

CHLOROQUINE-RESISTANT *PLASMODIUM FALCIPARUM* MALARIA IN AN EXTREMELY PREMATURE INFANT

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Malaria is an uncommon disease in neonates and young infants. Its prevalence, however, is rising in some developing endemic countries.¹ Most reported cases of malaria in this age group are caused by *P. falciparum* and *P. vivax*, and are sensitive to chloroquine. Common clinical features include anemia, fever, respiratory distress, apnea, jaundice and hepatosplenomegaly.¹⁻³ Data on treating chloroquine-resistant *P. falciparum* malaria in newborns and young infants is still limited.^{2,4} We present a case of chloroquine-resistant *P. falciparum* in an extremely premature baby who had heavy parasitemia, and was treated successfully with a combination of quinine and pyrimethamine-sulfadoxine.

Case Report

A female Saudi infant was born at 26 weeks of gestation with a birth weight of 730 grams, length of 36 cm and head circumference of 22.5 cm. Her Apgar score was 8 at one minute and 9 at five minutes. The patient's admission to the neonatal intensive care unit (NICU) was complicated by hyaline membrane disease, intraventricular hemorrhage (grade I), indirect hyperbilirubinemia, bronchopulmonary dysplasia, coagulase-negative staphylococcal bacteremia, and anemia. The latter was treated with a total of eight packed red cell transfusions. The last blood transfusion was 12 days prior to the current illness. She was extubated at the age of 36 days and was fed through a nasogastric tube. At 43 days of age, she developed repeated episodes of bradycardia.

On examination, her heart rate was 60-143/min, respiratory rate 50-65/min, temperature 37°C, and blood pressure 60/30 mm Hg (mean 46). She looked pale and inactive. The anterior fontanelle was normal and systemic examination was unremarkable. A presumed diagnosis of sepsis was made, and the patient was started on vancomycin and cefotaxime, after obtaining blood,

cerebrospinal fluid (CSF) and urine cultures. Chest x-ray did not show new infiltrates. CSF analysis was as follows: WBC 8 (98% lymphocytes, 2% monocytes), protein 749 mg/dL and glucose 3.5 mmol/L (blood glucose 6.0 mmol/L). No micro-organisms were seen on gram stain. On the third day of illness, a positive blood film for *P. falciparum* malaria was reported. This was an incidental finding observed while the laboratory technician was looking at peripheral blood smear. Chloroquine was started in the standard doses of 10 mg/kg/dose, followed by 5 mg/kg/dose six hours later, given via nasogastric tube on the first day of therapy. A dose of 5 mg/kg/day was given on two subsequent days. No vomiting or diarrhea was observed during treatment. The infant's weight at diagnosis of malaria was 990 grams. Antibiotics were discontinued after 96 hours of therapy, as all cultures were sterile. Response to chloroquine therapy was monitored clinically, and by daily blood smear for malaria. After three days, no clinical improvement was noted with chloroquine treatment. Instead, the infant got worse, with frequent apnea and desaturation. On the fourth day, she developed generalized mottling of skin, poor capillary refill (6 seconds), jaundice and hepatosplenomegaly. Because of this deterioration, the baby was ventilated. Three blood transfusions were given after diagnosis of malaria due to abrupt drop of hemoglobin. Results of hemoglobin, hematocrit, platelets, reticulocytes, and serum bilirubin are shown in Table 1.

After completing the course of chloroquine, the blood film for malaria showed no change in parasitemia, with only ring forms seen. At this point, chloroquine-resistant *P. falciparum* malaria was considered. Quinine 10 mg/kg every 8 hours was started. Results of blood film for malaria during therapy with chloroquine and quinine are shown in Table 2. Treatment with quinine was extended for six days as blood film continued to be positive (a sexual stage) on the fourth day of therapy. A quarter tablet of pyrimethamine-sulfadoxine (125 mg pyrimethamine, 6.25 mg sulfadoxine) was given at the end of quinine treatment, as G6PD activity was normal. The baby's condition improved, and she was weaned off ventilator on the second day of treatment. No blood transfusion was needed during the course of quinine. The baby's thrombocytopenia also subsided. Hepatosplenomegaly (initially liver was 5 cm

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below costal margin, spleen 3 cm below costal margin) persisted for two weeks after recovery from malaria. Four weeks after treatment of malaria, the patient was well. Blood films for malaria were followed weekly for three weeks after recovery, and all were negative.

The mother of the baby was a G2 P0+1, originally from the southwestern region of Saudi Arabia, an area endemic for malaria. She had not travelled to that area for at least one year before she became pregnant. She was admitted twice during pregnancy, at 22 and 26 weeks of gestation, because of fever, rigors and arthralgia. Her blood film for malaria was requested on the second admission and at the time of the diagnosis of malaria in her baby. Both blood films were negative. The infant had not left the hospital from the time of birth. All packed red cell transfusions were screened in accordance with the policy of the hospital blood bank. Screening blood for malaria during the malaria season is hospital policy. The blood transfused in this infant came from eight different donors, all of Saudi nationality. The remaining blood from all these donors was re-tested for malaria after the diagnosis was made in the infant, however, no donor had a positive blood film.

Discussion

Of the 16 *P. falciparum* malaria cases recently reported, 25% were resistant to chloroquine and 19% of this group were resistant to quinine.¹ Five cases of transfusion-acquired malaria in neonates have been reported from this country. Three of these were treated successfully with chloroquine.^{3,5} One case apparently had cerebral malaria and the fifth case failed to respond to chloroquine treatment, but details of in vivo or in vitro documentation were not reported.⁴ Our patient did improve, but only after starting quinine. We considered exchange transfusion, but because of rapidly declining parasitemia, this procedure was deferred. Exchange transfusion was not used in two recent series on neonatal malaria, but neither of the studies reported the level of parasitemia in their patients, which is a guide for severity.^{1,2}

Data on exchange transfusions in neonatal malaria is rare, as almost all exchange transfusion reports have been on adult patients.⁶ The southern and southwestern parts of Saudi Arabia are endemic areas for *P. falciparum* malaria. Saudi Arabia is still considered by WHO to be in the zone of chloroquine-sensitive countries.⁷ A case of chloroquine-resistant *P. falciparum* malaria in a pregnant Saudi woman was recently reported.⁸ The documentation of chloroquine resistance in our case (RIII) was based on WHO in vivo criteria for grading the level of resistance.⁹ Although both in vivo and in vitro documentation of chloroquine resistance is preferred, the latter is not available in routine practice. It is worth mentioning that these two cases are originally from the same Province, which is endemic for malaria. In our case, it is likely that the malaria was

TABLE 1. Results of CBC and bilirubin before diagnosis of malaria and during therapy with chloroquine and quinine.

	4 days before diagn	Day of diagn.	Chloroquine therapy (days)			Quinine therapy (days)				
			1	2	3	1	2	3	4	5
WBC (x10 ³ /μL)	12.2	12.2	10.4	4.88	11.8	7.1	5	8.3	9.5	9.9
Hb (g/dL)	13.3	9.6*	10.8	6.6*	12	8.8	13.3	10.3	11.8	11.4
HCT (%)	36.8	27.6	37.1	18.7	35.1	24.3	39	28.8	33.7	33.1
MCV (fl)	78.5	86	79.2	76.5	83.6	82.5	78.3	75.5	76.5	76.6
Platelets (x10 ³ /μL)	184	93	37	21	25.5	35.4	280	362	204	370
Retics (%)	1	NA	1.2	1.3	-	2	-	4.6	-	6
Bilirubin (μmol/L)**	61	62	116	519	-	737	637	315	125	104

*Received blood transfusion; **total bilirubin; NA=not available.

TABLE 2. Results of blood film for malaria after treatment with chloroquine and quinine.

	% Parasitemia (days of treatment)					
	1	2	3	4	5	6
Chloroquine	33	33	37	-	-	-
Quinine	37	11	4	1	0	0

acquired through blood transfusion. This assumption is based on the fact that the mother had not travelled to an endemic area prior to the onset of the disease, and that her blood films were negative for malaria on two occasions. Negative blood smears from asymptomatic donors do not exclude transfusional malaria, as donors from endemic areas may have low-level parasitemia that is difficult to detect by routine microscopy.¹⁰ Indirect methods like detection of antigens of the parasite are more sensitive for screening asymptomatic donors.¹¹ Although our case was diagnosed in the northwestern region of the country, many people living in this area are originally from endemic parts, and tend to visit these areas during holidays. These include some donors who bring malaria to their place of work.

Malaria should be considered in the differential diagnosis of neonatal sepsis, especially when the mother is from, or has a history of travel to, an endemic area. Blood transfusion is also a risk factor for induced malaria in newborn infants. It is worth noting that chloroquine-resistant malaria is on the rise in Saudi Arabia, as already documented in the nearby countries of East Africa. In the Southwest (Gizan) region, 2% and 15% of *P. falciparum* isolates from local residents were in vitro resistant to chloroquine in 1992 and 1995, respectively (personal communication). The recent report of a chloroquine-resistant *P. falciparum* malaria case of an adult patients⁸ and ours are probably just a fraction of the real prevalence of the disease in this country. Although pyrimethamine-sulfadoxine alone and halofantrine have been used in a few

patients, options for treating chloroquine-resistant malaria in neonates, and particularly in premature babies, are limited.¹² In part, this is due to lack of data on the pharmacokinetics and safety of antimalarials used in this age group. Until this data is available, we believe quinine combined with pyrimethamine-sulfadoxine (if glucose-6-phosphatase activity is normal) is the preferred choice.

References

1. Ibhanebhor SE. Clinical characteristics of neonatal malaria. *J Trop Paediatr* 1995;41:330-2.
2. Thapa BR, Naranga A, Bhakoo ON. Neonatal malaria: a clinical study of congenital and transfusional malaria. *J Trop Paediatr* 1987;33:266-8.
3. Vijayakumar E, Shaheed MM, Katugampola MS, Haque KN. Transfusional malaria in newborn infants: report of two cases. *Ann Saudi Med* 1990;10:569-72.
4. Gereige RS, Cimono D. Congenitally acquired chloroquine-resistant *P. falciparum* malaria in infant born in United States. *Clin Pediatr* 1995; 34:166-9.
5. Pejaver RK, Al Hifzi I, Al Temany F, Abdullah B. Transfusion malaria in sick neonates. *Indian Pediatr* 1997;34:1029-32.
6. Looareesuwan S, Phillips RE, Karbwan J, et al. *Plasmodium falciparum* hyperparasitemia: use of exchange transfusion in seven patients and a review of the literature. *Quart J Med* 1990;75:471-81.
7. World Health Organization. International Travel and Health Vaccination Requirement and Health Advice. Geneva: World Health Organization, 1994.
8. Manohar S, Baker A, Rao PA, Oridota T. Chloroquine-resistant plasmodium malaria in a pregnant woman. *Ann Saudi Med* 1997;17:247-9.
9. World Health Organization. Chemotherapy of malaria. Geneva: WHO 1967. Technical Reports Series, No. 375.
10. Choudhary N, Joky JG, Mahajan RC, Ganuly NK, Dubey ML, Aangiharti SK. Malaria screening to prevent transmission by transfusion: an evaluation of techniques. *Med Lab Sci* 1991;48:206-11.
11. Warhust DC, Williams JE. Laboratory Diagnosis of malaria. *J Clin Path* 1996;49:533-8.
12. Larkin GL, Thuma PE. Congenital malaria in a hyperendemic area. *Am J Trop Med Hyg* 1991;45:587-92.