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Congenital *Plasmodium Falciparum* Malaria: A Report of Three Cases

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Abstract

Background: Congenital Malaria is a life threatening infection of neonates occurring as a vertical transmission of malaria during pregnancy or at birth. Recent studies report a high burden of congenital malaria in sub-Saharan Africa. This case series emphasizes that routine checks for malaria parasites in all neonates presenting with fever is paramount in avoiding delays in the diagnosis of congenital malaria and unnecessary use of empiric antibiotics.

Case presentation: Herein, we report three cases of congenital *Plasmodium falciparum* malaria that occurred within 5 days postpartum in babies whose mother had no history of malaria during pregnancy, took sulfadoxine/pyrimethamine prophylaxis during antenatal visits and their thin and thick blood films to check for malaria parasite after delivery were negative. These neonates were initially managed for neonatal sepsis before the diagnosis of Congenital Malaria was made.

Conclusions: Congenital Malaria should be checked routinely in all neonates presenting with fever even without evidence of active infection of mother with malaria during pregnancy, before considering the use of empiric antibiotics. Further research is warranted to establish guidelines for the management of Congenital Malaria, investigate the efficacy of sulfadoxine/pyrimethamine prophylaxis in preventing Congenital Malaria and ensure the safety of artemisinin based combination therapy on infants with weight less than 5 kg.

Keywords

Congenital Malaria, *Plasmodium falciparum*, Neonatal sepsis, Guidelines

List of Abbreviations

CM: Congenital Malaria

Background

Congenital Malaria (CM) is a potentially life-threatening infection of neonates occurring as vertical transmission of malaria during pregnancy or at birth. CM is also defined as the presence of asexual stages of the parasite in cord blood or in the peripheral smear of the infant in the first seven days of life [1-3]. Clinical features of neonatal malaria are non-specific and overlap with those of neonatal sepsis. They include fever, refusal to suck, excessive crying and irritability, jaundice, convulsions, vomiting, diarrhoea, lethargy, anaemia and splenomegaly [2,4,5]. Although fever is a cardinal symptom of malaria, it may be absent in CM [6]. The main cause of CM in endemic regions is *Plasmodium falciparum* [1-3] while *Plasmodium malariae* and *Plasmodium vivax* are predominant in non-endemic regions like Europe and South East Asia [4-9]. Postulated mechanisms for transmission of malaria parasites from mothers to neonates include maternal transfusion through foetal circu-

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lation either during pregnancy or at the time of delivery through the birth canal [5]. Transplacental transmission of the malaria parasite to the foetus is either by direct penetration through the chorionic villiorpenetration through premature separation of placenta [5,6]. Recent studies report a high burden of CM in sub-Saharan Africa [10]. This case series emphasizes that routine checks for malaria parasite in all neonates presenting with fever is paramount in avoiding delays in the diagnosis of CM and unnecessary use of empiric antibiotics.

Case Presentation

Case 1

A 2-day-old male neonate was transferred to the neonatology unit of Saint Elizabeth Catholic General Hospital Shisong after developing a fever which peaked at 40.3 °C. This was associated with excessive crying and refusing to suck. The mother had an uneventful pregnancy which resulted to a spontaneous delivery at 40 weeks gestation. The birth weight was 3450 g, length 48 cm and head circumference 35 cm. Apgar score at birth was 9/10 and 10/10 five minutes after delivery. During antenatal visits, thin and thick blood film microscopies using Giemsa staining were routinely done and were all negative. The mother took sulfadoxine/pyrimethamine (1500 mg/75 mg) prophylaxis at the 20 weeks and 28 weeks gestation. Thin and thick blood film microscopy was equally done on the mother after delivery was negative. Physical examination revealed pink conjunctivae and anicteric sclerae. The baby was quadruflexed and primitive reflexes were present. The fontanels were flat and non-bulging. Breath sounds were vesicular and the heart rate was 172 beats per minute. The abdomen was soft and non-tender with no palpable mass. Two days following delivery, the baby was circumcised. A complete blood count was done which revealed white blood cell count of 17,000 cells/µl, haemoglobin of 13 g/dl and platelet count of 210,000/µl. The mother could not afford for a blood culture. The baby was initially managed as early onset neonatal sepsis with intravenous empiric triple antibiotics: gentamycin 8 mg 12 hourly, ampicillin 110 mg 8 hourly and ceftriaxone 150 mg 12 hourly. Fever was controlled with intravenous paracetamol 62.5 mg 8 hourly given rectally. The fever persisted two days following the initiation of antibiotics and a Giemsa-stained thin and thick blood film revealed *Plasmodium falciparum* trophozoites and a paracetemia of 4%. We concluded on a diagnosis of congenital *Plasmodium falciparum* malaria associated with neonatal sepsis and intravenous artenunate was added to treatment with a loading dose of 9 mg 8 hourly for one day and maintenance dose of 8 mg 24 hourly for 5 days. The fever subsided following the initiation of antimalarial therapy and the child was eventually discharged on the 9th day of admission.

Case 2

A 5-day-old male neonate was transferred to the neonatal unit of our centre following an intermittent fever of 2 days which peaked at 39.6 °C. Associated features included refusal to suckle and excessive crying. The mother had a spontaneous normal delivery at 40 weeks of gestation with no abnormal events during pregnancy. The mother had no history of malaria during pregnancy and took two doses of sulfadoxine/pyrimethamine (1500 mg/75 mg) prophylaxis during antenatal visits and she also tested malaria negative after delivery using thin and thick blood films. The baby weighed 3060 g at birth with a head circumference of 35 cm and length of 49 cm. He had an Apgar score of 6/10 at birth and after suctioning it was 8/10 and eventually 10/10 at 5 minutes. Physical examination revealed pale conjunctivae and mildly icteric sclerae. The baby was quadruflexed and primitive reflexes were present. There was a hepatomegaly of over 6 cm below the costal margin. The breath sounds were vesicular and a heart rate of 187 beats per minute. A complete blood count revealed a white cell count of 8,700 cells/µl, mild microcytic hypochromic anaemia with haemoglobin level of 13.0 g/dl and a mild thrombocytopenia with a platelet count of 129,000/µl. The neonate was placed on empiric triple antibiotics: ampicillin 100 mg 8 hourly, gentamycin 7.5 mg 12 hourly and ceftriaxone 150 mg 12 hourly but fever persisted following initiation of antibiotics as the general state of the baby deteriorated. Blood was sent for culture and a thin and thick blood film was done which revealed *Plasmodium falciparum* and a parasitemia of 6%. A definitive diagnosis of CM was reached and treatment with antibiotics was suspended. The baby was placed on artesunate 7 mg 8 hourly for the first day and 7 mg 24 hourly for subsequent days. Fever was controlled by paracetamol 45 mg 8 hourly given rectally. Symptoms subsided three days following antimalarial treatment and the baby was eventually discharged on the 8th day of admission.

Case 3

A 2-day-old female neonate was transferred to the neonatology unit of our centre 4 hours after she started convulsing. The convulsions were generalised and associated with a fever which peaked at 39.8 °C. She was refusing to suckle and was vomiting. The baby was delivered at 38 week gestation following prolonged labour that was augmented. There was no history of maternal malaria and the mother took two doses of sulfadoxine/pyrimethamine (1500 mg/75 mg) prohylaxis at the second and third trimesters and tested negative to malaria after delivery. The birth weight was 3230 g, head circumference 36 cm and length 46 cm. Physical examination revealed twitching of the arms, pink conjunctivae and anicteric sclerae. The baby was quadruflexed with flat fontanels

and primitive reflexes were present. The breath sounds were vesicular, the heart rate was 191 beats per minute and the oxygen saturation was 93%. The abdomen was soft with no palpable mass. A diagnosis of early onset neonatal meningitis was made and intravenous ampicillin 150 mg was administered every 8 hourly, ceftriaxone 150 mg 12 hourly and gentamicin 7.5 mg 12 hourly were started empirically. The convulsions were controlled by diazepam 2 mg given rectally and repeated after 10 minutes. Progress was marked by the persistence of fever and convulsions. The thin and think blood film microscopy which revealed *Plasmodium falciparum* and a parasitemia of 12%. Antibiotics were stopped and the baby was placed on intravenous artesunate at 8 mg 8 hourly for the first day and 8 mg daily in subsequent days. Symptoms subsided after the initiation of artesunate and a control malaria test at the 3rd day of admission was negative. Intravenous artesunate was continued and the baby was discharged on the 6th day of admission.

Discussion

CM was thought to be rare until recent years when it had been frequently reported from both endemic and non-endemic regions [4,5,11]. Menendez, *et al.* in an overview of CM, showed that this initial reports on the rarity of CM might have been probably due an underestimation of its prevalence. The underestimation in prevalence of CM could have resulted from the differences in the definitions that were used in the different studies, the differences in type of blood sample that was examined (some studies used peripheral blood while others cord blood), the method used to check for the malaria parasite (some studies used Giemsa staining thin and thick blood film microscopy while others used polymerase chain reaction), the expertise in blood smear examination amongst other factors [9]. Perrault, *et al.* found in the same population 0% of cord blood infection by microscopy and 10.8% of cord blood infection by polymerase chain reaction [12]. The rarity of CM in hyper endemic regions could have resulted from immunisation of babies by antibodies received passively during pregnancy. These antibodies offer a protective effect on neonates by helping them to clear of malaria parasites without developing symptoms [13]. Foetal haemoglobin equally plays an important role by slowing the rate of parasite development and reducing the number of neonates infected with the parasites that present with symptoms [12].

Studies in recent years have shown a rising incidence of CM [14]. This is due to an increase drug resistance, the virulence of the malaria parasites resulting from altered antigenic determinants, [3,7,14] or an increase in the number of neonates presenting with fever who benefit from routine checks for malaria parasite. Since CM was considered rare at first, blood film examination for *Plasmodium* parasites was not routinely performed in all neonates presenting with fever, [3] and this could have led to failure to diagnose some cases of CM or delays in diagnosis. Lesko, *et al.* in a retrospective case series in the United States, showed that delays in the diagnosis of CM are associated with an increase mortality [13]. Many studies suggest the need to suspect and routinely check for CM in all neonates in endemic regions, particularly if these neonates are febrile, [1,4,10,11,15] however many neonates presenting with fever are still initially managed as neonatal sepsis [1,3,7,8]. All the neonates in this case series received antibiotics empirically before the diagnosis of CM was made.

In endemic regions, CM can also occur despite the absence of an evidence of active malaria infection of mothers during pregnancy [1]. Proven history of malaria episodes of the mother during the gestational period or at birth is therefore not essential in the diagnosis of CM and relying on this can lead to failure to diagnose CM or unnecessary delays in the diagnosis. In this case series, all the mothers had no history of malaria infection during pregnancy and their blood films after birth revealed no malaria parasites. Just living in or travelling to an endemic zone makes a woman at risk of having a baby with malaria. The absence of travel history of mothers from non-endemic regions to endemic regions does not equally exclude the possibility of CM in babies presenting with fever [13]. Lesko, *et al.* showed that most women who had babies with CM were foreign born and not all of them had travelled to an endemic before or during pregnancy [13].

In this case series, all the neonates developed symptoms before 5 days of life and all the cases were caused by *Plasmodium falciparum*. Most cases of CM reported that revealed the clinical onset between 10 and 28 days of life were due to *Plasmodium malariae* and *Plasmodium vivax* [1,4,6,8,13,15]. Therefore, CM may tend to present earlier in neonates affected by *Plasmodium falciparum*. If CM caused by *Plasmodium falciparum* is not diagnosed and promptly treated, it would be rapidly lethal, especially in babies born to non-immune women [9]. Therefore, a possibility of infection with *Plasmodium* parasite most be considered in all neonates presenting with fever in both endemic and non-endemic regions to enable early diagnosis.

Current treatment guidelines on malaria do not focus on CM and there are no established protocols for management and prevention of CM [7]. Uneke concluded following a systematic review of cases of CM over decade that operational research into various aspects of CM is essentially lacking and new public health policies on malaria that should take into cognizance the importance of integrating guidelines on CM management and control are required

[7]. Common drugs currently used in the treatment of malaria in sub-Saharan Africa such as the artemisinin derivatives have no proven safety for use in infants less than 5 kg. Jaharam, *et al*. in 2010 suggested the adoption of better modalities of malaria treatment in infected pregnant females considering the prevention of CM [8]. Adequate treatment with quinine and use of intermittent sulfadoxine/pyrimethamine prophylaxis during pregnancy have no proven evidence of preventing transplacental transmission of malaria infection and CM [8]. In these case series, all the mothers used intermittent prophylaxis with sulfadoxine/pyrimethamine at least twice during pregnancy.

Conclusion

Congenital Malaria should be checked routinely in all neonates in endemic regions presenting with fever even without evidence of active infection of mother with malaria during pregnancy before considering the use of empiric antibiotics. Further research is warranted to establish guidelines for the management of Congenital Malaria, investigate the efficacy of the use of sulfadoxine/pyrimethamine prophylaxis in its prevention and the safety of artemisinin based combination therapy on infants with weight less than 5 kg. Clinical trials are still needed to prove the effectiveness of therapeutic drugs in preventing transplacental transmission of the malaria parasite especially in women who develop malaria during pregnancy.

Declarations

Consent for publication

Written informed consent was obtained from the patients carers for publication of this case reports. A copy of the written consents are available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EVY and BS managed the patients and wrote the original manuscript. MHA and PNT had a critical review and correction of the manuscript. All authors read and approved the final manuscript.

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