Case Report: Severe Congenital Malaria Acquired in utero

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Abstract. Vertical transmission of Plasmodium falciparum is under-recognized and usually associated with asymptomatic low-level parasitemia at birth. We report symptomatic congenital malaria presenting as a neonatal sepsis syndrome. The presence at birth of a high asexual parasitemia, gametocytemia, and splenomegaly indicated in utero rather than intrapartum transmission. The neonate was successfully treated with intravenous artesunate followed by oral dihydroartemisinin-piperaquine, without apparent adverse effects.

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 aperasitemic (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 ranitidine 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 febrile, 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 diarrhoea 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 diarrhoea 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

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Laboratory results

<table>
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<tr>
<th>Age (day)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
<tr>
<td>Asexual parasitemia (μL⁻¹)</td>
<td>7.575</td>
<td>26.688</td>
<td>12.649</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>139</td>
<td>Negative</td>
</tr>
<tr>
<td>Gametocytes (μL⁻¹)</td>
<td>Negative</td>
<td>556</td>
<td>Negative</td>
<td>278</td>
<td>208</td>
<td>69</td>
<td>208</td>
<td>139</td>
<td>11.5</td>
<td>14.4</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
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</tr>
<tr>
<td>Leukocyte count (μL⁻¹)</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
<td>13,900</td>
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Clinical data

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<tr>
<th>Weight (g)</th>
<th>2,350</th>
<th>2,200</th>
<th>2,250</th>
<th>2,250</th>
<th>2,250</th>
<th>2,250</th>
<th>2,400</th>
<th>2,450</th>
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<tbody>
<tr>
<td>Axillary temperature (°C; range)</td>
<td>36.3–38.2</td>
<td>36–37</td>
<td>36–36.8</td>
<td>36–37</td>
<td>35.9–36.2</td>
<td>35.2–36.6</td>
<td>36.6–37.2</td>
<td>36.2–37.6</td>
<td>36.2–36.6</td>
<td>36.6–37.2</td>
</tr>
<tr>
<td>Feeding</td>
<td>Unable to feed</td>
<td>Unable to feed</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
<td>Breast milk</td>
</tr>
<tr>
<td>Urine output</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Medications

| Artesunate IV | I | II–III |
| Dihydroartemisinin-piperaquine–oral | I | II | III |
| Procaine penicillin IM | I | II | III |
| Ranitidine IV | √ | √ | √ |
| Humidified oxygen | √ | | |
| Packed red cell transfusion | I | II |

(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, the majority of infections are asymptomatic, and severe manifestations, as in this case, are rare. In addition, the parasitemia is usually low.

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. 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 with P. falciparum infection are asymptomatic.

The incidence of malaria in Timika is estimated to be approximately 850 per 1,000 person years, making it highly likely that the 35-year-old Papuan mother resident in the malaria-endemic lowlands had prior exposure to malaria infection.

Antenatal malaria transmission is associated with placental malaria particularly in primi- and secundigravidae. There are limited data on the influence of parity on congenital malaria. In this case, vertical transmission occurred in an apparently well grand grand multiparous woman with longstanding malaria exposure. Relatively high in utero parasitemia developed despite presumed maternal immunity and the reduced parasite growth rates associated with fetal hemoglobin. It was not possible to determine other factors associated with an increased risk of vertical transmission, such as human immunodeficiency virus (HIV) infection. Grand grand multiparous women are known to have smaller and dysfunctional placenta, and this may have allowed a greater than normal maternal-fetal microtransfusion and a greater parasite inoculum than that hypothesized to occur in utero, resulting in a greater risk of symptomatic disease at birth.

The clinical manifestations in this case are similar to those seen with early neonatal sepsis, and without the policy of routine neonatal testing in this hospital, the diagnosis could easily have been missed. Although we cannot exclude concurrent bacterial sepsis, there were no risk factors for neonatal sepsis, the WCC was normal, marked splenomegaly is very unusual in neonatal sepsis, and the level of parasitemia made incidental parasitemia unlikely. Over the 4 years of the routine neonatal malaria screening program at this hospital, median asexual parasitemia among the other 29 neonates with detectable parasitemia at birth was 75/μL (range 37–1,730/μL) (JR Poepoprodjo, unpublished data), with this neonate having by far the highest parasitemia. Although World Health Organization (WHO) criteria for severe malaria are not defined in neonates, the pallor, hypothermia, lethargy, inability to feed, and respiratory distress justified a diagnosis of severe malaria and intravenous therapy. The clinical condition improved in parallel with a rapid clearance in parasitemia with intravenous artemesunate and oral DHP. Although safe and effective in reducing mortality from severe malaria compared with quinine in adults and children > 2 years of age, data on the safety and efficacy of intravenous artemesunate in infants are limited, with scant data on its use in neonates. Intravenous artemesunate (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.

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 artemesunate 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. However, because of the limited effective antimalarial options in Timika, 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, 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 P. 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 summary, this case shows vertical transmission 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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