Imported congenital malaria caused by *Plasmodium ovale*: A case report

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Abstract: We describe a 5-week-old term infant with *Plasmodium ovale* severe congenital malaria in a non-endemic setting. She presented with diarrhea, poor feeding, lethargy, hepatosplenomegaly, and severe anemia. She was fortuitously diagnosed with malaria on routine blood smear, and successfully treated with intravenous artesunate. Subsequent history revealed maternal malaria diagnosis and treatment during pregnancy in Nigeria. This case underscores the importance of obtaining maternal exposure history and considering malaria testing in pregnant women and infants with unexplained illness. It also contributes to the limited literature on congenital malaria and severe malaria caused by *P. ovale*.

Case presentation

A 5-week-old female presented to hospital with 3 days of diarrhea, poor feeding, decreased activity, and two episodes of unilateral leg shaking that self-resolved in less than 1 min. of 2 weeks prior, she had 1 day of fever. She had no respiratory symptoms, vomiting, rash, or decreased level of consciousness.

The infant's mother migrated from Nigeria 9 years prior. This pregnancy was conceived during travel to Nigeria. The mother returned to Canada at 5-months gestation. Testing for HIV, hepatitis B, and syphilis was negative at 7-months gestation.

The infant was delivered by caesarean section at 37 + 5 weeks gestation for breech presentation. The mother had fever at delivery and on postoperative day one, then defervesced without antibiotics. The baby's birth weight was 3.1 kg. Neonatal examination was normal. She fed and gained weight appropriately until the current illness.

In the Emergency Department (ED), the infant was afebrile, with vital signs in normal range. Examination revealed lethargy and a soft flow murmur. Hemoglobin was 64 g/L, hematocrit 20%, white blood cells 8.5×10^9/L, platelets 331×10^9/L, and glucose 5.2 mmol/L.

The Hematology technician contacted the ED to report having seen malaria parasites (at 0.1% parasitemia) on the blood smear performed for complete blood count with manual differential. Rapid diagnostic test for malaria (BinaxNOW; Abbott, Chicago, IL, USA) was done and was negative.

Further history revealed that the mother was treated for malaria at 6-weeks' gestation in Nigeria (see case timeline in Supplemental Figure 1). She did not know the causative species or medication. Fever recurred at 6-months gestation in Canada. The mother contacted her physician in Nigeria, who advised to take a course of antimalarial therapy she had brought back from Nigeria. Fever resolved.

The infant was transferred to the pediatric hospital and the Infectious Diseases service was consulted. The infant was alert but pale, and noted to have tachycardia, retractions, and desaturations with feeding. Hepatosplenomegaly was palpated. Hemoglobin was 55 g/L, hematocrit 17.3%, and lactate 2.1 mmol/L. Liver panel, creatinine, and C-reactive protein were normal.

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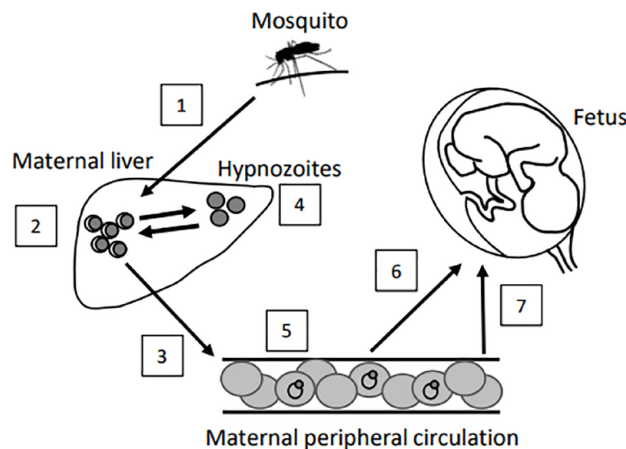
Figure 1. Malaria life cycle and mechanisms of vertical transmission leading to congenital malaria infection. (1) *Plasmodium* sporozoites are inoculated during the bloodmeal of a female *Anopheles* mosquito. (2) They undergo a liver phase, then (3) merozoites are released into the bloodstream to initiate the asexual intraerythrocytic cycle, during which time clinical symptoms present. (4) For *P. vivax* and *P. ovale*, some sporozoites transform into dormant liver hypnozoites, which can reactivate weeks to years later and cause relapse. (5) During pregnancy, maternal parasitemia may occur as a result of a new infection, chronic subclinical parasitemia in semi-immune individuals, or relapse of hypnozoites. (6) Parasites may be vertically transmitted *via* the placenta or with abruption, but (7) most transmission events are believed to result from mixing of maternal and fetal blood during parturition.

Red blood cells were transfused due to symptomatic anemia. Congenital malaria was presumed given absence of endemic malaria transmission in Canada, and managed as a severe case given progressive anemia and possible seizures. IV artesunate was initiated (3.0 mg/kg/dose at 0, 12, 24, and 48 h). Ceftriaxone, vancomycin, and acyclovir were started pending full septic workup. Repeat peripheral blood smear confirmed 0.1% parasitemia, and *Plasmodium ovale* was identified by microscopy and polymerase chain reaction at the provincial reference laboratory.

The infant clinically improved. Hemoglobin rose to 91 g/L. Septic workup and HIV screen were negative. Malaria smears showed parasite clearance at 72 h. The infant was transitioned to oral quinine and clindamycin for a total 7-day course. She remained well in follow-up, with no parasite recrudescence or post-artesunate delayed hemolysis. The mother was assessed by the local Tropical Disease Unit. She was clinically well, and malaria thick and thin blood films and rapid diagnostic test were negative. Given the diagnosis of congenital *P. ovale* malaria in her child, she was treated with 3 days of oral atovaquone-proguanil followed by 14 days of oral primaquine 30 mg (base) per day, following G6PD testing. Infant G6PD testing was not done due to recent red blood cell transfusion and cessation of breastfeeding prior to maternal primaquine course.

Discussion

Malaria infection in pregnancy is associated with adverse maternal, perinatal, and neonatal outcomes. Congenital malaria infection occurs when maternal blood-stage parasites are vertically transmitted in utero or at delivery[1] (Figure 1). In malaria-endemic areas, congenital malaria is often defined as the presence of asexual parasites in cord or peripheral blood smear in the first week of life, regardless of symptoms. Beyond that timeframe, vertical and vector-borne transmission cannot be distinguished. A systematic review using this definition found overall prevalence of 6.9% (95% CI 4.8–7.9; range 0–47%) for newborns in endemic areas, with large heterogeneity between settings.[2] Most studies reported on *P. falciparum* infections in sub-Saharan Africa. True prevalence may be underestimated due to poor sensitivity of microscopy at low parasitemia, and generally poor sensitivity of rapid diagnostic tests for non-*falciparum* malaria.[3]

Risk of congenital malaria is primarily determined by presence and severity of maternal malaria infection, which is in turn affected by maternal

malaria immunity, immune status (e.g. HIV infection), and malaria species.[1] Pregnant women may be asymptomatic or minimally symptomatic if they are semi-immune to malaria. Imported congenital malaria (denoting birth in a non-endemic area) typically occurs in infants of migrants and refugees, with predominance of non-*falciparum* species.[3] As in this case, there is often recent maternal migration or travel. However, last stay in an endemic area may be prior to pregnancy, up to 12 years earlier.[3,4] Semi-immune individuals can have prolonged subclinical *P. falciparum* or *P. malariae* parasitemia, and *P. vivax* and *P. ovale* liver hypnozoites can relapse weeks to years later (Figure 1). Thus, an asymptomatic pregnancy or remote migration do not preclude congenital malaria. In this case, the mother was most likely infected with *P. ovale* in first trimester, with subsequent fevers representing relapses, and transmission occurring at delivery. Canadian guidelines recommend malaria testing for unexplained fevers in migrants or travelers within 1 year of return from an endemic area;[5] thus, malaria screening was likely indicated during the mother's febrile episodes which, had it been performed, may have identified the *P. ovale* infection earlier.

Clinical presentation of congenital malaria is variable. In hyperendemic areas, most newborns are asymptomatic and may spontaneously clear parasitemia, thought to be mediated by transferred maternal antibodies and protective properties of fetal hemoglobin.[1] The proportion that progress to clinical disease in these settings is unclear, due to a paucity of long-term studies and confounding by vector-borne transmission. In a large prospective multicenter study in Nigeria, 34% of newborns who were parasitemic at birth developed symptoms by day 3 of life.[6] Imported congenital cases have demonstrated that symptom onset can be weeks to 2 months after birth for *P. falciparum* and non-*falciparum* infections.[3,4] Clinical features may include fever, irritability, lethargy, vomiting, diarrhea, jaundice, hepatosplenomegaly, respiratory distress, convulsions, anemia, and thrombocytopenia.[1] However, presentation can be non-specific, resulting in initial misdiagnosis.[3] Fever was not a prominent feature in the presented case; among cases of imported congenital malaria in the United States, fever was absent in 14%.[3] Severe disease is most often reported for *P. falciparum* but can be caused by any species.[1,7–9]

There is no consensus regarding treatment of congenital malaria. For non-severe infection, chloroquine is typically used for non-*falciparum* species. Quinine/clindamycin may be used for *P. falciparum* given widespread chloroquine resistance and limited safety data for atovaquone-proguanil and oral artemisinin derivatives in infants <5 kg.[1] Severe malaria regardless of species should be treated with intravenous artesunate,[5] and this has been extrapolated to congenital malaria. While pharmacologic data are lacking for neonates, intravenous artesunate appears to be effective and well-tolerated at 2.4–4.0 mg/kg/dose.[8,10,11]

Mortality has been reported for *P. falciparum* congenital malaria, mainly in infants born to non-immune mothers.[1] Most reports predate availability of artesunate. All reported cases of imported congenital malaria recovered,[3,4] perhaps reflecting a predominance of non-*falciparum* species and semi-immune mothers. Long-term outcomes are unknown.

At the time of writing, we found only three reported cases of *P. ovale* congenital malaria, all imported. One infant presented at 19-days old with fever and poor feeding; the mother, who was living with HIV, arrived from Angola 3 years prior and was asymptomatic with undetectable parasitemia.[4] Another infant presented at 21-days old with fever, grunting, and severe anemia. The mother had recently returned from a prolonged stay in Tanzania where she was treated for malaria, and was febrile at delivery.[7] Both infants recovered with chloroquine treatment. A third baby was born 1 week after mother migrated to the United States from a malaria-endemic area.[3] The rarity of *P. ovale* congenital malaria may be related to *P. ovale*'s low global burden, though this species may be underdiagnosed due to low parasitemia and misidentification as *P. vivax* on microscopy.[12] Our case contributes to the very limited literature on congenital malaria and severe disease caused by *P. ovale*.[13,14]

For *P. vivax* and *P. ovale* infections, primaquine or tafenoquine is added to blood schizonticidal antimalarial therapy to eradicate dormant liver forms and prevent relapse. These agents are contraindicated during pregnancy due to unknown fetal G6PD status and risk of hemolysis. Weekly chloroquine prophylaxis until delivery may prevent relapse,[5] and could have been implemented

in this case if the mother was known to have *P. ovale* infection during pregnancy. Primaquine or tafenoquine are not indicated in congenital malaria as only blood-stage parasites are transmitted, without development of dormant liver forms. Breastfeeding infants require G6PD testing prior to maternal treatment with primaquine.

Fortunately for this infant, an astute Hematology technician rapidly identified malaria and enabled prompt treatment of this severe infection. However, routine blood smears are unreliable for malaria diagnosis. Clinical suspicion is required to initiate appropriate testing. The gold standard diagnostic modality is microscopic examination of thick and thin blood films; these should be Giemsa-stained to increase sensitivity of parasite detection, and reviewed by an experienced technician. Other methods include rapid diagnostic tests (which can be poorly sensitive for non-*falciparum* malaria infections, as seen here) and molecular-based assays.

This case underscores the need for a thorough maternal infectious and epidemiologic history at prenatal and post-partum assessments in a globalized society. Symptoms, diagnoses, and travel during pregnancy should be elicited, as well as lifetime migration history. Potentially sensitive questions about country of origin should be contextualized. A significant maternal travel or migration history broadens the differential diagnosis for a symptomatic mother or infant. Malaria testing should be strongly considered in pregnant women with unexplained fever and exposure to malaria-endemic areas, and in unwell infants with maternal risk factors for malaria infection, particularly if the infant has an unexplained illness or poor response to empiric antibiotic therapy. This case also highlights the importance of pre-travel consultation to discuss malaria prophylaxis and fever management, including for migrants whose malaria immunity wanes over time.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Informed, voluntary, and written consent to publish the case report was obtained from the infant's mother.

Author contributions
Laura K. Erdman: Conceptualization; Writing – original draft; Writing – review & editing.

Andrea K. Boggild: Conceptualization; Supervision; Writing – review & editing.

Ari Bitnun: Conceptualization; Supervision; Writing – review & editing.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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Equator network guidelines
The reporting of this study conforms to the CARE (CAse REport) guidelines for case reports.

Supplemental material
Supplemental material for this article is available online.

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