involvement of the nervous system were treated with quinine alone. Darvon was used for headache and muscle pain. Diet and fluids were unrestricted. Intravenous fluids were administered for clearances and water load tests and in four patients who received intravenous saline because of clinically suspected salt and water depletion.

Methods

Thick and thin malaria smears were obtained daily until asexual parasites were no longer observed. The number of parasites per 1,000 red blood cells on the thin smear or per 500 white blood cells on the thick smear were related to the red and white blood cell count respectively and expressed per mm³.

Electrolytes, osmolality, BUN, creatinine, liver function tests protein, and protein electrophoresis were done by standard laboratory techniques. Electrolyte determinations included sodium, potassium, chloride, and bicarbonate. Liver function tests included total and direct bilirubin, thymol turbidity, alkaline phosphatase, glutamic oxalic and glutamic pyruvic transaminases.

Inulin PAH clearances were performed by standard techniques. The patients received a water load of 5% D/W IV (20 cc/kg) prior to the test and thereafter hydration was maintained. Following a priming dose of inulin and PAH, blood levels were maintained by constant infusion. After one hour equilibration, four 15-minute clearances were performed.

For the water load test, the patients received intravenously, 20 cc/kg of 5% D/W in 60 minutes. Urine was collected at 60, 80, 95, 110, 125, and 140 minutes for osmolality determinations. Blood was obtained before and after the test for osmolality. Oral fluids were administered during the first two collection periods equivalent in volume to the uring output. The response was expressed by urine osmolality (U_{osm}), solute clearance (C_{osm}), and free water clearance (C_{H_2O}) during the periods of maximum flow.

The body space determinations included plasma volume, total body water, sodium space and exchangeable sodium. The plasma volume was determined by RISA or Evans Blue dye. Three blood samples were obtained between 10 and 45 minutes after the injection and the volume determined by extrapolating to zero on semilogarithmic paper. The blood volume was estimated from the plasma volume and the hematocrit. The venous hematocrit was corrected for trapped plasma and by the empirical factor 0.91. Total body water was determined following the oral administration of tritiated water by a single blood specimen drawn at 3 hours. The blood sample was processed by distilling with benzene and counting in a liquid scintillation system. The sodium space and exchangeable sodium was determined by standard isotope dilution techniques employing Na^{22} or Na^{24} and allowing a 22-24 hour equilibration period.

The whole pH was determined on "arterialized" venous blood with an Astrup pH meter. The blood was obtained from the antecubital vein without a tourniquet after warming the forearm for 15 minutes with a heating pad. The pH of the whole blood was determined after equilibration of the blood with 2 gases of known P^{CO_2} . From these determinations the P^{CO_2} and the base excess was determined from the Astrup nomogram.

Serologic tests for Dengue, Chikungunya and Japanese B encephalitis were performed on paired sera.

Kidney biopsy was performed with a VIM Silverman modified cannula biopsy needle. There were no complications of the procedure. Eighteen specimens were fixed in Bouin's solution and then changed to 70% alcohol 24 Hours later. Three specimens were fixed in 5% buffered formalin.

Results:

The age range of the patients was from 15 to 64 with a mean age of 27. There were twenty-three males and two females. Twenty-four were infected with *P. falciparum* and one with *P. vivax*. Patient no. 13 had a serological titer rise for Chikungunya which was diagnostic for infection with this virus. However, he had a clinical picture compatible with severe malaria and had 28,000 asexual parasites/mm³. Therefore it was felt that the patient had a double infection and was included in the series.

Fifty-two percent of the patients were studied during their initial attack of malaria. This was defined as an illness of less than 30 days whether or not the patient had received treatment. The

average length of sickness was 8.3 days (range, 1 day to 7 weeks). Eleven out of twenty-five had received antimalarial drugs before admission. The maximum parasitemias for the cases are given in table 2. Patients with higher parasitemia had a greater weight loss, more day of fever after treatment and more severe biochemical abnormalities.

On admission, 48% had splenomegaly and 80% hepatomegaly. Neurological signs were present in 5 patients and included organic psychosis in one, confusion in one, bobbing tremor of the head and body in one, and coarse tremor of the hands in two.

The summary of admission and discharge laboratory determinations is shown in table 3. The hematocrit fell an average of 3% during the study. On admission there were 6 patients with leucopenia (24%) and one with leucocytosis (4%). There was a rise in both relative and absolute eosinophile count in 13 patients (52%). The eosinophile count rose from low levels to over 20% in 3 patients and stabilized at this level. Approximately 60% of the patients examined had intestinal parasites. The degree of eosinophilia was the same whether or not intestinal parasites were found. Admission urinalysis showed proteinuria in 32%. Minimally increased numbers of red blood cells (1-5/HPF) were seen in 28% of the patients. The proteinuria was mild in all except two. These had 3 to 4 + proteinuria which lasted for three days and had the highest admission creatinines, 1.6 and 1.8 mg./100 ml. One had broad granular casts. Significant abnormalities of routine blood chemistries included hyponatremia, hypopotassemia, hypochloremia, hypoosmolality, and elevation of the BUN and creatinine. Liver function studies were abnormal in a significant number of patients as outlined in the table. The most common abnormality was in thymol turbidity (60% abnormal) and least common abnormalities were in SGPT and direct bilirubin (16%). The abnormalities of bilirubin and transaminase were mild except for three patients with bilirubin of 5.0, 11.5, and 4.1 and one patient with a SGOT of 194 and a SGPT of 230.

Seventeen patients had acid base determinations by Astrup technique. Forty-seven percent had alkalemia (pH 7.440-7.460). No patient had acidemia. Fifty-nine percent had respiratory alkalosis, (p^{CO_2} , 20-34). None had respiratory acidosis. Twenty-nine percent had mild metabolic acidosis (Base excess, -3-6.7); none had metabolic alkalosis. The five patients with metabolic acidosis had p^{CO_2} of 30 mm Hg or below. Those patients with a fever above 101°F. had a significantly lower p^{CO_2} than those without fever. It was not possible to attribute the respiratory alkalosis to other factors.

The inulin-PAH clearance data have not been completed yet.

The patients were divided according to their initial serum sodium into a hyponatremic group (serum sodium < 135) which had 16 patients and into a normonatremic group which had 9 patients. Certain clinical aspects and laboratory determinations of these groups were then compared as shown in table 4. Those with a first acute attack were mainly in the hyponatremic group. The parasitemia was greater and the days of fever after treatment were longer in this group. The hyponatremic group showed more marked urinary changes of proteinuria and granular casts. There was a significant change in serum creatinine between admission and discharge in the hyponatremic group and no change in the normonatremic group. The BUN decreased in both groups but the decrease was more marked in the hyponatremic group. There was a marked increase in the chloride and osmolality in the hyponatremic group as would be expected. There was a minimal but significant increase in potassium in the hyponatremic group. There were 5 abnormal water load tests in the hyponatremic group. The patients with abnormal tests also conserved sodium (24 hr. urinary excretion < 15 meq.) during their hospital course, whereas the patients in the hyponatremic group with normal water load tests did not conserve sodium. Early morning urines during the first 3 days of hospitalization in the hyponatremic group showed higher osmolality than did plasma in all patients (721 ± 167 mOsm/kg H_2O). There was no change in blood volume between admission and discharge in either group.

When the values for exchangeable sodium and total body water are examined the patients can be divided into those with a marked increase in serum sodium and/or osmolality (group II), and those without a marked change (group I). Group III had a decrease in serum sodium and osmolality. Group II had a significant decrease in total body water (1.7 liter) whereas group without a change in serum sodium did not have a significant change in total body water. The number of patients with exchangeable sodium determinations was too small to be broken into two groups. They showed a small but significant increase in exchangeable sodium (200 meq.).

Study of the kidney biopsy specimens is not complete. The following preliminary comments can be made. No malaria pigment is seen. Some vacuolization of the convoluted tubules in the cell area near the brush border is seen. There was one case with heavy iron deposit (? hemosiderosis-hemochromatosis). There was some light brown pigment in some cases, probably associated with clinical jaundice. Occasional hyalinization of glomeruli in some cases was seen (degenerative changes).

Discussion

Final conclusions and discussion of the data presented will be submitted following completion of the clearance studies.