Factors Associated with Decreased Survival from Neonatal Malaria Infection in Jos, North Central Nigeria

1.Christopher S. Yilgwan MBBS,FWACP, 2.Hyacinth I. Hyacinth MBBS, 1.Stephen Oguche MBBS, FMCPaed

1.Department of Paediatrics University of Jos/Jos University Teaching Hospital, Jos Nigeria; yilgwan@yahoo.com
2. Genomics and Hemoglobinopathy training program Department of Microbiology, Immunology, Biochemistry, Morehouse School of Medicine, Atlanta Georgia, USA

ABSTRACT

BACKGROUND: Malaria is a serious cause of morbidity and mortality in the neonatal period and account for a significant number of fetal wastage. Its diagnosis is difficult because of the overlap in clinical presentation with other infectious disease in the neonatal period. This study set out to examine the factors that are associated with an increased risk of mortality in neonates admitted with malaria.

METHOD: Forty one neonates presenting between January and June 2009 were enrolled after obtaining ethical approval and informed consent from the mothers. Information collected include gestational age, age at presentation, birth weight, clinical symptoms, associated medical conditions and pertinent pregnancy history.

RESULTS: Of the 41 neonates studied, 24(58.5%) were females, 29(70.5%) were term neonates and 12(29.3%) had low birth weight. Overall mortality was 24.4%, more male neonates (70%) had malaria compared to females (50.0%) and neonatal malaria was associated with a longer hospital stay ($p<0.001$). Female neonates (RR=0.81, CI=0.69 0.95), neonatal malaria (RR=0.63, CI=0.54 0.73) and maternal negative HIV status (RR=0.22, CI=0.15 0.32) was associated with lower risk of mortality. Whereas, multiple symptoms at presentation (RR=1.67, CI=1.42 1.96), multiple medical conditions (RR=1.59, CI=1.37 1.84) and maternal malaria in pregnancy (RR=1.54, CI=1.23 1.29) were associated with increased risk of mortality. Maternal IPT use, gestational age and birth weight did not have any statistically significant relationship with mortality.

CONCLUSION: Neonatal malaria is a significant cause of neonatal mortality; the risk of which is higher with the presence of other co-morbid factors. We suggest a review of the IPT program and the introduction of maternal malaria screening at time of delivery.

INTRODUCTION

Malaria continues to be a serious public health problem in the world and more so in tropical countries, affecting more than 2.4 billion people worldwide.1 In Africa, malaria is responsible for an estimated 1 million "under five" deaths annually,1, 2 with about 500 700 children dying from malaria daily in Nigeria3. In Jos which is located in the North Central part of Nigeria, malaria ranks among the top three cause of mortality among children visiting the emergency paediatrics units of a tertiary hospital.4 Malaria in the neonate has been thought of as a rare condition5, 6 probably because of some intra-uterine, extra-uterine and neonatal/foetal factors thought to serve a "protective function", thus reducing their risk of being infected or developing the disease.7-10 Contrary to prior assertion,5, 9 the situation with malaria in the neonatal period is getting worse.11

It has been suggested by several investigators, that maternal third trimester malaria infection is a very strong risk factor for developing malaria and death in the neonatal period.10, 12-14 Fatality from neonatal malaria is related to the fact that their presentation is not different from that of other neonatal problems like sepsis, a situation that is worsened by the fact that some neonates have atypical presentations of neonatal malaria.15-20 The difficulty with making a diagnosis of neonatal malaria has been thought to be due to inconsistencies in the results reported from the available samples for testing.14 This difficulty in diagnosis is also thought to contribute to the morbidity and mortality associated with this form of malaria.14 Thus it was suggested that the diagnosis of neonatal malaria need to be considered in critically ill neonates with fever that is unresponsive to antibiotics in spite of a positive history of maternal use of the intermittent preventive treatment 15. This is especially so as Thapa et al reported that the same complications and fatalities seen in older children with malaria were also observed in the neonates.13

There have been several case reports and also some report of prevalence of neonatal malaria with little reports on the mortality associated with neonatal malaria. Also, little to nothing has been said about how other clinical conditions and presentations co-existing with malaria could modify perinatal mortality associated with neonatal malaria. It is against this backdrop that we are carrying out this study at the Special Care Baby Unit (aka Neonatal Intensive Care Unit) where neonates are cared for at our facility.

MATERIALS AND METHOD

This is a prospective study conducted at the Special Care Baby Unit (SCBU) i.e. Neonatal Intensive Care Unit of the Jos University Teaching Hospital (JUTH); a 500-bed

Correspondence to: Christopher S. Yilgwan, Department of Paediatrics University of Jos/Jos University Teaching Hospital, Jos Nigeria yilgwan@hotmail.com or yilgwanc@unijos.edu.ng

tertiary Hospital in North Central Nigeria with a referral area spanning 6 of Nigeria's 36 states. It serves both as a secondary and a tertiary centre because of its peculiar location and affordability to both the rich and poor. JUTH is a training centre in neonatology for resident doctors in paediatrics, obstetrics and gynaecology, medical students as well nurses in midwifery and intensive care. The unit cares for all preterm babies especially those that have low birth weight (LBW) and very sick term neonates. For the purpose of this study and ease of data analysis the following definitions were used: Normal weight infant as one whose birth weight is 2,500 grams and above, Low birth weight infant (LBW) as an infant whose birth weight is <2500 grams, Preterm as an infant whose gestational age is less than thirty seven completed weeks. Also, congenital malaria was defined as any neonate with microscopy confirmed malaria in the first 7 days of life while neonatal malaria was taken as malaria confirmed after the first 7 days of life. 11

All infants seen from January 2009 to June 2009 in the SCBU were considered for recruitment. This period covers the last three and first three months of the dry and rainy season respectively and is the period before peak malaria transmission which in Jos is usually between July and August4. Parental consent was sought for and obtained prior to inclusion in the study, while ethical approval was obtained from the Jos University Teaching Hospital ethical committee.

The maturity of these infants was determined, based on Dubowitz method. Each baby was weighed unclothed using an electronic scale (BabyWeight™ MedelaR Inc. model no. 040.7012).

Pertinent pregnancy history was obtained from the mothers, while maternal HIV status, malaria diagnosis (using microscopic Giemsa stain examination) and use of intermittent preventive treatment of malaria in pregnancy (index pregnancy) was documented from the pre-natal clinic record. It is the practice in our institution to screen and treat all mothers with malaria in pregnancy. As part of the investigations for evaluation of sick neonates admitted into the unit, thick and thin blood films were made for malaria parasite identification and quantification. The films were fixed and stained using 4% Giemsa stain for thirty minutes. The stain was washed off in tap water and the dried slides examined under X100 magnification with oil immersion lens for malaria parasite. Blood samples were also sent for complete blood count and culture and sensitivity studies to exclude or confirm other co-morbidities.

STATISTICS

The data was analyzed using SPSS 18/PASW for statistical test of associations, while relative risk and odds ratios were estimated using Epiinfo StatCalc. A p-value of <0.05 was set as indicating a statistically significant result; which are presented in the tables below.

RESULTS

A total of 41 neonates were recruited for this study. All of which had a positive malaria parasitaemia (This was the selection criteria for participation).Table I shows the mean and standard deviation, of some of the major clinical characteristic of the neonates enrolled into the study and admitted at the SCBU during the six months period of this study. There were a total of 17(41.5%) males and 24(58.5) females. Twelve patients (29.3%) were born pre-term (<37 weeks gestation) while 29(70.7%) were termed (=37 weeks) gestation. Twenty nine (70.7%) had normal birth weight (=2.50kg), while 12 patients (29.3%) had low birth weight. Using the data from table II, the mortality among this study sample was 24.4% or 244/1000, meaning that 10 out the total 41 or approximately 1:4 neonates died.

Table I. Shows clinical and birth characteristics of the neonates

Characteristics	Mean	SD
Gestational Age (weeks)	36.22	3.76
Age (days)	5.88	4.52
Birth weight (kg)	2.54	0.64
Duration of hospitalization (days)	3.07	2.23

Table II. Frequency and percentage distribution of admitting features and mortality for all the neonates

Feature	Frequency	Percentage
Sex		
Male	17	41.5
Female	24	58.5
Gestational age at delivery		
Term	29	70.7
Preterm	12	29.3
Birth weight distribution		
LBW	12	29.3
NBW[1]	29	70.7
Associated medical problems		
No	7	17.1
Yes	33	80.5
Multiple symptoms		
No	16	39.0
Yes	25	61.0
Nutritional deficiency related presentation	30	73.2
No	11	26.8
Yes		
Outcome		
Alive	31	75.6
Died	10	24.4

A stratified analysis was done, comparing the demographic characteristics, elements from the pregnancy history and outcome of neonates with and without neonatal malaria. Table III shows that neonates whose mothers were not on IPT were more likely to develop neonatal malaria (75.0%) compared to those whose mother were on IPT (25.0%). Although little conclusion can be made based on it, but our result

showed that there twice as many neonates whose mothers were HIV positive in the group without malaria compared to the groups with malaria. Also this table shows that 1 in 3 i.e. 33% of neonates with a HIV positive mother developed neonatal malaria compared to 23 (60.5%) of the neonates with a HIV negative mother. The proportion of males that developed neonatal malaria was much higher than females i.e. 70.6% compared to 50.0%, while the mortality between the two groups was essentially the same.

As seen in table III, the average gestational age was lower for the group with neonatal malaria compare to those without neonatal malaria. The same is seen with the average age at presentation; those neonates with malaria presented at a slightly younger age 6.17±4.98 days compared to 5.47±3.89. While there is almost no difference in the average birth weight of the neonates with malaria compared to neonates without malaria, on the other hand those with malaria appears to have a greater morbidity as evidenced by a longer hospital stay 3.17±0.40 compared to 0.18±0.18, for neonates without malaria p<0.001.

The next set of analysis represented by table IV, compared how the various clinical variables modify

Table III. Comparison of some characteristics between neonates with and without malaria *n*(%)

Characteristics	With Malaria (*n*=24)	No Malaria (*n*=17)	Odds Ratio	Confidence Interval	*P-value*
Maternal IPT during index pregnancy					
Yes	18(54.5)	15(45.5)	0.41	0.21 – 0.77	0.003
No	6(75.0)	2(25.0)			
Maternal HIV status					
Positive	1(33.3)	2(66.7)	0.23	0.12 – 0.45	
Negative	23(60.5)	15(29.5)			<0.001
Sex					
Male	12(70.6)	5(29.4)	2.45	1.31 – 4.59	0.002
Female	12(50.0)	12(50.0)			
Outcome					
Alive	18(58.1)	13(41.9)	0.92	0.52 - 1.68	0.770
Died	6(60.0)	4(40.0)			
Average gestational age (weeks)[1]	36.88(3.71)	37.35(3.82)			0.697
Average Birth weight (kg)[1]	2.513(0.653)	2.582(0.628)			0.736
Average weight presentation (days)[1]	6.17(4.98)	5.47(3.89)			0.633
Average duration of treatment (days)[2]	3.71(0.40)	0.18(0.18)			<0.001

[1] Mean(SD) [2] Mean(SEM) SEM = Standard Error of Mean

mortality in the group of neonates with neonatal malaria. In Table IV, proportionally more females survived than males (RR=0.81, CI=0.69 0.95), maternal IPT use was not associated with improved survival from neonatal malaria (RR=0.86, CI=0.72 1.02), although it did confer a marginal survival advantage. Neonates presenting with other symptoms like seizures etc, had a higher risk of mortality compared to those presenting with fever as the only presenting symptom (RR=1.67, CI=1.42 1.96). Presence of malnutrition causing or malnutrition related symptoms (defined as poor suck, poor weight gain and or weight loss) was not associated with increased risk of mortality, while the presence of associated medical conditions such as neonatal sepsis, birth asphyxia, anaemia, etc in addition to a diagnosis of neonatal malaria was associated with increased risk of mortality (RR=1.59, CI=1.37 1.84). Another important risk of mortality that was noted from our data was the type of malaria, i.e. congenital versus acquired neonatal malaria. Neonates presenting with acquired neonatal malaria had a lower risk of mortality (RR=0.63, CI= 0.54 0.73) compared to those neonates presenting with congenital malaria. On the other hand, gestational age at term and birth weight did not have any statistically significant effect on mortality (RR=1.06, CI=0.91 1.26 and RR=1.00, CI=0.61 1.63) respectively. Maternal HIV status and maternal malaria infection in the index pregnancy had statistically significant effect on the risk of mortality in the neonate with neonatal malaria. Among our population, there was a lower risk of mortality (RR=0.22, CI=0.15 0.32) among neonates with malaria whose mother's HIV status was negative compared to those whose mother's HIV status was positive. Similarly, neonates with malaria and a positive maternal history of malaria in pregnancy had a higher risk of mortality (RR=1.54, CI=1.23 1.93) as shown in table IV, compared to those with a negative maternal history of malaria in pregnancy (referring to the index pregnancy in both cases).

Table IV. Relative risk of mortality associated with the clinical and demographic factors among neonates with malaria (*n*=24)

Factor	Frequency (%)		RR	95% CI	*p-value*
	alive	died			
Sex					
Male	8(66.7)	4(33.3)	0.81	0.69 – 0.95	0.009
Female	10(83.3)	2(16.7)			
Maternal IPT use during index pregnancy					
No	4(66.7)	2(33.3)	0.86	0.72 – 1.02	0.08
Yes	14(77.8)	4(22.2)			
Presenting symptoms					
Fever only	9(100.0)	0(0.0)	1.67	1.42 – 1.96	<0.001
Fever plus other symptoms	9(60.0)	6(40.0)			
Presence of malnutrition causing symptom					
No	12(70.6)	5(29.4)	0.83	0.71 – 0.96	0.01
Yes	6(85.7)	1(14.3)			
Associated medical problems					
No	8(100.0)	0(0.0)	1.59	1.37 – 1.84	<0.001
Yes	10(62.5)	6(37.5)			
Malaria type					
Congenital	11(62.5)	6(37.5)	0.63	0.54 – 0.73	<0.001
Neonatal	7(100.0)	0(0.0)			
Gestational age at delivery					
Term	13(76.5)	4(23.5)	1.07	0.91 – 1.26	0.42
Preterm	5(71.4)	2(28.6)			
Birth weight					
NBW[1]	12(75.7)	4(25.3)	1.00	0.61 – 1.63	0.68
LBW	6(75.0)	2(25.0)			
Maternal HIV status					
Negative	18(78.3)	5(21.7)	0.22	0.15 – 0.32	<0.001
Positive	0(0.0)	1(100.0)			
Maternal malaria infection in pregnancy					
No	17(77.3)	5(22.7)	1.54	1.23 – 1.93	<0.001
Yes	1(50.0)	1(50.0)			

DISCUSSION

Neonatal mortality rate is very high in Nigeria in general and the situation is made worse by the surging incidence of neonatal malaria.11, 21, 22 The incidence of neonatal malaria (580/1000) and mortality (244/1000) from our study is higher than what has been reported.23 Despite the fact that we carried out this study during the period of less than peak malaria transmission.4 Contrary to what has been published, there was no statically significant difference in the average gestational age and birth weight between neonates with and without neonatal malaria despite the fact that more than two-thirds of the neonates with malaria had congenital malaria which has been documented as a cause of low birth weight and prematurity.5, 10, 24

To our knowledge, there has been little report14 on the impact of maternal HIV infection and/or malaria infection on mortality from neonatal malaria. With regards to maternal malaria infection and perinatal death, there is little consensus on the relationship between the two5,25. But our data showed that these two factors had significant impact mortality, with maternal HIV infection producing a 100% mortality rate in this case. Among the neonates with neonatal malaria, one was the baby of a HIV positive mother was had highly active antiretroviral therapy (HAART). This baby also happens to be among the mortality. Subsequent investigation showed that the child had similar presentations to the other neonates with malaria and the only variable different for this neonate was the maternal HIV status as the level of parasitaemia was also very mild compared to the other neonates. Thus this risk factor is significant as it was also associated with a 50% mortality among the neonates without malaria. Also our data supports the report that maternal third trimester malaria infection is a strong risk factor for neonatal malaria13, 14, 16 and also agrees with the findings of Nyirjesy et al, who reported that maternal malaria infection in pregnancy increases the risk (RR=12.4) of perinatal mortality.14

It is worth mentioning that there was no statistically significant difference in mortality between neonates with and without malaria although the former had a higher morbidity evidenced by longer hospital stay. Although the use of the IPT has been criticized by some as one of the factors responsible for increase in the incidence of neonatal malaria25 because it "robs the mother of exposure which enables them to form antibody which can be transferred to the neonate transplacentally". But our data suggest that IPT decrease the risk of neonatal malaria and also decreased the risk of perinatal mortality. This finding is also supported by the study from Zaire14 which made a similar observation. It is worth noting, that despite being offered free in our centre in order to prevent malaria in pregnancy, the uptake of IPT is still only about 80% as shown by our study. This is a serious cause for concern considering the mortality associated with malaria in the mother and in the unborn child and subsequently the neonate.1 Interestingly, a lower proportion of neonates with a HIV positive mother had neonatal malaria 33.3% versus 60.5% for those whose mother had a HIV negative status. Further analysis showed that all the mothers with a HIV positive status were on IPT; this may explain our observation of a lower malaria incidence among their neonates (table III). It is also worth mentioning that the fact that some of the patients mother on IPT developed neonatal malaria and had fatalities from it underscores the need to review the way the program is operated or probably increase in the frequency of administration of IPT as is done for women with a positive HIV status. Thus education about and aggressive use of this approach need to be pursued to ensure that uptake is as close to 100% as possible; helping to achieve goal number four(4) of the Millennium Development Goals (MDGs).

The policy of screening every pregnant woman for HIV instituted at the Jos University Teaching hospital has made it possible to know for certain the HIV status of the mother and thus institute management modalities to reduce vertical transmission. But the same cannot be said of malaria infection because apart from the IPT program which is just a chemo-prophylactic modality, there no concerted effort aimed determining maternal malaria status at the time of delivery or the immediate postpartum period, neither are neonates routinely screened for malaria after delivery even in a hospital setting. Both approaches could lower the incidence of neonatal malaria.

Finally, we note that our data revealed that certain factors co-existing with neonatal malaria increases the risk for mortality and as such, where these factors exist, the need for prompt and aggressive management should be emphasized to reduce the risk of heightened mortality. Many neonates present with conditions other than malaria and usually are very ill from such co-existing medical condition, thus making it less likely that any attention will be paid to the possibility of neonatal malaria being the reason for the debilitating state of the neonate. It is thus suggested by some14, 15, 26 and by the results of this study that any critically ill neonate presenting with a fever should have a test for malaria parasite done even in regions where malaria has been "eradicated".

CONCLUSION

The findings from this study is striking and thought provoking, but there is need to interpret our findings with caution because of the small sample size. Our data alludes to the fact that neonatal malaria still remain a significant cause of neonatal mortality; ruling out malaria infection in neonates born in malaria endemic

areas especially when they have multiple medical conditions (because of the higher mortality we have seen to be associated) needs to be considered. Finally, maternal malaria testing at time of delivery and a more aggressive approach to the IPT program is needed in order to reduce the incidence of neonatal malaria , its associated mortality and overall the infant mortality rate.

ACKNOWLEDGENT
The staffs of the Jos University Teaching Hospital and Special Care Baby Unit (SCBU or NICU).

This work was supported in part by; NIH/NHLBI-R21HL092358 (to J.M.H).

REFERENCES

1. World Health Organization expert committee on malaria. Current global Malaria situation: World Health Organization; 2000.
2. United Nations Children's Fund (UNICEF). Malaria prevention and teatment. The Prescriber: A United Nations Children's Fund (UNICEF) Publication 2000;18:1 - 16.
3. Health and Millennium Development Goals. World Health Organization Department of MDGs Health and Development Policy, 2006. (Accessed 3rd October, 2006, at http:// www. Who. Int/ mdg/ goals/en/.)
4. Oguche S, Bode-Thomas F, Hyacinth HI, Toma BO , Okupe S, Ebonyi A. The triple scourge of HIV/AIDS, tuberculosis and malaria are the leading cause of morbidity and mortality in the Emergency Paediatrics Unit in North Central Nigeria. Int'l J Mal Trop Dis. 2009;5:256-63.
5. Covell G. Congenital malaria. Trop Dis Bull. 1950;47:1147 - 65.
6. Bruce-Chwatt LJ. Malaria in African children in Sounthern Nigeria. Ann Trop Paediatr. 1952;46:173 - 5.
7. Jellife EF. Low birth weight and malaria infection of the placenta. Bull WHO. 1968;38:69 - 78.
8. Marsh K. Immunology of human malaria. In: Gilles HM, Warrel DA, eds. Essential Malariology. 4 ed. London: Edward Arnolds (Publishers) Ltd; 1993:60 - 77.
9. McGregor FA. Congenitally acquired malaria. Postgrad Doc Afr. 1986;8:52 - 4.
10. McGregor FA, Wilson MME, Belliwicz WZ. Malaria infection of the placenta in the Gambia, West Africa. Its incidence and relationship to stillbirth, birth weight and placenta weight. Trans R Soc Trop Med Hyg. 1983;77:232 - 44.
11. Mukhtar M. The growing incidence of neonatal malaria--a situational review in developing countries. Nig J Med. 2007;16:25-30.
12. Ibhanesebhor SE, Okolo AA. Placental malaria and pregnancy outcome. Int'l J Gyn Obst: 1992;37:247-52.
13. Thapa BR, Narang A, Bhakoo ON. Neonatal Malaria: a Clinical Study of Congenital and Transfusional Malaria. J Trop Paediatr. 1987;33:266-8.
14. Nyirjesy P, Kavasya T, Axelrod P, Fischer PR. Malaria during pregnancy: neonatal morbidity and mortality and efficacy of chloroquine chemoprophylaxis. Clin Infect Dis. 1993;16:127 - 32.
15. Ibhanesebhor SE. Clinical Characteristics of Neonatal Malaria. J Trop Paediatr. 1995;41:330-3.
16. Singh T. Neonatal malaria. Indian Pediatr. 1985;22:785 -6.
17. Krishnamurthy BJ, Niketan ST. Hemolytic anemia in neonatal malaria. Indian Pediatr. 1986;23:95 - 6.
18. Davenport M. Neonatal malaria and obstructive jaundice. Arc Dis Child. 1986;61:515 - 7.
19. Kesaree N, Banapurmath CR, Krishnamurthy SN, Prasad S. Neonatal Malaria. Indian Pediatr. 1981;18:352 - 4.
20. Patwari A, Aneja S, Berry AM, Ghosh S. Neonatal malaria - A clinico-hematologic profile. Indian Pediatr. 1978;15:847 - 9.
21. Aribodor DN, NwaorguOC, Eneanya CI, Okoli I, Pukkila-Worley R and Etaga HO. Association of low birth weight and placental malarial infection in Nigeria. J Infect Dev Ctries 2009; 3(8):620-623.
21. Mukhtar MY, Lesi FEA, Iroha EU, Egri-Okwaji MTC, Mafe AG. Congenital malaria among inborn babies at a tertiary center in Lagos, Nigeria. J Trop Pediatr. 2006;52:19 - 23.
22. Njokanma OF, Olanrewaju DM. A study of neonatal deaths at the Ogun State University Teaching Hospital, Sagamu, Nigeria. J Trop Med Hyg. 1995;98:155-60.
23. Ogala WN. Malaria. In: Azubuike JC, Nkanginieme KEO, eds. Pediatrics and Child Health in a Tropical Region. 1st ed. Enugu: African Educational Services; 1991:426 - 37.
24. Logie DE, McGregor IA. Acute malaria in newborn infants. B M J;1970:3:404.
25. Ibhanesebhor SE, Okolo AA. Malaria parasitaemia in neonates with predisposing risk factors for neonatal sepsis: Report of six cases. Ann Trop Paediatr. 1992;12:297-302.