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CONGENITAL MALARIA IN A PRETERM NEONATE: CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Congenital malaria occurs infrequently in endemic areas and is even more uncommon in the United States. Although more than 300 cases of congenital malaria have been reported, only four reports describing this disease in preterm infants exist in the English-language literature. We report the first case of congenital malaria in an extremely low-birth-weight infant born in the United States. The maternal history and clinical findings and treatment of this infant are discussed and a summary of the prior reported cases is provided as aids to the early identification and management of infants with congenital malaria. The diagnosis of congenital malaria should be considered in infants with suspected congenital infection who are born to mothers with a history of even remote travel to endemic areas.

Keywords: Malaria; congenital malaria

Worldwide, more than 200 million people are annually infected with malaria. Congenital malaria (CM), in comparison, occurs infrequently. Between 1950 and 1991, only 49 cases of CM were reported in the United States (US).[1] The majority of these occurred in the last decade in parallel with an increase in immigration from and travel to endemic areas. We report here the first case of CM in an extremely low-birth-weight (LBW) infant born in the US. In addition, we review the four cases in premature infants previously reported in the English-language literature. As global mobility continues to increase, similar cases may be observed in this country, and CM will need to be considered in the differential diagnosis of congenital infections.

CASE REPORT

An 818-g male infant was delivered vaginally at 28 weeks' gestation to a 23-year-old gravida 1, para 1 woman with preeclampsia who had immigrated from Zaire 2 months before delivery. During pregnancy the mother had had three episodes of malaria, the most recent 3 months before delivery, for which she was treated with oral quinine. Prenatal serological tests revealed absence of antibodies to human immunodeficiency virus and *Toxoplasma gondii*, a negative hepatitis B surface antigen test, a nonreactive rapid plasma reagin test and immunity to rubella.

At delivery, a placental clot suggestive of partial abruption was noted. The infant required endotracheal intubation for respiratory distress. Physical examination revealed an afebrile infant with normal vital signs, a liver palpable 1.5 cm below the right costal margin in the midclavicular line and a spleen palpable 2.5 cm below the left costal margin. Laboratory studies showed a hemoglobin level of 135 g/L, hematocrit of 44%, white blood cell (WBC) count of 5.9 $\times 10^9$/L, and a platelet count of 41 $\times 10^9$/L. At a few hours of life, the platelet count decreased to 15 $\times 10^9$/L, and the infant received a transfusion of platelets. On the second day of life, phototherapy was initiated secondary to a total bilirubin level of 10.4 μmol/L with a direct fraction of 0.9 μmol/L. On the third day of life, *Plasmodium falciparum* malarial forms were found incidentally on a complete blood count smear; fewer than 1% of the erythrocytes were involved.

Review of the mother's peripheral blood smear from the day of delivery showed *P. falciparum* forms with <1% of the erythrocytes involved. She had been afebrile at the time of delivery with a hemoglobin of 75 g/L, a hematocrit of 23.4%, WBC count of 10.4 $\times 10^6$/L, and platelet count of 20 $\times$

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10^9/L. Histological evaluation of the placenta demonstrated abundant malaria pigment but no malarial forms. She was treated with mefloquine with resolution of parasitemia after 1 day.

The Centers for Disease Control and Prevention (CDC) was contacted for consultation regarding therapy. Given the high prevalence of chloroquine-resistant malaria in Zaire, oral quinine (25 mg/kg/day divided every 8 hr for 5 days) was recommended followed by trimethoprim-sulfamethoxazole (TMP-SMX, 8 mg/kg/day of the TMP component divided every 12 hr for 5 days). Because of the potential for altered pharmacokinetics secondary to extreme prematurity, the infant was started on two daily doses of quinine. This was changed to 3 daily doses when the thin peripheral blood smears showed persistent parasitemia after 3 days of therapy. Clearance of parasitemia occurred after an additional 3 days of therapy. Quinine was subsequently discontinued and treatment with TMP-SMX was initiated. Thin blood smears remained negative for an additional 2 days.

Hepatosplenomegaly noted at birth in the infant resolved before initiation of antimalarial therapy. The platelet count normalized after 2 days of therapy without need for additional transfusion. A urine culture for cytomegalovirus obtained on the first day of life was sterile. The elevated indirect bilirubin noted on Day 2 of life increased to 13.3 μmol/L on Day 3 and thereafter declined with phototherapy, which was discontinued on Day 6 when the total bilirubin was 9.5 μmol/L. At the initiation of TMP-SMX therapy, the total bilirubin was 6.8 μmol/L and decreased to 1.6 μmol/L by the completion of therapy. No complications related to malaria or antimalarial therapy were noted during the subsequent nursery course. The infant was discharged to home at 2 months of age.

DISCUSSION

In 1950, based on a review of 135 cases, Covell[2] estimated that CM occurred in 0.3% of infants born to immune mothers in endemic areas and in up to 7.4% of those born to nonimmune mothers.[1] Subsequent studies confirmed the attack rates of CM in endemic areas although more recent investigations have reported frequencies varying from 9.6 to 41%.[3–5] Underreporting and differences in methodology contribute to the discrepancies, and the overall incidence of CM, although probably low, remains unknown.

Since Covell's review, more than 200 cases of CM have been reported in the world literature.[6] In reviewing the English-language literature from 1967 to the present (MEDLINE), we found only 3 case reports describing CM in 4 premature infants.[7–9] Only one of these infants, a 1-month-old twin born at 33 weeks' gestation, was born in the US; the remaining infants were born in areas where malaria is indigenous. The clinical findings and treatment of these infants are summarized in Table 1.

The paucity of reports of CM in premature infants may be due to the lower survival of such infants in endemic areas. Nevertheless, the scarcity of reports is remarkable given that preterm delivery as well as spontaneous abortion and LBW have been associated with malaria during pregnancy.[3,5] Several investigators have documented that maternal malaria is an important infectious cause of LBW in the tropics.[3,4] The role of maternal malaria in premature delivery, however, is based on early studies that defined prematurity by birth weight (<2500 g) rather than gestational age,[3–5] and a causal relationship between maternal malaria and preterm delivery independent of LBW remains poorly defined. More recently, a comparison of 19 parasitemic with 46 nonparasitemic newborns demonstrated a mean difference of 469 g in weight without any difference in incidence of prematurity (<37 weeks).[10] For the mothers of the 5 cases reviewed here, preeclampsia in 2 (reference 7, present case) and twin gestation in another[9] likely contributed to preterm delivery; the role of a malarial attack in any of the cases, however, cannot be excluded.

Compared with nonpregnant women, pregnant women in endemic areas are at increased risk for developing parasitemia, presumably due to diminished immunity.[3–5] Relapse or recrudescence of past infection may also occur in women immigrating to the US because immunity wanes with absence from an endemic area. Recrudescence of *P. falciparum* infection rarely occurs more than 1 year after exposure, whereas that with *P. malariae* may occur several years later. The dormant stages of *P. ovale* and *P. vivax* also allow for delayed relapse. A report of CM due to *P. malariae* in an infant born to a woman 25 years after immigration[11] underscores the importance of even a remote history of maternal malaria in the pathogenesis of CM.

Vertical transmission of malaria is postulated to occur not by direct penetration of parasites through chorionic villi but rather through a breach in the placental barrier.[1] Fetal exposure to maternal blood may occur in utero through a damaged placenta or intrapartum as the placenta separates. The infant described in the present report may have received a transfusion of infected erythrocytes through a partial abruption suggested by the placental clot noted at delivery.

Clinical manifestations of CM in term infants are usually not apparent at birth.[1,6] In the review by Hulbert,[1] mean age of onset was 5.5 weeks with 96% of the infants presenting between 2 to 8 weeks of age. In contrast, 2 of 5 preterm infants with CM had signs of congenital infection at birth and another 2 presented in the first week of life (Table 1). Hepatosplenomegaly was the most frequent clinical manifestation; this nonspecific finding is common among all congenital infections. In term infants, transplacentally acquired maternal antimalarial antibody contributes to the delay in presentation and may even modify symptomatology.[1,4,6] That preterm

Table 1. Preterm Neonates with Congenital Malaria Reported in the English-Language Literature from 1967 to Present

Country of birth (Reference)	*Gestational age/ Birthweight*	*Age at Presentation*	*Plasmodium Species*	*Clinical Findings*	*Treatment*	*Outcome*
India (7)	34 weeks/ 1450 grams	4 days	*P. vivax*	SGA†, hepatomegaly, splenomegaly	Chloroquine‡	Cured
India (7)	30 weeks/ 1300 grams	Birth	*P. vivax*	SGA, hepatomegaly	Chloroquine‡	Cured
Nigeria (8)	32 weeks/ 1500 grams	7 days	*P. falciparum*	Fever, jaundice, hepatomegaly, splenomegaly, anemia, hyperbilirubinemia	Chloroquine¶	Cured
United States* (9)	33 weeks/ Not reported	1 month	*P. vivax*	Jaundice, hepatomegaly, splenomegaly, anemia, hyperbilirubinemia	Chloroquine‡	Cured
United States (present case)	28 weeks/ 818 grams	Birth	*P. falciparum*	Hepatomegaly, splenomegaly thromtocytopenia, hyperbilirubinemia	Quinine/ Trimethoprim-sulfamethoxazole	Cured

*Mother from India.

†SGA, small for gestatational age.

‡Oral, 10 mg base/kg first dose followed by 5 mg base/kg 6, 24, 48 hours later.

¶Intramuscular chloroquine (5 mg/kg) followed by oral chloroquine 10 mg base/kg/day in two doses for two days. With persistent parasitemia, parenteral quinine 10 mg/kg orally followed by 10 mg/kg in two doses for five days.

infants do not benefit from this passive immunity may account for an apparent earlier presentation. However, the prompt medical attention afforded these high-risk infants also facilitates earlier detection.

Fever is almost uniformly present in term infants with CM, but the periodicity seen in older children is usually absent.[1] Hepatomegaly, splenomegaly, and jaundice are observed in the majority of these infants, and anemia, thrombocytopenia, and hyperbilirubinemia are the most frequently reported laboratory abnormalities.[1,6] These characteristic features are also found in preterm infants (Table 1) although fever was observed in only 1 of 5 cases. The findings of CM are nonspecific and mimic those of other congenital infections. A lack of clinical suspicion results in diagnosis being delayed and often, as with our patient, incidental. Although rare in comparison with other congenital infections seen in this country, CM should be considered in the differential diagnosis in the appropriate epidemiological setting.

There exist no guidelines for the treatment of CM in preterm infants. Except for those cases due to chloroquine-resistant *P. falciparum*, recommended therapy for term infants is oral chloroquine sulfate (10 mg base/kg followed by 5 mg base/kg 6, 24, and 48 hr later).[1,6] This regimen was used without complications in the treatment of all preterm infants previously described. For chloroquine-resistant *P. falciparum* CM, oral quinine sulfate (25 mg/kg/day every 8 hr for 3 to 5 days) is recommended.[6] Parenteral quinine, or quinidine in the US where quinine is no longer available, is reserved for severely ill infants or those with greater than a 5% parasitic load.[6] Because of the high incidence of resistance to chemotherapeutic agents, the course of oral quinine is followed by either TMP-SMX, pyrimethamine-sulfadoxine or clindamycin (20 to 40 mg/kg/day every 8 hr for 3 days).[6,12] Alternative agents in older children include tetracycline or mefloquine hydrochloride; the latter should not be used in children less than 15 kg. Use of agents with sulfonamide components raises concerns about potential displacement of bilirubin from albumin and consequent kernicterus. Only two infants with CM born in the US since 1950 have required treatment with these drugs.[6,12] Quinn et al[6] used quinine and TMP-SMX, recommending the latter instead of pyrimethamine-sulfadoxine. More recently, pyrimethamine-sulfadoxine was used with quinine in the successful treatment of *P. falciparum* CM in a 2-month-old infant,[12] and this antimalarial is frequently used outside the US in neonates with CM.[13] Ours is the first preterm infant with CM born in the US to be treated with TMP-SMX. Initiation of therapy did not exacerbate his hyperbilirubinemia, which continued to resolve after completion of therapy. The potential toxicity of antimalarial agents as well as changing patterns of resistance should prompt the clinician to seek advice from the CDC for the most current treatment recommendations.

Cases similar to the one reported here will continue to occur as travel to and from endemic areas becomes more accessible. CM should be considered in infants with suspected congenital infection born to women with such histories of travel. The interval between maternal exposure to malaria and CM in the infant may be prolonged, and the mother may manifest no symptomatology or evidence of infestation on peripheral blood smears. Furthermore, the presenting signs may mimic other congenital infections, emphasizing the importance of clinical suspicion for timely diagnosis and prompt initiation of antimalarial therapy.

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