Case Report: Severe Congenital Malaria Acquired in utero

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INTRODUCTION

Congenital malaria is increasingly recognized as a potentially serious, though usually delayed, complication of maternal malaria. Reported prevalence varies widely in malaria-endemic areas from 0% to 33%,1-3 At birth, infections are usually asymptomatic with low parasitemia and the diagnosis is often missed. Although described at birth,2-4 symptoms usually do not appear until 10–30 days of age.1 Because of the very low parasitemia usually found at birth, it was previously hypothesized that infection occurs predominantly from transplacental passage of parasites during disruption of the placental barrier at the time of delivery, with subsequent clinical illness in the infant attenuated by transfer of maternal antibodies.1 However, recent evidence suggests that antenatal transplacental transmission occurring before the onset of parturition is more frequent than previously realized,5 although the clinical consequences of in utero transmission are not well characterized and its management poorly defined.

In Papua, Indonesia, an area endemic for multidrug resistant *Plasmodium falciparum* and *Plasmodium vivax,*6 malaria is a major cause of morbidity in pregnancy7 and infants.8 We report a case of a neonate with high-level *P. falciparum* parasitemia and gametocytemia at birth showing vertical transmission in utero, with severe disease requiring intravenous therapy. We describe the successful use of artesunate and dihydroartemisinin-piperaquine in this neonate.

CASE REPORT

At birth, a female neonate weighing 2,350 grams was pale, lethargic, unable to feed, hypothermic (36.3°C), and tachypneic (respiratory rate 96/minute), with chest indrawing and a normal heart rate (124/minute). An enlarged spleen was palpable at the umbilicus. Delivery was by uncomplicated vaginal delivery at 40 weeks gestational age estimated by Ballard score, with normal passage of meconium. A blood film performed on the day of delivery as part of routine hospital practice showed a *P. falciparum* peripheral parasitemia of 7,575/μL. Her hemoglobin was 10.6 g/dL with a leukocyte count of 13,900 cells/μL.

The mother, a 35-year-old grand grand multiparous Papuan lowland woman (P11 A0), had not received any antenatal care but denied any history of fever or other complications during her pregnancy. Maternal peripheral blood examination was negative both on the day of delivery and 24 hours later, as was a *P. falciparum* histidine-rich protein (HRP2) rapid antigen detection test (Paracheck). The placenta was unavailable for analysis. At birth maternal hemoglobin was 8.5 g/dL with a leukocyte count of 9,600 cells/μL. Her 10 other children were reportedly well.

The screening blood film from birth was reported at 36 hours, at which time the parasitemia had risen to 26,700/μL. Because of the severity of illness, antimalarial therapy was commenced intravenously, using artesunate, standard treatment of severe malaria in older children at this hospital. Three doses (8 mg [3.4 mg/kg]) were administered at 24, 36, and 48 hours after birth. With clinical improvement, therapy was changed to oral dihydroartemisinin-piperaquine (DHP), 2 mg/kg dihydroartemisinin and 16 mg/kg piperaquine crushed in a suspension of water, administered once daily for 3 days. Procaine penicillin was also given for 3 days.

The neonate had clinically improved within 24 hours and by 48 hours was aparasitemic (Table 1). *Plasmodium falciparum* gametocytes were present on Day 2 and Days 4–8. In view of brown gastric aspirates, oral intake was restricted for the first 48 hours and intravenous rantiidone administered. On Day 3 breast milk was initiated by an orogastric tube and the baby was breastfed from the following day. Because of progressive anemia (Table 1), a transfusion of 25 mL of packed red cells was administered on Day 4 and again on Day 10.

At the time of discharge (Day 11), the infant was afebrile, feeding well, with hemoglobin of 14.4 g/dL. On follow up 8 days later, she was active, breastfeeding well, without any signs or symptoms. She was readmitted at 9 months of age with acute diarrhea and dehydration, with weight for age less than the third percentile, but with no neurodevelopmental delay. She was anemic (Hb 9.4 g/dL) with a normal white cell count (WCC) (9,800 cells/μL) and no parasitemia. She recovered from diarrhea and was discharged with nutritional education.

DISCUSSION

This report documents congenital malaria with severe manifestations at birth. The presence of relatively high parasitemia within 24 hours of an uncomplicated delivery, gametocytemia
...data on the influence of parity on congenital malaria. It developed despite presumed maternal immunity and the reduced malaria exposure. Relatively high grand multiparous women with longstanding infection in Timika, 6 DHP was administered to this neonate because the majority of cases are asymptomatic, and severe manifestations, as in this case, are rare. In addition, the parasitemia is usually low, 1, 10, 11

The lack of maternal parasitemia and HRP2 antigenemia suggests that maternal infection was localized to the placenta and/or had cleared. Discordance between maternal peripheral blood microscopy/antigen testing and placental parasitization is well described. 12 Placental analysis was not routine and we could not determine whether there was associated placental infection.

Although the mother denied a history of febrile illness during the current pregnancy, in this area 66% of adults and 58% of pregnant women are known to have asymptomatic malaria infection. 1, 2, 3, 4 In Timika, 6 12 years based on locally derived safety and efficacy data with DHP for oral step-down therapy following intravenous artesunate. 8 Although symptomatic malaria transmission is associated with placental parasitemia and/or had cleared. However, because of the limited effective antimalarial options in Timika, 6 the efficacy of intravenous artesunate and oral DHP. Although safe and effective in reducing mortality from severe malaria in infants are limited, 8 with scant data on its use in neonates. Intravenous artesunate (three doses of 3.4 mg/kg over 24 hours) appeared safe, and rapidly cleared parasitemia, in keeping with clinical experience in older age groups. 15, 16

Because of the high prevalence of multidrug-resistant P. falciparum and P. vivax in Papua, RSMM Hospital protocols for oral step-down therapy following intravenous artesunate therapy recommend DHP in children weighing more than 5 kg based on locally derived safety and efficacy data with DHP in treating uncomplicated malaria in children in this weight range. 16 However, because of the limited effective antimalarial options in Timika, 6 DHP was administered to this neonate by the treating pediatrician with close monitoring of potential adverse reactions. Although it appeared to be well tolerated, further studies are required to evaluate the safety, efficacy, and pharmacokinetics of DHP in very young infants.

Potential causes for the intrauterine growth retardation in this neonate include maternal anemia, 7 congenital malaria

(a marker of chronicity), and marked splenomegaly all indicate that vertical transmission occurred before delivery with parasite replication in utero. Although symptomatic malaria at birth has been reported, 2, 3, 4 the majority of infections are asymptomatic, 1, 3, 9 and severe manifestations, as in this case, are rare. In addition, the parasitemia is usually low, 1, 10, 11

The incidence of malaria in Timika is estimated to be approximately 850 per 1,000 person years, 7 making it highly likely that malaria transmission occurred in an apparently asymptomatic 1, 3, 9 and severe manifestations, as in this case, are rare. In addition, the parasitemia is usually low, 1, 10, 11

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Potential causes for the intrauterine growth retardation in this neonate include maternal anemia, 7 congenital malaria
infection per se, and the anemia associated with congenital infection in this instance. In areas of high endemicity, fetal anemia is associated with maternal hemoglobin concentrations below 8g/dL. Although *Plasmodium falciparum* placental parasitemia and maternal peripheral parasitemia increase the risk of fetal anemia, it is unclear in this case whether the maternal anemia was associated with placental malaria or not. Low birth weight is also associated with higher susceptibility to infectious diseases and poor growth in later life as seen in this infant 9 months later.

In this case, the transmission is vertical *in utero* causing severe congenital malaria at birth, associated with neonatal anemia and growth restriction. Symptomatic neonates in malaria-endemic areas presenting with neonatal sepsis syndrome, should be screened for malaria. Although further data in neonates are required, intravenous artesunate followed by oral DHP treatment appeared safe and effective.

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REFERENCES


