Learning from errors

Congenital malaria in a European country

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Summary

A newborn of 26 days, born in Lisbon, Portugal, presented with fever, anaemia and thrombocytopaenia. She was admitted considering neonatal sepsis, but *Plasmodium vivax* was identified in the second peripheral blood smear performed. Parenteral quinine was started with good evolution. Despite clinicians' unfamiliarity with congenital malaria in non-endemic areas, this diagnosis, although rare, should not be forgotten in the evaluation of newborns/infants born to women from endemic areas or with recent trip to these areas.

BACKGROUND

Congenital malaria is usually defined as malaria acquired by the fetus or newborn directly from the mother in uterus or during delivery.

Pregnant women are at higher risk of infection because of pregnancy-specific immunological factors that make them more susceptible to malaria infection, and to a particular attraction to anopheles.¹ However, congenital malaria seems to occur in less than 5% of infected pregnant women, ranging its incidence from 0.3% to 33%,² with variations between endemic and non-endemic areas. The low frequency of mother-to-child transmission (MTCT) of malaria may be due to the placental barrier as well as the protective effect of maternal antibodies crossing placenta.

In non-endemic countries, cases of congenital malaria are rare: in the USA in 2004, only 3 of 1324 cases of malaria reported were due to MTCT; in Germany between 1993 and 2003, 9248 cases of malaria were identified and none was by MTCT.¹

In 1973, WHO declared eradication of malaria in Portugal, and to date, this is the only case of congenital malaria reported in this country.

CASE PRESENTATION

A female newborn (26 days old), born in Lisbon, Portugal, presented to our paediatric emergency room with two fever spikes (maximum 38.9°C rectal), 24 h apart, in the last 2 days, and a few episodes of vomiting. On admission she had a weight in the 50th percentile; she showed pallor but the physical examination was otherwise normal.

The mother was born in India and emigrated to Portugal 5 years previously. She was 22 years old, healthy, ARh+, gravida 2 para 2. The current pregnancy had irregular follow-up, but was apparently uneventful. At 32 weeks of gestational age, maternal serology was irrelevant (negative for hepatitis B virus, hepatitis C virus, *Toxoplasma*, HIV and Venereal Disease Research Laboratory (syphilis); and showing immunity to *Rubella* and Cytomegalovirus). Group B *Streptococcus* screening test was not performed.

The child was born at term (40 weeks) by C-section. No history of prolonged rupture of membranes or maternal fever during labour. Apgar scores were 9 at first and fifth min. At birth, her weight and length were in the 50th percentile.

She was discharged clinically well at 3 days of life and was breastfeeding from birth.

Laboratory evaluation showed a normochromic normocytic anaemia (haemoglobin: 9.7 g/dl, mean corpuscular volume 89.5 fl, mean corpuscular hemoglobin 31.6 pg, mean corpuscular hemoglobin concentration (CHGM) 35.4 g/dl) and thrombocytopaenia ($39 \times 10^9/l$) confirmed by the absence of platelet aggregates in peripheral blood smear; leucocytes 6470/ μl (neutrophils 16.4% and 62.6% lymphocytes) and C reactive protein 1.6 mg/dl. Chest x-ray showed no pathological changes. Urinalysis was normal.

The patient was admitted and we started her on empirical antibiotic therapy after we had collected blood and urine cultures, which were later known to be negative.

During hospitalisation she was always clinically well, maintaining spikes of fever (once a day). On the second day of hospitalisation, laboratory evaluation showed thrombocytopaenia ($40 \times 10^9/l$), more severe anaemia (haemoglobin: 6.9 g/dl) and increasing C reactive protein (7.5mg/dl). Accidentally, in peripheral blood smear, *Plasmodium* was identified in various stages of maturation, with morphology suggestive of *Plasmodium vivax*.

Tracing back the pregnancy history, the mother had travelled to India during the second trimester without any prophylaxis for malaria. During this trip, she had a febrile illness for which she did not seek medical care.

In the same day, maternal blood was tested and *Plasmodium* suggestive of *P vivax* was identified.

DIFFERENTIAL DIAGNOSIS

In a newborn with fever, anaemia and thrombocytopaenia, we have to consider neonatal sepsis due to bacterial or viral infection as the most likely diagnosis.

However, the diagnosis of congenital malaria was made by the identification of *P vivax* in the peripheral blood of the newborn (and also of her mother), this being the method recognised as the gold standard laboratory confirmation of malaria.¹

TREATMENT

Intravenous quinine (initially 20 mg/kg followed by 10 mg/kg/dose q8h) was given for 7 days.

OUTCOME AND FOLLOW-UP

After the fourth day of treatment *Plasmodium* was no longer present in the blood smear. Due to persistent haemoglobin value of 6.9g/dl a packed red cell transfusion was performed on the sixth day of hospitalisation.

The newborn was discharged after 10 days of hospitalisation, clinically well with haemoglobin level of 10 g/dl and platelets count of $409 \times 10^9/l$.

DISCUSSION

There has been no consensus on the definition of congenital malaria. Some consider that parasites must be seen in the peripheral blood of the newborn during the first day of life; others accept within the first 7 days. Nevertheless, in countries that are free of malaria, like Portugal, when there is no possibility of postpartum infection the clinical onset in a congenital infected infant can be delayed for weeks and rarely even for months. In these cases age-specific criteria are not useful for the diagnosis.³⁻⁵ Also there is no malaria transmission through human milk,¹ and thus, the fact that this newborn was breastfeeding since birth, was not a risk of postnatal infection.

In most cases of congenital malaria, the early signs or symptoms of malaria arise at 10–28 days of age, as it occurred in our case. However, onset occurring as early as 8 h and as late as 8 weeks of age have been reported.³⁻⁵

The prolonged interval between birth and onset of clinical manifestations may be explained by transmission late in pregnancy or at delivery, such that multiple erythrocytic life cycles are required to produce clinically evident disease. Alternatively the delay may be attributed to the presence of transplacentally acquired maternal antibodies. When such antibodies are present in sufficient concentrations, as in infants born to immune mothers, parasitic replication can be prevented or attenuated and clinical signs can be mild, delayed or even absent. The high concentration of fetal haemoglobin in newborns can also promote resistance to replication of *Plasmodium*.³

Pregnant women are more susceptible *P vivax* and *Plasmodium falciparum* although the four *Plasmodium* species can cause disease.¹

The diagnosis of malaria is established by the microscopic identification of organism on Giemsa-stained smears of peripheral thick or thin blood smears. However, a single smear without parasites is not sufficient to rule out malaria.⁵⁻⁶ In this case, the peripheral blood smear had already been observed to exclude platelets aggregates but parasites were observed only on a second routine smear.

Albeit *P vivax* was identified in mother peripheral blood smear, this is not an essential condition to establish the diagnosis of congenital malaria. Only 42% of mothers had parasitemia detected after either symptomatic disease or malaria diagnosis in their infants.³

In this case, it was not possible to distinguish if it was a recurrence of malaria before pregnancy or a reinfection. The mother was born in an endemic area but emigrated to Portugal 5 years before which could explain waning immunity from lack of continued exposure. For this reason, it could be a recrudescence episode of hepatic that retaining the ability to reactivate and cause relapses months or even years after initial infection.⁷ Nevertheless, this mother travelled to India during pregnancy without antimalarial prophylaxis and she had fever during this trip, and thus a reinfection must be considered.

Malaria infection during pregnancy has been associated with complications like miscarriage, prematurity and low birth weight.¹⁻³⁻⁸⁻⁹ *P vivax* malaria in pregnancy is reported to be more common in primigravidae and increased risk of low birth weight but not associated with miscarriage, stillbirth or prematurity.⁶⁻⁷ However in this case, the newborn was delivered spontaneously at term, mother was multigravidae and the newborn had a normal birth weight.⁸⁻¹¹

In cases of congenital malaria fever is almost present, although the classical paroxysmal pattern described for malaria in older children and adults may not be present.³ The clinical manifestations of congenital malaria do not differ significantly from bacterial or viral sepsis and include also anaemia, splenomegaly, hepatomegaly, poor feeding, lethargy, irritability and jaundice.¹⁻³⁻⁸ Severe thrombocytopenia without bleeding, like our case, is also a frequently reported feature of congenital malaria.⁸ Prompt diagnosis and treatment were essential for the good prognosis.

The treatment of congenital malaria by *P vivax* requires a blood schizonticide, and the severity of disease (mainly the haematological repercussion in our case) warrant an intravenous drug, as indicated by Centers for Disease Control and Prevention (CDC) – so quinine was the choice.¹⁻¹¹⁻¹² In congenital malaria, as well as in transfusion-associated malaria, the infection is transmitted by trophozoites and not by sporozoites. Hence there is no exoerythrocytic phase, no hypnozoites and so no need for specific therapy for eradication of latent hepatic forms.¹⁻³⁻⁸⁻¹¹

As an increasing number of people travel to and emigrate from malaria endemic countries, one may expect a greater number of malaria cases and consequently more cases of congenital malaria in Europe. Despite clinicians' unfamiliarity with this diagnosis, congenital malaria, although rare, should not be forgotten in the approach to newborns/infants born to women from endemic areas or with recent trip to these areas—even if the mother is asymptomatic. A complete and accurate travel and residency evaluation of the infant's family will contribute to a high index of suspicion, avoiding delay in diagnosis and consequently reducing morbidity and mortality associated to this disease.

Learning points

- Congenital malaria, although rare, should not be forgotten in the differential diagnosis of fever in newborns/infants born to women who have been exposed to malaria, even if risk of exposure was not high or mother was not symptomatic; a high index of suspicion is necessary to establish this diagnosis.
- A complete and accurate travel and residency history on the infant's family should be sought during evaluation of a newborn with fever.
- A high index of suspicion is necessary to establish this diagnosis, avoiding delay in diagnosis that could lead to increased morbidity and mortality associated to this disease.
- Pregnant women who were born in malaria endemic areas, but are living in non endemic areas, may have no significant immunity and therefore, when travelling to endemic areas of malaria, they should receive the same recommendations for malaria prevention as non-immune women.
- The treatment of congenital malaria by *Plasmodium vivax* requires a blood schizonticide, like quinine. Treatment with primaquine was not necessary because congenitally malaria by *P vivax* or *Plasmodium ovale* does not involve the exoerythrocytic phase.

Competing interests None.

Patient consent Obtained.

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