REVIEW ARTICLE

The Growing Incidence Of Neonatal Malaria- A Situational Review in developing countries

M. Mukhtar-*Yola MBBS, MWACP, FMCPead.*Department of Paediatrics, Aminu Kano Teaching Hospital, Kano, Nigeria.

Abstract.

Background: *Neonatal malaria was said to be a rare entity. However there are increasing reports from many parts of the world about the occurrence of malaria in the newborn.*

Methods: *A review of the literature on this subject was done with emphasis on developing countries. Literature search was done using Medline, as well as local and international journals.*

Results: *The reasons for earlier reported rarity of neonatal malaria, and those for the recent rising incidence are discussed along with diagnostic and management issues.*

Conclusion: *The physician must have a high index of suspicion to make a diagnosis of neonatal malaria, as the clinical features are non-specific and very similar to those of Neonatal sepsis. Neonatal malaria is a contributor to neonatal morbidity and mortality, which must be drastically reduced in order to achieve the fourth millennium development goal.*

Keywords: *Neonatal, Malaria, situational review, developing countries.*

Paper accepted for publication 10th August 2006.

Background

Malaria in the neonate was said to be rare. [1, 2] Congenital malaria was first described in 1876 with an incidence of 0.18-0.3%. [1] The postulated reasons for the rarity of neonatal malaria include the protective effects of transplacentaly transferred maternal antibodies (IgG) to the foetus, [3] the presence of the foetal haemoglobin, (HbF) which retards the growth of parasites (possibly due to its high affinity for oxygen, thereby impeding oxygen availability to malaria parasites) [3,4] and the role of the placenta, which when uninfected can be an important site of local antibody formation because of its heavy infiltration with lymphocytes. [5] Other reasons include the deficiency of para-aminobenzoic acid (PABA) in breast milk (which the parasite needs for growth and development), [6] and the immunologic role of the spleen. [6] It has also been suggested that the disease was under reported.

Malaria was said to be uncommon in children less than 6 months of age and rare in the neonate. [1, 2] The infection occurs more commonly in babies born to non immune mothers infected with malaria. [7] However, reports of neonatal malaria are increasing in both endemic [8-11] and non endemic areas [8-11] and the rates over time are variable with higher prevalence rates reported more recently, ranging between 0.3-46.7% [1,4,8-9,11-12]

The recent increase in the incidence of congenital malaria in holoendemic areas has been attributed to many factors. These include increased resistance of *P. falciparum* to antimalarial drugs resulting in increased maternal parasitaemia, [13-14] increased virulence resulting from altered antigenic determinants, [10] and increased reporting of cases. [10] It has also been suggested that mothers on regular malaria chemoprophylaxis have low malaria antibody titres and so might transfer little protective antibodies to their newborns. [15] These are probably the babies that may manifest with congenital malaria. [15] More recently antibody dependent cellular inhibition of malaria parasites mediated by Fc gamma RIIa [16] has been suggested as a possible cause of this rising trend.

The increased incidence in non-endemic areas may be due to travelling to endemic areas, increased emigration from endemic to non-endemic areas and the ineffectiveness of anti malarial drugs given to infected mothers. [9]

Malaria continues to be a serious public health problem in the world, especially in tropical countries. It threatens the lives of 40% of the World's population, affecting 2.4 billion people. [17] Its incidence worldwide is estimated to be 300-500 million cases annually, with about 90% occurring in Africa south of the Sahara. [17] Malaria caused by *Plasmodium falciparum* results in the highest morbidity and mortality in endemic areas [17] with young children, old people and pregnant women being more affected.

In Africa, about one million children under the age of 5 years die of malaria annually. [17-18] In Nigeria about 500-

Correspondence: ***Dr. M. Mukhtar-Yola***
E mail- mariyamukhtar@yahoo.com

700 children die from malaria every day. [19] Nigeria has a perinatal mortality of 90/1000 total births, [19] a neonatal mortality rate of 48/1000 live births and an under 5-mortality rate of 198/1000 live births.[20] These are disturbing figures and the target of millennium development goal (MDG) 4 is to reduce these by two thirds by the year 2015. The major causes of under-5 mortality outside the neonatal period are malaria, diarrhoeal diseases, respiratory tract infections, HIV/AIDS, vaccine preventable diseases in synergy with the underlying malnutrition in a very poor socio-economic environment. Globally, based on the year 2000 estimates, neonatal deaths account for 38% of deaths in children younger than 5 years. [21] Every year, an estimated 4 million babies worldwide die in the neonatal period, ¾ occur in the first week of life and 99% occur in low income and medium income countries. [22] Every hour, 450 newborns die globally and the most common causes are prematurity (28%), severe infections (36%) and asphyxia (23%). [22] Though neonatal malaria is not amongst the most frequent causes of neonatal death, it is an infestation that is being increasingly recognised as a cause of neonatal morbidity and mortality.[9,12] The United Nations Millennium Summit held in September 2000 set out eight-millennium development goals with the aim of reducing global poverty and improving the lives of people. The fourth MDG particularly refers to reduction of under-5 mortality by two thirds by the year 2015. To achieve this goal, neonatal mortality, which accounts for 38% of these mortalities, must be significantly reduced. As such there is a need for a high index of suspicion of neonatal malaria as an increasing contributor to neonatal morbidity and mortality.

Definition

Neonatal malaria is defined as the presence of malaria parasites in the peripheral blood smear of a baby within the first one month of life. [23] There are three types of neonatal malaria viz. congenital, acquired and transfusional malaria.

Congenital malaria: Occurs when malaria parasites cross the placenta either during pregnancy or at the time of delivery, and is diagnosed when asexual forms of the parasite are seen on the blood smear of the baby within the first week of life.[3, 23]

Acquired malaria: This results from mosquito bites anytime after delivery, when asexual parasitaemia is detected after a minimum incubation period of greater than one week.[24]

Transfusional malaria: This occurs when malaria parasites are detected in the blood of a neonate whose peripheral blood film was previously negative prior to receiving blood transfusion.[24] The mean time interval reported between blood transfusion and the presence of symptoms is 3-26 days.[24-25]

Clinical Presentation and laboratory findings

Most cases of neonatal malaria are initially misdiagnosed because of a general lack of awareness of this disease and its nonspecific clinical features.[7] This is due to the non specificity of the clinical signs of malaria and their similarity to those of neonatal bacterial infections.[14, 25-26] Since neonatal sepsis is very common in our environment, the physician must have a high index of suspicion to consider the possibility of neonatal malaria in the differential diagnosis of the sick neonate. Nyirjesy reported that neonatal malaria increases the risk of perinatal deaths (RR=7.2) and maternal malaria also increases the risk of perinatal death and low birth weight. [27] Failure to consider the diagnosis might worsen the prognosis for survival in the infected baby. [25, 27] It has been recommended that in endemic areas, all babies born to mothers who had malaria should be screened for congenital malaria and also all babies with suspected sepsis should be screened for malaria, as the clinical features are indistinguishable.[14, 26]

The mean incubation period for neonatal malaria is from less than one week to eight weeks.[25] Babies with transfusional malaria tend to present between 4-26 days after transfusion.[25] Earlier workers [15] found with some exceptions that, the primary attack is usually mild, in some instances being confined to a transient asymptomatic parasitaemia. Observed clinical features may include temperature instability, irritability, poor feeding, respiratory distress, pallor, jaundice, lethargy, hepatosplenomegaly, vomiting, diarrhoea and bloody stools. [14,24-26,] Less commonly, seizures, apnoea, cyanosis, abdominal distension, hypoglycaemia, jitteriness and poor weight gain may be observed.[14] Haemolytic anaemia with thrombocytopaenia, hyperbilirubinaemia and elevation of hepatic enzymes secondary to intravascular haemolysis and hepatic congestion are the common laboratory findings. [7]

Plasmodium falciparum is the predominant specie causing malaria in endemic areas. [10] It is responsible for over 90% of reported cases of neonatal malaria. [14, 26] However mixed infections with *Plasmodium malariae* have been reported. [26] *Plasmodium vivax* has been reported as a cause of neonatal malaria in non-endemic

areas. [7] The parasite density in babies with parasitaemia is generally low even in those that eventually developed clinical symptoms. [3, 9, 14, 26] Though the placenta may not completely prevent transmission of malaria parasites to babies, it significantly reduces the parasite load in an effort to protect the baby. Trophozoites and ring forms of the parasite are the usual stages seen. Schizonts are usually confined to areas of deep tissue schizogony except in heavy infestations in which they may be seen in peripheral blood.

A strong association has been found between congenital malaria, placental and maternal parasitaemia with most infected babies having infected mothers and placentae. [12, 26, 28] The density of parasites identified in foetal blood may indicate the extent to which the placental barrier might have been breached. The mechanisms postulated to explain this include, mechanical damage to the placenta at the time of parturition, [29] acute fever in the pregnant woman resulting in increased friability of the placenta, [29] and premature separation of the placenta.[29] The significance of this association is that maternal and placental malaria could result in premature delivery, [4] low birth weight [4] and symptomatic congenital malaria. [3] These mothers should be treated for malaria in pregnancy and thereafter be placed on an effective chemoprophylactic regimen.

Diagnosis

A high index of suspicion is required and a strong differential diagnosis is neonatal sepsis. In non-endemic areas, history of travel to an endemic area or emigration, in addition to the above listed clinical features is important. In endemic areas, newborns with above clinical features should be investigated for malaria and neonatal sepsis. Congenital malaria is diagnosed when asexual forms of malaria parasites are identified in the peripheral blood of the newborn within 7 days of life. [3, 23] Typically thick and thin films are made and stained with Giemsa, Fields or Leishman's stains. Giemsa stain however remains the gold standard. The parasite density can also be determined by a parasite count. Less commonly antibody detection techniques like the indirect fluorescent antibody techniques and quantitative buffy coat method are used. Antigen detection tests like parasight-F and immuno-chromatographic technique (ICT) that detect histidine rich protein 2 produced by P. falciparum may also be used and are highly sensitive but very expensive.[30] Optima assay is another rapid diagnostic technique, which detects the presence of lactate dehydrogenase produced by the parasites. [30] For research purposes, in cases of low parasite density, polymerase chain reaction and in vitro cultures can be used.

Treatment

There is no standard recommendation regarding the treatment of neonatal malaria. The World Health organization recommends the use of oral chloroquine at a dose of 25mg/kg bodyweight over three days for uncomplicated malaria in children residing in chloroquine sensitive areas, and artemisinin combination therapy in chloroquine resistant areas. Recently there has been a change in the Nigerian National policy on the treatment of malaria recommending artemisinin combination therapy as first line in adults and children because of the high rate of chloroquine resistance in different parts of the country.[31]

There is limited experience in the treatment of neonatal malaria, as most of the reported cases involved a small number of subjects. Thapa and Narang [25] in India treated thirty neonates with oral chloroquine with 85% success rate; Ibhanesebhor [24] treated sixteen neonates with malaria using chloroquine with 75% success rate but had to use quinine in four babies who were resistant to chloroquine. Larkin and Thuma [28] also treated nineteen babies with chloroquine with 79% success rate but had to use sulphodoxine/pyrimethamine for four babies that were resistant to chloroquine. These studies were however done in the late 80's and early 90's and the sensitivity pattern may have changed further. There is also no uniformity in the way chloroquine was used by various authors. Some workers, [23-24,] suggested the use of chloroquine at 5mg/kg/day for five consecutive days while others [3,25] used 10mg/kg/day for two days, and others [26] have used the WHO recommendation for older children. Using the new WHO recommendation for testing efficacy of drugs using adequate clinical and parasitological response, the Nigerian National average of chloroquine sensitivity in 2002 was 39.2%; it is least sensitive in the South East (4.3%) and more sensitive in the North West (77.3%). [31] The national average for sulphodoxine/pyrimethamine sensitivity was 56.7%, lowest in the South East (14.9%) and highest in the North West (94.2%). [31] The WHO has defined any sensitivity level of less than 90% as unacceptable. [31] Several case reports of neonatal malaria involving smaller numbers of babies [3,7,32] have also documented resistance to chloroquine but found quinine and Halofantrine useful. There is little documented experience on the use of artemisinin derivatives and combination therapy in neonates. [33] A case report from India [33] reported clinical and parasitological resistance to chloroquine and quinine in a neonate who subsequently responded to a combination of artemisinin and mefloquine. Oral

artemisinin derivatives have been found to be safe and highly effective in the treatment of resistant falciparum malaria. [34] Artemisinin, artesunate and artemether are well tolerated in both children and adults and they also have an advantage of rectal administration especially in children with difficult intravenous access and in rural areas where less expertise is available. [34]

However, the various classes of antimalarials have not been studied in neonates and therefore as at this time a clear recommendation will be difficult. However from the foregoing review it may be wise to use Quinine as a first line drug. Chloroquine may however be used in combination with another antimalarial in areas of low resistance. Severe malaria in neonates has been reported by Thapa et al [25] and Quinine remains the WHO recommended drug of choice for the treatment of severe malaria. Some authors have recommended that babies with malaria parasitaemia symptomatic or not should be treated to avert clinical malaria in the near future, [9] while others have recommended follow up for these babies and treatment when symptomatic [26] and others have been silent about it. [14] This is basically because most samples were small. However it might be safer to treat such babies until such a time when we have clear guidelines from evidence based studies as these patients are often lost to follow up and can develop clinical malaria as the incubation period of malaria in the newborn may be from less than 1 week to 8 weeks. [7, 25,]

Prevention and control.

For the prevention and control of neonatal malaria, provision of early diagnosis and prompt treatment of the infected mother is essential. The World Health Organisation has recommended provision of intermittent therapy for pregnant women using sulphodoxine/pyrimethamine.[18] Feeding with breast milk is recommended because of its paucity in Para-Amino-Benzoic Acid, which will prevent the growth and multiplication of malaria parasite.[6] During periods of exposure, the newborn should be clothed with only the face exposed. Clothing should be of light cotton material in the tropics. For the prevention of transfusional malaria banked blood should be screened for malaria parasites before transfusion to neonates. [14] Alternately transfused babies should be screened for malaria 48-72 hours after transfusion.

Generally, the WHO [18] has recommended the use of selective and sustainable prevention measures for vector control, through the use of insecticide treated materials, bed nets (ITNs) and curtains, Indoor residual spraying with insecticides along with environmental management. Roll-Back Malaria (RBM) Initiative was launched jointly by WHO, UNICEF, UNDP and World Bank on 30th October 1998 as a bold new effort to mobilize global partnerships including governments, donors, non-governmental organizations (NGOS) and communities, to effectively tackle the increasing global problem of malaria.

It aims at reducing the overall mortality due to malaria by 50% by the year 2010 using a number of evidence based cost effective interventions as recommended by WHO. [18] Since the 2001 Abuja Declaration by African leaders to reduce morbidity and mortality from malaria, significant progress has been made in some countries while other countries like Nigeria are yet to achieve the set goals. A recent survey [35] showed that the proportion of women sleeping under nets in Africa averages 15% with only 2.8% sleeping under ITNs, and the use of sulphodoxine/pyrimethamine in pregnancy averages less than 10% in Africa except in Malawi where it has reached 47%. [35] The proportion of children sleeping under ITNs in endemic countries is still very low ranging 0.1%-38%. [35] However ITNs distribution has recently successfully scaled up in Malawi, Zambia, Rwanda and Eritrea. Togo and Eritrea have achieved the Abuja target of 60% of under-5's sleeping under mosquito nets and ITNs. Malawi has also made significant progress with 38% of under-5's sleeping under ITNs. Sadly only 1.2% of under-5 children sleep under ITNs in Nigeria.[35]

Conclusion

Neonatal malaria is no longer a rare entity in malaria endemic areas, and the physician must have a high index of suspicion, as the clinical signs of malaria are non-specific and very similar to those of neonatal bacterial infections. There are however a number of grey areas in the diagnosis and management of neonates with malaria. There is need for continuing research in this area. The pharmacokinetics and pharmacodynamics of antimalarials in neonates should be studied, in order to choose and formulate correctly the right dose and schedule of treatment.

It is recommended that babies presenting with features of neonatal sepsis in endemic areas and babies born to mothers that had malaria in pregnancy should also be screened for malaria as a routine practice, and if malaria parasites are found in them they should be treated for neonatal malaria. A treatment policy and protocol on the management of neonatal malaria should be put in place.

References

1. Covell G. Congenital malaria. Trop Dis Bulletin 1950; 47: 1147-65.
2. Bruce-Chwatt L J. Malaria in African infants and children in Southern Nigeria. Ann Trop Med Parasitol 1952; 46: 173-175.
3. McGregor FA. Congenitally acquired malaria. Postgrad Doctor Afr 1986; 8: 52-54.
4. Jellife E F. Low birth weight and malaria infection of the placenta. Bull World Health Org 1968; 38: 69-78.
5. McGregor FA, Wilson MME, Billewicz WZ. Malaria infection of the placenta in the Gambia, West Africa. It's incidence and relationship to stillbirth, birth weight and placental weight. Trans R Soc Trop Med Hyg 1983; 77: 232-44.
6. Marsh K. Immunology of Human malaria In: Gilles HM and Warrel DA (eds) 4th edition. Essential Malariology. London: Edward Arnold (Publishers) Ltd; 1993; 60-77.
7. Quinn TC, Richard FJ, Gregory JM et al. Congenital malaria a report of four cases and a review. J paediatr 1982; 101(2): 229-32.
8. Egwuyenga OA, Ajayi JA, Popova-Dahlinska DD, Nmorsi OP. Malaria Infection of the cord and birth weights in Nigerians. Cent Afr J Med 1996; 42;(9): 265-268.
9. Akindele JA, Sowunmi A, Abohweyere AE. Congenital malaria in a hyperedemic area; a preliminary study. Ann Trop Pediatr 1993; 13: 273-276.
10. White NJ. Malaria. In: Cook GG (ed.) Manson's Tropical Diseases 20th edition. London. Edward Arnold. 1998; 1087-1164
11. Ezeoke ACJ, Ibanga NJ, Braide EI. Congenital malaria at University of Calabar Teaching Hospital, with reference to haemoglobin and immunoglobin. Cent Afr J Med 1985; 31: 241-247.
12. Obiajunwa PO, Owa JA, Adeodu OO. Prevalence of congenital malaria in ile- ife Nigeria. J trop Pediatr 2005; 51(4): 219-22.
13. Nahlen BI, Akintunde A, Alakija TI. Lack of efficiency of Pyrimethamine prophylaxis in pregnant Nigerian women. Lancet 1989; (ii): 830-834.
14. Ibhanesebhor SE. Clinical characteristics of neonatal malaria. Trop Paediatr 1995; 41(6): 330-333.
15. Ogala WN. Malaria. In: Azubuike JC, Nkanginieme KEO (eds.) Paediatrics and Child Health in a Tropical Region 1st edition. Nigeria. African Educational Services 1991; 426-437.
16. Kimberly C, Brouwer A, Altaf A, et al. Polymorphism of Fc receptor IIa for Immunoglobulin G is associated with placental malaria in HIV-1-positive women in western Kenya. Journal of Infectious Diseases 2004; 190:1192-8.
17. Current global malaria situation. WHO Expert Committee on malaria. WHO Technical Report Series 2000; 892: 3-12.
18. Malaria Prevention and Treatment. The Prescriber, UNICEF publication 2000; 18:1-16.
19. WHO: Health and the Millennium Development Goals. http://www.who.int/mdg/goals/en/ WHO 2006. Source WHO Department of MDGS Health and Development Policy. Downloaded 3rd October 2006.
20. Childhood Under Threat. The State Of The World's Children. United Nations Children's Fund. Geneva 2005:115.
21. Dormstadt GL, Bhutto ZA, Cousens S, Adam T, Walter N, Bernis L. Neonatal survival series 2. Evidence based cost effective interventions: how many newborns can we save? Published online March 2005. Http//image.thelancet.com/extras/05art1217web .pdf.
22. Lawn JE, Cousens S, Zupan J. Neonatal survival series 1. 4 million neonatal deaths: when? Where? Why? Published online March 2005. Http//image.thelancet.com/extras/05art1217web .pdf.
23. Sodeinde O, Dawodu AH. Neonatal transfusional malaria: A growing clinical problem. Nig J Paediatr 1985; 12: 57-60.
24. Ibhanesebhor SE. Clinical characteristics of neonatal malaria. Trop Paediatr 1995; 41(6): 330-333.
25. Thapa BR, Narang A, Bhakoo ON. Neonatal malaria: a clinical study of neonatal and transfusional malaria. J Trop Peadiatr 1987; 33:266-269.
26. Mukhtar MY, Lesi FEA, Iroha EU, Egri-okwaji MTC, Mafe AG. Congenital malaria among inborn babies at a tertiary centre in Lagos, Nigeria. J Trop Paediatr: 2006; 52: 19-23.
27. Nyirjesy P, Kasasiya T, Axelord P. Malaria during pregnancy; Neonatal morbidity and mortality and the efficacy of chloroquine chemoprophylaxis. Clin Infec Dis 1993; 16 (1): 127-32.

28. Larkin GL, Thuma PE. Congenital malaria in a hyperendemic area. Am J trop Med Hyg 1991; 45 (5): 587-92.
29. Wicramasuriya GAW. Some observations on malaria occurring in association with pregnancy with special reference to transplancetal passage of parasites from maternal to foetal circulation. J. Obstet Gynaecol 1935; 42: 816-34.
30. Salako. Malaria in Nigeria. Lecture delivered at 31st Annual scientific conference of Paediatric Association of Nigeria 2000: 19-20.
31. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. WHO, 2003. (WHO/HTM/RBM/2003:50).
32. Airede L. Congenital malaria with Chloroquine resistance. Ann Trop Paediatr 1991; 13(3): 273-6.
33. Archana BP, Hrishikesh SB. Resistant malaria in a neonate. Indian paediatrics 2002:39:585-588.
34. Price R, Luxemberger C, van Vugt M, Nosten F, Kham A, Simpson J, et al. Artesunate and mefloquine in the treatment of uncomplicated multidrug-resistant hyperparasitemic falciparum malaria. Trans R Trop Med Hyg 1998; 92: 207-211.
35. Special session of the African union on HIV/AIDS, TB & Malaria. http://www.africa-union.org. Abuja May; 2006: 23-28.