Congenital malaria in a neonate: case report with a comprehensive review on differential diagnosis, treatment and prevention in Indian perspective

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Abstract Although malaria in pregnancy, lactation and congenital malaria can be a disease burden in the endemic zones of Africa and Indian sub-continent, it is still epidemiologically less investigated in India. As it may lead to considerable maternal and perinatal morbidity and mortality, awareness and timely intervention is necessary for desirable outcome and prevention of the condition. Very few reports of congenital malaria are available in the literature from an endemic country like India. Herein we describe a case of congenital malaria from north India in a 21-day neonate. Clinical presentation of this condition in the neonate may offer a considerable diagnostic challenge, and differentiation from vector borne malaria in infants may be important from the management point of view. Hence a review of the differential diagnosis, management and prevention of congenital malaria has been attempted in the Indian perspective.

Keywords Congenital · Neonatal · Malaria · Sepsis · Transplacental · Transmission

Introduction

Congenital malaria, occurring as a result of vertical transmission of parasites from mother to child during pregnancy or perinatally during labour is a rare clinical condition. It

occurs as a consequence of clinical attacks of malaria during pregnancy but also may be detected rarely in infants of asymptomatic women, where the diagnosis may be missed both in the mother and the neonate (Davies et al. 1992). However, recently the incidence of congenital malaria is on the rise due to increased resistance and virulence of parasite resulting from altered antigenic determinants, in addition to increased awareness (Valecha et al. 2007). The importance of this report lies in the fact that though India falls in the endemic zone for malaria, studies and reports are sparse from this part of the globe (Valecha et al. 2007; Sankar et al. 2010; Singh et al. 2003).

Protective immunity through transplacentally acquired maternal antibody may delay the onset of symptoms up to 3 to 6 weeks after birth. Past history and relevant investigations of the mother may help in differentiation from vector borne malaria in infants in these situations. This differentiation is important as congenital malaria, due to the absence of the exoerythrocytic cycle, does not require radical treatment with potentially deleterious antimalarials like primaquine.

Case presentation

A 21-day male neonate was admitted for intermittent high grade fever and rapid breathing of one week duration. The mother had an uneventful pregnancy with spontaneous, normal delivery at 38 weeks gestation. The birth weight of the newborn was 2,900 g. The infant was on exclusive breast feeding, and no physiological jaundice was detected. On admission, physical examination revealed pallor, poor feeding and mild hepatosplenomegaly. Mild tachypnea and tachycardia were also appreciated. Complete blood count showed severe anaemia with haemoglobin (Hb) 6.0 g/dl,

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hematocrit 18.8 %, MCV 89.1 fl, MCH 28.4 pg, MCHC 31.9 g/dl, red blood cell count $2.12 \times 10^6/\mu\text{l}$, total leucocyte count $3.5 \times 10^3/\mu\text{l}$ and platelet count 76,000/cu mm (thrombocytopenia). No ABO or Rh incompatibility was detected. Other laboratory findings included mild hyperbilirubinemia with total bilirubin 3.4 mg/dl (conjugated bilirubin 2.0 mg/dl, unconjugated bilirubin 1.4 mg/dl), aspartate aminotransferase 23 U/l, alanine aminotransferase 15 U/l, and an elevated alkaline phosphatase (2,050 U/l). C reactive protein (CRP) was mildly elevated (34 mg/l), and serum electrolytes were within normal range. Blood and urine cultures were sterile. Cerebrospinal fluid examination was also within normal limits. Based on these clinical and laboratory findings, differential diagnoses of neonatal pneumonia or sepsis were considered, and antibiotics were started.

One day after admission, examination of the peripheral blood smear revealed growing trophozoites of *Plasmodium vivax* with a parasitemia of 0.12 % (Fig. 1). Differential count revealed 82 % lymphocytes, 11 % monocytes, 5 % neutrophils and 2 % eosinophils. Rapid malaria test for pan malaria genus specific lactate dehydrogenase (pLDH) was also positive (Parabank rapid test for Malaria, Zephyr Biomedicals, Goa, India). Antibiotics were discontinued and antimalarial therapy with intravenous artemisinin was initiated. Three days after treatment peripheral parasitemia was completely cleared, the white blood cell count increased up to $4.2 \times 10^3/\mu\text{l}$, Hb was 6.5 gm/dl and platelet count $1.3 \times 10^3/\mu\text{l}$. The neonate was also transfused with packed red cells (10 ml/kg body weight) for 3 h to raise the Hb content.

The history of the mother was re-evaluated. She was a primigravida and history of overt fever or other clinical symptoms of malaria during pregnancy or related treatment history could not be elicited. Her peripheral blood smears

were negative for malaria parasites. However rapid malaria test for pan malaria pLDH was positive, implying low parasitemia not recognized on peripheral smears. She was given a full course of antimalarial treatment with chloroquine.

Discussion

Malaria in pregnancy and newborn causes significant burden of disease, and estimated to cause more than 300,000 fetal and infant deaths and 2,500 deaths of pregnant women worldwide annually (Menendez et al. 2007; Rodriguez-Morales et al. 2008). In spite of this serious health problem very few epidemiological studies have been conducted to investigate the disease burden, approach to diagnosis, management and prevention of congenital malaria.

Congenital malaria was first described in 1876 (Romand et al. 1994). It was considered rare in endemic areas until recent studies reporting higher prevalence rates (Sotimehina et al. 2008). It can be acquired by transmission of parasites from mother to child during pregnancy or perinatally during labour. Malarial infection of placenta is characterized by syncytiotrophoblast and villous disruption, syncytial knot formation and fibrin-type fibrinoid deposition. Syncytial destruction may result in low birth weight and congenital infections (Crocker et al. 2004).

Hence, malaria during pregnancy may cause two extreme effects on the neonatal outcome. On one hand it can result in premature labour, intrauterine growth retardation, high perinatal mortality, anemia, miscarriage, low birth weight, and maternal deaths, both in cases infected by *P. vivax* and *P. falciparum* (Rodriguez-Morales et al. 2007). On the other hand malaria in pregnancy may protect the infant against malaria infection and severe disease via acquired maternal immunity (Rasheed et al. 1995). IgG and IgM antimalarial antibodies can be detected in maternal blood, only IgG crosses the placental barrier to be normally found in the infant's blood.

Though some authors describe the occurrence of congenital malaria in newborns aged less than 7 days (Sotimehina et al. 2008), the interval between birth and onset of symptoms may be prolonged. This can be explained by the transmission of infection in late pregnancy or during delivery or by presence of transplacentally acquired maternal antibody (IgG). Transfer of protective immunity is thus one of the main factors that affects the age of symptom onset. Available literature usually describes the onset of symptoms of congenital malaria typically between 3 and 12 weeks after birth, coinciding with the half-life of maternal IgG antibody in infants. However, cases have been seen where onset of congenital malaria occurred as late as 15 months after the birth of the child (Quinn et al. 1982). In addition, studies have also

Fig. 1 Peripheral smear of the neonate showing growing trophozoites (arrow)

shown that HIV co-infected pregnant women have a significantly increased burden of placental malaria due to impairment of antibody responses, which increases the risk of congenital infection (Perrault et al. 2009).

Hence, the neonates with congenital malaria are usually healthy at birth, and symptoms appear when the level of passively acquired maternal antibodies starts to wane. Fever may be occasionally absent, and accompanying features which need to be examined include irritability, hepatosplenomegaly, anorexia, haemolytic anaemia, jaundice and thrombocytopenia. The case described here demonstrates many of the usual features of congenital malaria. CRP level in this patient was mildly elevated. Increased CRP is seen in infectious and inflammatory conditions, tissue necrosis and apoptosis. It has been reported to rise in malaria also (Gillespie et al. 1991; Ansar et al. 2006). The diagnosis of congenital malaria in this patient at the age of 21 days was established by the presence of growing trophozoites of *P. vivax* in the peripheral smear, and positive rapid malaria test in the mother. In addition, the onset of symptoms and parasitemia in the neonate during the low transmission period of the year also favoured the diagnosis of congenital malaria.

The smears in the mother were negative for the parasite, but the rapid antibody test was positive. The negative smears can be explained by the very low parasitemia, not detected by thorough screening of peripheral blood. The mother may have some past infection with mild clinical symptoms during or before pregnancy, but such clinical or treatment history could not be elicited. Patients from the rural belts of India often cannot recollect the detailed history properly, and may not have taken adequate treatment, resulting in incomplete clearance of parasites from the blood. To recall, congenital malaria may be detected rarely in infants of asymptomatic women (Davies et al. 1992).

The majority of studies on congenital malaria are in the context of *P. falciparum* infections in Africa. However, congenital malaria due to *P. vivax* has also been described in few countries (Valecha et al. 2007; Wiwanitkit 2006). This case suggests that the diagnosis of congenital malaria should be considered as an important differential diagnosis of neonatal infections and sepsis in infants who are born from mothers coming from malaria endemic countries with or without an obvious well recollected history of malaria during pregnancy. Similar information was also conveyed by Del Punta et al. (2010).

The treatment of neonatal *vivax* malaria comprises of a blood schizonticide, like chloroquine (CQ) in a dose of 10 mg/kg body weight of base followed by 5 mg/kg of base at 6, 24 and 48 h. Primaquine is not given in congenital malaria as there is no exoerythrocytic stage of the parasite (Del Punta et al. 2010). Since primaquine is also contraindicated in pregnancy and lactation, there is no

radical malaria treatment strategy for pregnant women with absolute safety to the foetus. Due to the high prevalence of multidrug resistance in both *P. falciparum* and *P. vivax*, infants of less than 5 kg weight and women in the first trimester with malaria can be treated with oral quinine. Dihydroartemisinin–piperaquine can be used for uncomplicated malaria in infants weighing more than 5 kg and in pregnant women in the second and third trimesters. Neonates and pregnant women with severe malaria are treated with intravenous artesunate (Poespoprodjo et al. 2011).

Emphasis should be given on use of preventive measures like chemoprophylaxis and bed nets in the community and adequate management of suspected malaria cases during the antenatal period. It has been shown that weekly CQ prophylaxis in pregnant women is safe and effective in preventing *vivax* malaria (Villegas et al. 2007) but it has been not used widely. The introduction of a highly effective artemisinin combination therapy for malaria treatment in the second and third trimesters of pregnancy has decreased the risk of vertical transmission and hence the incidence of congenital malaria. Routine screening of newborns for asymptomatic parasitemia followed by prompt, effective antimalarial treatment could further reduce the burden of congenital malaria (Poespoprodjo et al. 2011).

To conclude, *P. vivax* congenital malaria is a relatively rare condition that should be included in the differential diagnosis of neonatal infections, sepsis, unexplained fever or in infants presenting with haemolytic anemia, jaundice and hepatosplenomegaly in malaria endemic zones. Though quite prevalent in tropical countries like India, the condition is still epidemiologically under-investigated and diagnostic, therapeutic and preventive measures are not adequately implemented in every part of this country. Clinical onset of symptoms may be delayed, and it may also occur in infants of asymptomatic women. Awareness of the condition and timely intervention of the mother and the newborn may prevent both maternal and neonatal morbidity and mortality. Treatment protocol for malaria in pregnancy, lactation and congenital malaria is different from the usual recommendations, and needs to be individualised.

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