Review Article

Malaria in newborn: A missed entity for primary care physician

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Abstract

Neonatal malaria and congenital malaria, though thought to be a rare entity in non-endemic areas but incidences from epidemic countries are eye openers. It is still thought by primary care physicians that its existence among neonates is not common even in endemic areas due to a low index of suspicion. In order to attain the objective set out in the global technical strategy against malaria 2016–2030, it is important to have a gravity of this disease in all age groups, especially in children and neonates in which misconception of low burden of infection results in underestimation of its morbidity and mortality in these age groups. This disease is only the tip of the iceberg due to unidentified, underreported and neglected illness and being a pointer towards higher circulation among society and pregnant women. So this review article highlights pathophysiology, epidemiology, clinical features, complications, prognosis, treatment and prevention of malaria in newborns and intends to bring awareness among the caregivers to understand the need for attention towards this neglected disease of neonates so that they should be able to identify and manage the disease in this vulnerable age group.

Keywords: Congenital, diagnosis, malaria, neonatal, newborn, plasmodium

Introduction

The physicians' poor acumen for the existence of malaria in neonates resulted in the missed opportunity to manage easily treatable disease in them when picked early, so contributing neonatal and infant mortality in endemic regions.[1]

Malaria is one of the leading causes of mortality and morbidity among children in resource-poor countries, though this disease in newborns is considered rare.[2,3] The first case of neonatal malaria is described in literature in 1876 as congenital malaria.[4]

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But recent reports indicate that the incidence of malaria in neonates is on a rising trend.[5,6] About 3,00,000 fetal and infant deaths are attributable to malaria.[7] Important terminologies related to malaria in newborns are the following.

Neonatal Malaria: Neonatal malaria is defined as symptoms attributed to malaria parasites in the erythrocytes of an infant within the first 28 days of life.[8] It can be the following.

Congenital Malaria: Congenital malaria is defined as an asexual form of malaria parasites demonstrated in the peripheral blood smear or cord blood of the newborns from birth to seven days of life[9] or later if there is no possibility of postpartum infection by either mosquito bite or blood transfusion,[10]

Acquired Neonatal Malaria: When malaria occurs within the first 28 days of life due to an infective mosquito bite or through

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transfusion of blood products after birth, it is called acquired neonatal malaria.[3]

But it is difficult to decide the mode of transmission of malaria parasites in newborns, especially in endemic areas for malaria.[11]

Etiology: Malaria in newborns can be caused by any Plasmodium species: P. *vivax*, P. *falciparum*, P. *ovale,* P. *malariae or* P. *knowlesi* or mixed infection by more than one species.[12]

P. *falciparum* species is common in Africa and responsible for severe and fatal malaria. P. *vivax* species is common in South America and Asia. *P knowlesi* is a new species[13], and no evidence about neonatal malaria caused by this species is available yet in literatures, though malaria in pregnancy caused by the species is continuously being reported, alerting the risk to newborns too.[14]

Pathophysiology

Modes of transmission can be through female Anopheles mosquito, mother-to-child transmission and transfusion of infected blood products, which is rare now in the era of modern screening tools.[15]

Possible mechanisms responsible for mother-to-newborn transmission include direct penetration through chorionic villi during pregnancy, physiological transfusion of infected maternal blood to the fetal circulation in utero or at the time of birth, or premature separation of the placenta during labour.[16,17] Though there are certain mechanisms that prevent malaria to occur in the neonatal period[18-21], so earlier this entity was thought to be rare in newborns, especially in holo-endemic areas. Factors which are thought to prevent malaria in newborns such as maternal antibodies passing to the newborn, fetal Hb, abnormal hemoglobins in newborns, lymphocytes as macrophage-derived toxic substances across placenta to fetal circulation, partial chemotherapy for malaria during pregnancy, lactoferrin (binding iron) and secretory IgA, found in breast milk, in maternal and infant sera, para-aminobenzoic Acid in breast milk inhibit growth and development of the parasite.

Parasite antigen P. *falciparum* erythrocyte membrane protein-1 (PfEMP-1) mediates cytoadherence of infected erythrocytes to the endothelial cell lining of blood vessels. HbF and maternal IgG act cooperatively to impair the cytoadherence of parasitized erythrocytes in the first four month of life in newborns by altering PfEMP-1 display on HbF RBCs and binding PfEMP-1 and preventing sequestration of parasitized RBCs, respectively.

HbF levels decrease after a peak at six weeks and maternal IgG also disappear from circulation, which makes infant susceptible to malaria infection in later infancy.[18,22]

Despite multiple factors playing a role in protecting newborns from malaria infection, increasing reports of neonatal malaria suggests that these protective factors are not as effective as was thought earlier but may be responsible for delayed clinical presentation (8 hours to 8 weeks)[12,23,24] and variable levels of parasitemia (<50–304,000 parasites/μL).[25]

Epidemiology

Prevalence

In Africa, 1500 perinatal mortality in a day occurs due to malaria. Prevalence of neonatal malaria is considered as the percentage of neonates having positive slide for malaria parasite out of admitted neonates during the same period. Malaria is a significant contributing factor to perinatal disease burden in terms of abortions, prematurity and intrauterine growth restriction. Apart from these indirect effects, the direct burden of malaria on newborns in terms of prevalence and outcome is not available, even in malaria-endemic regions. Prevalence of malaria in newborns may vary worldwide or in studies from the same country because of many reasons as levels of maternal immunity varying according to endemicity of the area, expertise level in blood smear examination, method of parasite detection (Geimsa/PCR) and true environmental difference.

Though some studies from various countries have documented the prevalence of neonatal and congenital malaria, because of all these limitations, it is difficult to generalize so far. In Nigeria, parasitemic prevalence in majority of cross-sectional studies in recent past was 58.5% for neonatal malaria.[26] While in India, Sri Lanka and Nigeria, the prevalence of congenital malaria is found to be 3.17%, 4.3%, 6.9% and 4.45%, respectively, in various studies.[27-29] In a recent hospital-based study from Nigeria, the prevalence of malaria among hospitalized neonates was found to be very high (37%).[30]

Risk factors

There are certain risk factors which make newborns for getting an infection with malaria parasite like untreated or ineffectively treated malaria infection in pregnant mother, primigravida mother infected with malaria, placental malaria-positive mother, prolonged labor, prolonged length of separation of membranes, maternal genital infections, HIV infected mother, preterm delivery, low birth weight, residence in malaria-endemic area, visit an endemic area for malaria by pregnant mother or newborn and rainy season.

Clinical Manifestations

Clinical features of malaria in neonates are not specific, indistinguishable from other neonatal infections and can be missed easily if not specifically looked for being suspicious of the possibility of malaria. In endemic area, signs and symptoms of malaria may be delayed up to 10–30 days because of the presence of maternal antibodies and other protective factors. But congenital malaria even in 8 h old newborn is also reported in literature.[12] Newborn may present with few mild symptoms

in the endemic area, but serious manifestations may occur in the non-endemic area. Neonates usually present with fever being the most common feature, apart from that she can have pallor, splenomegaly, hepatomegaly, jaundice/cholestasis, vomiting, convulsions, loose stools, poor feeding, drowsiness, restlessness, cyanosis, respiratory distress, cough, bleeding manifestations and intravascular hemorrhage sufficient enough to be confused with other prevalent diseases of newborns.

Fever in neonates should be a strong pointer towards malaria, especially if the mother had fever two weeks prior to delivery or mother during pregnancy or newborns from a non-endemic area travelled to a malaria-endemic area. The occurrence of infection in utero can be reflected by splenomegaly at one month of age and indicates an early development of a splenic response to infection.

Differential Diagnosis

Malaria in neonates can be confused with septicemia and TORCH infections. Some African studies suggest malaria parasitemia is more common in neonates with sepsis as compared to newborns without sepsis.

Diagnosis

Although the proportion of misdiagnosis in India is consistent at around 17%–18% since 2015, it is still significant enough to collapse the system of disease tracking and management,[31] and in neonates, due to the lack of this, aspect thought to be worse in view of overlapping clinical features of various common illness in neonates and low parasitemia.

Routine screening and diagnosis for malaria should always be done in a neonate from an endemic area who presents with a history of fever. It can be done by Geimsa staining under microscopy, PCR and rapid diagnostic tests (RDT) for antigen detection.

Microscopy is the gold standard for the detection of Plasmodium species, but it needs expertise as the parasitemia level is low in newborns. PCR may offer an attractive addition for confirmatory identification and diagnosis, but as a first-line investigation of choice its role is uncertain because of its ability to detect parasite macromolecules and not necessarily live parasite. Its cost and availability are other issues for its use as a routine test. RDT seems useful, but sensitivity can be low because of low parasitemic levels, but it can be used at odd hours or where the facility of microscopy is not feasible. In a recent study, done in Colombia, all CM cases were found to be submicroscopic with a frequency of 12.2% infections.[32] Here, submicroscopic refers to negative with Thick Blood Smear and positive with PCR. The same study showed better yield with umbilical cord blood as compared to peripheral blood (16.2% vs 2.2%. Test $Z = 5.3$. $P < 0.001$). So umbilical cord sample may prove to be good sample for the detection of infection if we are suspecting CM or for screening purposes in endemic areas.

Complete blood counts should be advised as anemia, thrombocytopenia and reticulocytosis are also common. Anemia in newborns even at low parasitemia (1–500/μL) can occur if left untreated and also can lead to death. Thrombocytopenia in newborn can cause bleeding manifestations, so always be looked for and should be promptly treated. Serum bilirubin levels should be done as jaundice may be associated with hemolysis or cholestasis.

Complications

Malaria in pregnant mothers or in newborns can cause potential hazards to newborn, i.e., low birth weight, prematurity, intrauterine growth restriction, perinatal mortality, abortion and stillbirth. Anemia is very common in the infected newborn due to hemolysis, increased splenic clearance and subsequent infection of infected and uninfected erythrocytes and cytokine-induced dyserythropoesis. The occurrence of sepsis is more in newborns infected with malaria.

Treatment

It is thought that symptomatic malaria is rare in neonates, only a few studies report on appropriate management of malaria in neonates, and no established treatment protocols exist.[33]

Even WHO treatment guidelines are lacking in the formulation of antimalarial combination therapy for malarial infection in this age group. WHO recommends antimalarial drugs doses only for babies weighing >5 Kg (>4.5 Kg for artesunate + amodiaquin). Because of certain factors like slow gastric emptying, absorption of drugs depending on intestinal motility and villous formation maturing by 20 weeks and immature hepatic enzymes (antimalarials are typically metabolized in liver), pharmacokinetics of antimalarial drugs in newborns differ so doses need to be adjusted according to age.

Worldwide various antimalarial drugs like Chloroquine, Quinine, halofantrine, Artesunate alone, and Artesunate combination therapy (with Amodiaquine) are safely used for neonatal malaria.[34-36] However, anecdotal evidence suggests neonates can be treated safely and effectively with these antimalarials using the same dosing regimens as in older infants. As in older infants, IV artesunate treatment seems favorable to use in ill children due to its PK profile.[33]

Chloroquine can be used for uncomplicated P. *vivax, malariae* and *ovale* malaria, but in Nigeria, 25% cases of congenital malaria are found to be Chloroquine resistant.[34] For severe cases, Quinine and Artesunate can be used, but effective and clearance rates are more with Artesunate and Quinine. Quinine resistance in newborns is also reported from Nigeria. Among the recommended ACT, excluding the combination containing sulphadoxine-pyrimethamine that is not recommended during the first 6 weeks of life,[37] there is no evidence of specific serious toxicity.[38] However, more studies are needed to establish their safety profile, adequate dosage and formulation, so that newborns

with malaria can be managed safely and properly. Treatment should not be given on an empirical basis.

Apart from this empirical evidence, no specific PK or PD information on antimalarial treatment in neonates exists. IV treatment has the theoretical benefit of bypassing the absorption phase (as opposed to oral, IM, or rectal medication), which in ill, vulnerable patients with unknown absorption parameters seems prudent.[33]

In congenital and transfusional malaria, there is no need for radical cure as there is no hepatic phase in the life cycle of the parasite, but in acquired malaria by mosquito bite, it can be needed. Primaquine is contraindicated in newborns because they are already G6PD deficient. No data available so far for radical cure in newborns.

Prognosis

Lower maternal age (teenage pregnancy), concurrent bacterial infection and duration of illness significantly affect the outcome negatively but the outcome of neonatal malaria is good if treated effectively and promptly.

Prevention

Prevention in mothers is the mainstay of a prevention strategy to decrease the incidence of congenital malaria. Pregnant women must be screened for malaria infection, and if positive should be treated effectively. More sensitive tests to detect malaria, i.e. PCR can be used to detect malaria during pregnancy. Intermittent prophylaxis for malaria to mothers during pregnancy should be given uniformly in endemic districts. Other preventive measures like use of insecticide-treated nets and covered clothing should be used by pregnant mothers. Educational campaigns can help the women of the childbearing age group to understand the dangers of malaria in pregnancy and its potential risk to their newborns.

High suspicion, detection and effective treatment in all age groups including newborns can decrease the circulation of parasite as neonatal malaria is the only reflection of the circulation of infection in the community. Integrated vector management by indoor residual spray, insecticide-treated bed nets, and antilarval measures including source reduction should be done from time to time in the endemic community. Exclusive breastfeeding may be protective, but more evidences are needed to support it.

Vaccination with candidate malaria vaccine RTS/S/AS01, which began in three pilot countries in April 2019, is of no use in newborns because of the presence of maternal antibodies in high titers and is recommended to administer at 6–12 weeks of age.

Conclusion

Poor suspicion of malaria in neonates among physicians of primary contact can have severe health consequences, delay recovery in them, and sometimes call for harmful treatment contributing to the collapse of the malaria control program of any country.

So it has to be understood by ground health care providers that malaria in newborn is not so rare as was earlier thought, but it can occur in any low to high transmission area without any characteristic feature and can be hazardous for a newborn if not treated effectively and timely, so with high suspicion of its possibility in a newborn, who presents with fever, malaria should be investigated along with a routine battery of tests for other infections such as sepsis, for its prompt and adequate management. This will definitely lead to reduce the neonatal mortality rate.

Larger studies especially from endemic regions with a capacity to conduct molecular diagnosis, parasite count and clinical trial, and long-term follow up would help better refine definitions, outcomes and interpretation of malaria infection in neonates. However, this study has been able to demonstrate the prevalence of neonatal malaria and equally give a clear illustration in the appropriate description of the spectrum of disease among this age group and will draw the attention of the researcher towards research gaps in the related areas especially antimalarial pharmacokinetic and dynamic studies in this population in relation to the physiological immaturity. So it would be helpful to primary care physicians at the ground level if evidence-based literature is available related to the field for optimum management of neonatal with this infection contributing to achieving goals of malaria control programs of the country.

Informed consent statement

All study participants, or their legal guardian, provided written consent prior to study enrollment.

Data sharing statement

There is no additional data available.

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Conflicts of interest

There are no conflicts of interest.

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