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Review Article

NEONATAL MALARIA

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Abstract
Neonatal malaria, once considered a rare diagnosis is frequently being diagnosed in Neonatal Intensive Care Units in infants admitted with suspected neonatal sepsis, particularly in highly endemic regions. Most infections are caused by Plasmodium falciparum, and Plasmodium vivax. The signs and symptoms are indistinguishable from neonatal septicemia, requiring a high index of suspicion for its diagnosis. Blood smear examination remains the gold standard; however several rapid diagnostic tests are now available, particularly for diagnosing Plasmodium falciparum infection. Chloroquine remains the drug of choice for treating congenital malaria, other antimalarials have been used with success in treating chloroquine-resistant neonatal malaria.

Keywords : Neonatal Malaria, Congenital malaria, Plasmodium falciparum, Plasmodium vivax, Chloroquine, Antimalarial

Introduction

Nowadays, Neonatal malaria is no more a rare diagnosis particularly in highly endemic countries like India, Srilanka, Thailand, Singapore, Nigeria and other African countries. Previously malaria was thought to be rare in neonatal period due to protection conferred by passively transferred maternal antibodies, and/or partial resistance due to the presence of fetal red blood cells[1-5]. Malaria diagnosis frequently relies on the patient's symptoms. The first symptoms of malaria (fever, chills, sweats, headaches, muscle pains, nausea, and vomiting) are not specific to malaria and while the clinical diagnosis is inexpensive and can be effective, clinicians often misdiagnose malarial infection. Symptomatic diagnosis is further complicated in highly endemic areas because a large proportion of the population can be infected but are not symptomatic. Neonates admitted to newborn special care units are often presumed to have neonatal sepsis. Consequently, blood films for malaria parasites are not routinely included

in the sepsis screening protocol for such neonates. In view of the fact that a significant proportion of neonates with malaria may be missed in neonatal units on the assumption that the disease condition is rare. This article aims at documenting the prevalence of malaria in neonates admitted in our neonatal ward. Specifically, we hope to describe its clinical features and outcome of this illness. Knowledge of these may ensure early diagnosis and institution of prompt management. Till date, there is no consensus statement regarding diagnosis and treatment of neonatal malaria. By this article, we attempt at eliciting the signs and symptoms, and management of neonatal malaria.

Malarial parasite

Neonatal malaria is mostly caused by Plasmodium falciparum and Plasmodium vivax. Theoretically, Plasmodium ovale and Plasmodium malaria may also cause neonatal malaria. Ojukwu et al in 2002 evaluated eighty-four neonates for septicemia and malaria and he observed that 28 (33.3 percent) had positive blood smears for malaria parasites alone, 10 (11.9 percent) had septicemia alone, while four neonates (4.8 percent) had both malaria and septicemia. Plasmodium falciparum was found in all positive blood smears. Twenty-four (75.0 percent) of the 32 neonates with positive malarial parasitemia had congenital malaria, while the remaining eight (25 percent) most probably had acquired malaria. None of the neonates had transfusional malaria[3]. Lt Col C Vidyashankar et al reported two cases of neonatal malaria due to mixed infection with Plasmodium falciparum and Plasmodium vivax[4]. A retrospective study in the United States reported 81 cases of congenital malaria reported to the US National Malaria Surveillance System between January 1, 1966, and December 31, 2004, and the predominant infecting species was Plasmodium vivax (81%)[6]. As per Ekanem et al during the three-year period of their study, a total of 546 newborn babies were admitted to the neonatal unit. Out of these, 202 (37%) presented with the clinical symptoms and signs of sepsis (112 boys and 90 girls), 71 (35.1% of 202 or 13% of total admissions) had congenital malaria – these included one set of twins. P. falciparum was the only species detected[7]. Another study in Zambia also showed the similar result as 19 (29%) among 65 newborns showed Plasmodium falciparum in peripheral smear[8]. Thapa et al reported 31 cases of neonatal malaria in 10 year period at Postgraduate Institute of Medical Education & Research, Chandigarh. Among them, Plasmodium vivax was found in 25 babies and Plasmodium falciparum in 09 babies[9]. Recently one case report reported plasmodium malariae as a cause of neonatal malaria[10]. All these reports and case series suggest that either Plasmodium falciparum or Plasmodium vivax or both are the main agents behind congenital or neonatal malaria

Mode of infection

Neonatal malaria can be either due to vertical transmission from mother following a breach in the placental barrier or due to fresh infection either due to transfusion or mosquito bites. Congenital malaria is believed to occur when asexual parasites of the Plasmodium species are detected in the peripheral blood of newborns within the first week of life. Plasmodium falciparum, the causative agent for severe malaria in high endemic regions, is capable of crossing the placenta into the fetal circulation thereby causing congenital malaria. Vijay Kumar et al reported two cases of neonatal malaria in Saudi Arabia[11]. In 1996 an article published in "Journal of Tropical Pediatrics" reported 16 neonates with malarial parasitemia diagnosed on Giemsa stained smear suggesting an 8% incidence of neonatal malaria. Seventy-five percent of

these neonates had congenital malaria, 13 percent transfusion malaria, and 13 percent had acquired malaria. Plasmodium falciparum was found in all positive smears [12].

Pathophysiology

The pregnant woman runs a higher risk of contracting malaria than her non-pregnant counterparts. The transient depression of immunity to allow for the development of the allograft (fetus) is one of the reasons adduced for the increased susceptibility of the pregnant woman to malaria [13]. Although malaria in pregnancy is often asymptomatic, in the semi-immune woman it nevertheless is the cause of unfavorable pregnancy outcomes both in the mother and in her baby. The outcomes of the invasion of the placenta by parasites, inflammatory cells and cytokines include abortion, premature labor, small-for-date babies and fetal/maternal death in some instances. These unfavorable pregnancy outcomes are associated with sequestration of malarial parasites in the placental intervillous spaces by attaching to chondroitin-sulphate-A. Pro-inflammatory cells and cytokines also invade the placental bed. The net result is impairment of fetal blood and nutrient supply, which in turn predisposes to low birth weight (LBW). LBW, as occurs in small-for-date babies or babies born prematurely, is the greatest risk factor for neonatal mortality and a major contributor to infant mortality [14,15].

Clinical features

Placental Malaria is invariably asymptomatic and it may silently kill the fetus. Amongst the first born, it can significantly affect the birth weight. Routine administration of chloroquine to all mothers during the third trimester of pregnancy can improve birth weight in their offsprings. Congenital malaria in newborn manifests usually within seven days of birth. Sign and symptoms of congenital malaria are similar to those of neonatal malaria. Clinical features of neonatal malaria are considerably different from those of older children and adult. Neonatal malaria usually manifests around 2 to 8 weeks of age with fever, jaundice, progressive anemia, refusal to feed, excessive irritability, respiratory distress, thrombocytopenia, hepatosplenomegaly [16]. The Indian studies on neonatal malaria have reported fever in 90–100% cases. Hepatosplenomegaly is reported in 70 – 86% of cases and the refusal of feeds and loose motions are reported in 40–70% and 23.3 to 40% of cases respectively. Respiratory distress has been reported in 20% of cases[11,17-20]. Diallo et al found 59 neonates infested by P.falciparum among the 212 newborns surveyed for one year. Of these 59 cases, 46% were completely asymptomatic, 18% had respiratory signs and 14% had gastrointestinal signs. Fever was present in 14% of cases[13].

Diagnosis

Diagnosis of neonatal malaria is based on a high suspicion as it mimics neonatal septicaemia.

Blood smear examination

Geimsa stained blood smear examination is the gold standard test in making a diagnosis of neonatal malaria. Both thick and thin smear is necessary, thick smear for easy detection of the parasite, while thin smear is essential for species identification. The only drawback of this test is a high rate of false negative reports, particularly in cases of Plasmodium falciparum as it completes its life cycle in the perivascular region. In most of the reports, diagnosis is based on blood smear examination.

Rapid Diagnostic test

Rapid diagnostic tests, or RDTs, are becoming an increasingly important method for detecting malaria. The tests are ideal for rural areas – accurate, easy to use and at less

than one dollar per test, inexpensive. Prior to RDT's, blood samples had to be sent to labs to be examined under a microscope. With the prick of a finger, the RDTs can detect in less than 10 minutes the most common and deadly malarial parasite in the tropics, Plasmodium falciparum.

These are an immunochromatographic test (ICT) to detect Plasmodium-specific antigens in a blood sample. Test employ monoclonal antibodies directed against targeted parasite antigen. Two types of rapid tests are available, ones that identify the circulatory histidine-rich protein-2 (PfHRP-2) antigen of falciparum malaria only, and others based on detection of falciparum malaria and for either vivax malaria or all four malarial species in the same test. However, this test also has some limitations- its sensitivity considerably decreases with the lower parasitic count.

According to one study in which performance of rapid antigen test (OptiMAL test) and blood smear test comparison was done. In this study, 192 newborns were screened for malarial parasitemia with immunochromatographic test (OptiMAL) and blood microscopy. Twenty one of 192 newborns were diagnosed with congenital malaria by blood film microscopy. The OptiMAL test was negative in all new borns (aged 0-3 days)[21]. As per this report, OptiMAL rapid malarial antigen might not be useful for diagnosing congenital malaria. In this report sample size was small and study population was limited to first 3 days of life. We think that further studies are required to confirm the usage of this test in the neonatal period.

Quantitative buffy coat analysis (QBC Method)

In this method, acridine orange is used as a fluorescent stain, taken up by parasitic DNA. The sensitivity and specificity of this method are slightly better than routine microscopy. However, differentiation of species and stage is difficult.

Other methods

Additional malaria diagnostic methods also exist, however they require both financial and technical resources, frequently unavailable in resource-limited settings. Enzyme immunoassays, for example, are roughly equivalent in sensitivity to microscopy and have limited sensitivity due to use of only Plasmodium falciparum antigen instead of antigens of all four human species. Using molecular amplification techniques, multiplex PCR tests have been developed for all four malarial species using target 18S single-stranded rRNA and circumsporozoite stage DNA sequences. Also, the Royal Tropical Institute (Amsterdam, NL) has developed a qualitative NASBA method for detection and semi-quantification of as few as 50 malarial parasites/ml of blood, which is many times more sensitive than microscopy.

Management

Supportive treatment

Good nursing care with proper positioning, meticulous attention to airways, eyes, mucosa, and skin should be done. Oxygen therapy and respiratory support should be given if necessary. Neonates with malaria are usually dehydrated and hypoglycemic hence blood glucose level and appropriate fluid management are mandatory in treatment. Close monitoring of the vital signs preferably every 2 hours till the neonate is out of danger. Broad-spectrum antibiotics should be started till the diagnosis of neonatal malaria is confirmed because clinical differentiation of diagnosis of neonatal septicemia with neonatal malaria is impossible.

Anemia

Progressive pallor is almost a constant feature in neonatal malaria. Many times it is severe enough to compromise cardiovascular function, that warrants for

blood transfusion rather than arbitrary hemoglobin level. In the present survey, 42.3% of the parasitized infants were anemic with 7% needing a blood transfusion. The mechanism of the development of anemia in malaria is multifactorial and complex, involving hemolysis, inappropriate marrow response and other factors.

Antimalarial drugs

Chloroquine sulphate –

As per a report by Ojukwu et al, good clinical response to chloroquine sulfate was recorded in 32 (86.5 percent) of 37 babies. Among 71 babies with congenital malaria 60 (84.5%) responded to chloroquine, rest 11(15.5%) were resistant to chloroquine and were successfully treated with quinine[3]. Other case reports also showed similar results.

Chloroquine-resistant malaria

Drug resistance in malaria is described by the World Health Organization (WHO) as the ability of the parasite strains to survive and/or multiply despite administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the tolerance of the subject[23,24]. Lt Col C Vidyashankar et al reported 2 cases chloroquine-resistant neonatal malaria from India Amongst the two, one was premature. One received oral quinine and other received intramuscular artesunate, both responded well clinically and their blood smear became negative for malarial parasite[4]. Another case report by Al Arishi et al, reported an extremely premature neonate with chloroquine-resistant malaria who responded to quinine[16]. Khichi O K et al analyzes 45 cases of neonatal malaria, among them 13 cases were chloroquine resistant. Quinine was used as a second-line drug for chloroquine-resistant cases and for some babies with quinine resistance, halofantrine was used [25]. However, halofantrine is not available in India. So we recommend the use of either quinine, sulphadoxine-pyrimethamine combination, artesunate, or artemether.

Conclusion

The magnitude of the impact of maternal malaria infection on neonatal mortality is unclear. A study suggested that there is little or no association between neonatal mortality and transmission intensity. Direct reports show that malaria can cause significant morbidity and even mortality in neonates, with its clinical signs being similar to that of neonatal sepsis. A high index of suspicion is therefore required for the diagnosis which should be considered as a possibility in all critically ill neonates in malarious areas, despite regular maternal anti-malarial prophylaxis with sulfadoxine-pyrimethamine combination or chloroquine. Initial work-up for presumed neonatal sepsis in such areas should routinely include blood films for malaria parasites.

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Table 1: Antimalarial Drugs and Doses

Chloroquine sulphate	10 mg of chloroquine base per kg body weight as a loading dose followed by 5 mg of base per kg body weight after 6-8 hour and then 5 mg of base per kg body weight on day 2 and 3.
Quinine	10 mg of quinine salt per kg body weight orally three times per day for 7-10 days. It can be given intravenously in same doses.
Artesunate	2.4 mg/kg iv (loading dose), followed by 1.2 mg at 12 and 24 hours then 1.2 mg/kg daily for 6 days.
Artemether	3.2 mg of artemether per kg body weight on the first day, followed by 1.6 mg/kg for the next six days.
Sulfadoxine-pyrimethamine combination	A single oral dose of pyrimethamine-sulfadoxine (25 mg/Kg of sulfadoxine and 1.25 mg/ Kg of Pyrimethamine)