Congenital malaria: Importance of diagnosis and treatment in pregnancy

Selvi Gülaşı,[1] Nureddin Özdener[2]

[1]Mardin Maternity and Children's Hospital and [2]Mardin Public Health Office, Mardin, Turkey.
E-mail: selvigulasi@mynet.com
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Congenital malaria, in which infants are directly infected with malaria parasites from their mother prior to or during birth, is a potentially life-threatening condition that occurs at relatively low rates in malaria endemic regions. We report an unusual case of a 23-day-old girl with neonatal *Plasmodium vivax* malaria, suspected primarily on the basis of positive maternal history that her mother had malaria during her pregnancy and was cured with chloroquine therapy. Infant presented with fever, thrombocytopenia and a significant parasitemia. She responded to chloroquine antimalarial therapy and was discharged successfully 10 days after admission. We emphasize the importance of diagnosis and treatment in pregnancy and follow-up with these newborns after birth by neonatologists and pediatric specialists.

Key words: congenital malaria, plasmodium vivax, neonate.

Malaria is an acute systemic illness caused by *Plasmodium* type protozoan parasites. The *Plasmodium* types transmitted to humans by female *Anopheles* mosquitoes. But it can also be transmitted by the transfusion of infected blood products and congenital transition. The *Plasmodium* types which cause malaria on humans are *P. falciparum, P. vivax, P. ovale* and *P. malariae*. In recent years it has been determined that *P. knowlesi* which normally infects primates, can cause acute and severe infection in humans[1]. The most virulent type for humans is the *P. falciparum* malaria. There are an estimated 135-287 million clinical cases of malaria and 482,000 deaths due to malaria annually in children under five years old around the world[2]. Approximately 660,000 deaths have been caused by malaria in the sub-Saharan countries in 2010 and 86% of deaths caused by malaria in this region were children under the age of five[3,4]. The most common *Plasmodiums*' type in Turkey is *P. vivax*[5]. Malaria eradication studies are being conducted since 1926 in our country for free by specially trained teams which are connected to the Ministry of Health. In 2013 the incidence of malaria has been reported as 0.4 per 100,000 population in Turkey[6].

Malaria during pregnancy can cause miscarriage, low birth weight, premature labour, intrauterine growth retardation, high perinatal mortality, anemia and maternal death, even in *P. vivax* cases[7]. Malaria in pregnancy is a major contributor to morbidity and mortality, resulting in an estimated 100,000 neonatal deaths and 10,000 maternal deaths annually[3,8]. In hyperendemic regions mothers are usually immune and pass their antibodies to their babies, therefore congenital malaria cases are rare. The symptoms may appear at any period during the pregnancy on the mother but she might also have the disease asymptomatically. In endemic areas such as sub-Saharan African countries, where adult women have considerable acquired immunity, *Plasmodium* infection during pregnancy does not cause symptomatic malaria and congenital malaria is not frequently seen in their babies[3,4,9]. In recent years, workers from endemic areas have reported the incidence of congenital malaria to be between 0-37%[10,11]. The immunity against *Plasmodium* is low in regions which are not endemic, and having the disease during pregnancy has a significant life threatening effect on the fetus[12].

There is no consensus on the definition of

congenital malaria. While it can be defined as the illness caused by malaria parasites' placental transmission or transmitting during birth from the birth canal, it can also be defined as the presence of asexual malaria parasites in the erythrocytes of newborns aged less than seven days[13-15]. The initial symptoms in congenital malaria may occur in the first seven days as well as in the first 50 days in regions which are not endemic. The most common symptom is fever. Fever may not be in typical paroxysmal forms. Other symptoms can be listed as follows according to their frequency; anemia, jaundice, pallor, diarrhea, vomiting, lethargy, shivering, abdominal distension, convulsion, malnutrition, milk regurgitation, hemolysis, irritability, fetal macrosomia, dyspnea, dehydration, weight loss, skin ulcer, purpura and hepatosplenomegaly[16].

We report a 23-day-old girl with neonatal *Plasmodium vivax* malaria, suspected primarily on the basis of positive maternal history that her mother had malaria in her pregnancy at eighth month of gestation. This case shows that the diagnosis of congenital malaria should be considered in infants with suspected congenital infection who are born to mothers with a history of malarial disease. We emphasize the importance of diagnosis and treatment in pregnancy and follow-up these newborns after birth by neonatologists and pediatric specialists.

Case Report

The 23-day-old female infant was brought to our hospital with the complaints of high fever, decrease in feeding and rapid breathing. The mother was primigravida. After the untroubled delivery, baby was clinically normal and her feeding and activities were fine. Ten days prior to her admission to our hospital she started having a fever, abdominal distension and vomiting. The fever occurred commonly at night, stating that she had a fever every night and that every two nights the fever would be very high and very difficult to reduce. Therefore patient was prescribed oral ampicillin 50 mg/kg/day and nasal drops but she did not obtain any benefit from oral ampicillin in this period.

On physical examination: the infant body weight was 3,500 g (75p), body length was 50 cm (50-75p) and head circumference was 35 cm (75p). Her body temperature was 39°C, respiratory rate was 76/min, heart rate was 220/min and oxygen saturation without oxygen was 92%. There was moniliasis in her mouth and serous nasal secretion. Her skin turgor and tone was reduced and she looked pale. The respiratory sounds in the auscultation were normal and there was no murmur in the heart. There was abdominal distention, the liver was palpable three cm and the spleen at one cm below costal margin. The examination of other systems were normal. Electrocardiographic monitoring was evaluated as sinus tachycardia.

In laboratory examinations the hemoglobin count was 9.1 g/dl, hematocrit count was 25.1%, total leukocyte count was $6.1x10^9$/L (lymphocyte 72%, neutrophils 28%), platelet count was $41x10^9$/L and C-reactive protein count was 10.6 mg/dl (0-5mg/dl). Alanine transaminase, aspartate transaminase, lactic dehydrogenase, urea, electrolytes and thyroid hormones were normal. The liver and spleen sizes were reported large at the abdominal ultrasound measurement, there was no additional pathology. Blood and urine cultures were negative.

Since sepsis could not be excluded, after the cultures were taken, ampicillin 50 mg/kg/dose was administered every 8 hours and cefotaxime 50 mg/kg/dose every 8 hours via intravenous route was started empirically. We had learned that the mother suffered from malaria. We had received information from Mardin Public Health Office that she was diagnosed with *P. vivax* malaria in her pregnancy at eighth month of gestation and she was treated with chloroquine. The first dose of chloroquine was given to her with 600 mg and second dose 300 mg after six hours from the first dose, then continued with 300 mg on the second and third days by Mardin Public Health Office. After the treatment, mother was examined for parasitemia every 15 days until the end of her pregnancy, and no problem was detected. After birth, neither mother nor baby had gone back for a check-up. Therefore, the Mardin Public Health Office was informed that there could be a congenital malaria case.

The patient was hydrated, her fever was reduced with paracetamol, then erythrocyte suspension was given because her tachycardia continued to be around 170-180/min. Then the tachycardia was recovered. On the second day of her hospitalization her thick and thin

smear samples were taken by the Ministry of Health officials. The *Plasmodium vivax* parasite was detected and it was reported that the parasite was concentrated in the samples. Chloroquine 10 mg/kg/day first dose and 5 mg/kg/day second dose after six hours from the first dose was given by orogastric tube, then continued with 5 mg/kg/day at second and third days. On the 2nd day of the treatment the patient did not have fever and her platelet count increased to $84x10^9$/L, and significant reduction of parasites in the thick and thin smear samples was seen. On the 4th day of the treatment it was detected that the parasites had completely disappeared, the platelet count had increased to $250x10^9$/L so the treatment was stopped. The 6th day we were informed that no parasites were detected. The infant whose nutrition was improved and physical examination was normal was discharged from the hospital without any complications on the 10th day. The family was informed about the disease and their consent was taken to publish this case.

Discussion

Malaria in pregnancy is still an important cause of fetus, infant and pregnancy deaths. Malaria during pregnancy is a potential risk of carrying disease for both the mother and the fetus and can cause premature birth, intrauterine growth deficiency, low birth weight, abortus, stillbirth, fetal anemia, and maternal deaths. Women are susceptible to malaria infections during pregnancy, because *P. falciparum*, the most common parasite responsible for malaria, can avoid being cleaned in the spleen with a binding protein Chondroitin Sulphate-A (CSA) which is expressed in the placental intervillous area and therefore the fetus can be exposed to *Plasmodiums* from the intrauterine period[3].

While the parasitemia has a high density in the first infant, this density decreases with every birth due to the increasing immunity[15]. The transitions of the *Plasmodiums* to the infant are not directly through the penetration to the villus, but by the violation of the placental barrier. Exposure to infected erythrocytes can be intrauterine or intrapartum. Since the infection is prenatal the classic symptoms usually appear within 10–20 days. The appearing period of the symptoms may differ according to the existence of immunglobuline G type antibodies passed from the mother and the degree of the parasitemia[17].

Early and correct diagnosis is crucial for starting anti-malarial medication in pregnancy. The World Health Organization (WHO) guidelines stress prioritizing the life of the mother when treating malaria[18]. In all trimesters of pregnancy, the WHO recommended treatment for uncomplicated *P. vivax* malaria is chloroquine, a total dose of 25 mg base/kg body weight in three days[19]. In our country, Malaria-Control Department of the Health Ministry recommended treatment for pregnant woman is chloroquine the first dose at 600 mg and second dose 300 mg after six hours from the first dose, then continued with 300 mg at second and third days. After this treatment patients are checked with thick and thin blood smear every 15 days until birth; if there are any parasites this three day treatment is repeated[20,21]. After birth, if the mother does not breastfeed her baby, primaquine and chloroquine are given together regardless of the presence of parasites. If mother is breastfeeding, primaquine and chloroquine are given to her after the baby is six months old. In infants who are diagnosed with malaria and are younger than six months, after a three day chloroquin treatment the infant is monitored with thick and thin blood smears taken every 15 days. If plasmodium is found, the three day chloroquine treatment is repeated. After the infant is six months old, primaquine and chloroquine are given together regardless of the presence of parasites. *P. vivax* has liver stages (hypnozoites) that cause recurrent blood-stage infections (relapses). Primaquine, the only drug effective against liver stages, is contraindicated in pregnant women because fetal red blood cells are susceptible to hemolysis. Pregnant women should receive suppressive prophylaxis with chloroquine until delivery, at which point they can receive radical treatment with primaquine[22].

Congenital malaria is defined as the presence of asexual malaria parasites in the erythrocytes of newborns aged less than seven days[13-15]. The newborn child can manifest with fever, irritability, feeding problems, hepatosplenomegaly, anemia, and jaundice. Although fever is a cardinal symptom of malaria, it may be absent in congenital malaria. In our patient the pattern

of fever was periodic. With the tearing of the mature schizont in the newborn, many parasites are released and infect the new erythrocytes and increasing parasitemia occurs. Because its workload has increased due to cleaning up the infected erythrocytes the spleen grows, anemia and jaundice occur. The infant seems normal until jaundice, anemia and splenomegaly occur. In our case no problem was observed until 10 days after birth. Thrombocytopenia is a complication of malaria infection with Plasmodium vivax and might be due to hypersplenism or bone marrow suppression[23]. Although significant bleeding is uncommon, platelet counts can diminish to 10,000-20,000/mm^3. In our case, platelet count was 41x10^9/L at admission and she did not require platelet transfusion.

The golden standard in the diagnosis is the demonstration of parasites in the giemsa dyed peripheral blood smear. The thick and thin smears are evaluated together. The thick smear is valuable in increasing density of parasites, the thin smear is valuable in detecting the *Plasmodium* type, and thus this is valuable in determining the severity of the disease. In the evaluation of the response to treatment, daily thick and thin smears should be taken and seen that the parasitemia has decreased to lower than 1%. To say that there is full response to treatment, two separate examinations which are taken at 48 hour intervals should be negative[24]. We have monitored our patient with thick and thin smears taken every other day, and were informed that on the 4th day of treatment no parasites were found. 48 hours later thick and thin smears were taken again and no parasites were found, therefore we decided that we had received proper response to treatment.

In the treatment of congenital vivax malaria, chloroquine which is a blood schizontocide, is sufficient. Apart from chloroquine resistant *P. falciparum* cases, the first option for treatment is chloroquine, 10 mg/kg/day loading dose and following days 5 mg/kg/day maintenance dose given every 24 hours. In our presented case, chloroquine was given with orogastric tube successfully. In cases where intravenous use is necessary, the medication that should be used is kinidin gluconate, which has a 10 mg/kg loading dose and should be given with normal saline within 1-2 hours, and treatment should continue with 0.02 mg/kg/minute infusion[15,25].

In congenital malaria since the transmission is directly from the mother's blood to the fetus, there is no time for the formation of hipnozoids in the liver. Since there is no hepatic period there is no need for primaquine. Primaquine has potential side effects for newborns, such as bone marrow suppression, anemia, leukopenia, methemoglobinemia, and should be avoided from unnecessary uses. Primaquine is contraindicated during pregnancy and lactation. Since there can be relapses, the mothers who were not treated with primaquine should receive primaquine treatment post-partum. Mothers should not breastfeed their babies during primaquine treatment period.

Vector control is essential in protection from the disease. Such precautions can be taken as: preventing the mothers' traveling to the endemic regions, if she must go to travel applying prophylaxis with chloroquine, if there is resistance to chloroquine using mefloquine in prophylaxis.

The prognosis of the disease depends on the type of *Plasmodium*, the region it appeared in, the immunity of the pregnant and the degree of the parasitemia. Rapid diagnose and proper treatment is important.

This case indicates that congenital malaria is a disease that should be remembered in infants who have an unexplainable fever and whose mothers live in regions where malaria is not endemic. In our case, the mother's history of having malaria during pregnancy had a primary role in our diagnosis but neither mother nor baby have gone back for follow-up for malaria after birth. We emphasize the importance of adequate antenatal medical therapy for mothers infected with *Plasmodium* and the importance of follow-up with these newborns after birth by neonatologists and pediatric specialists.

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