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Original Article

Risk Factors and Clinical Features of Malaria Among Newborns With Fever In Federal Teaching Hospital Gombe: A Cross-Sectional Study

Yasangra Rabo Adeniji[1], Iliya Jalo[1], Ikechukwu Okonkwo[2], Hassan Kamiludeen Shina[1] Mercy Raymond Poksireni[1], Yakubu Mohammed Yakubu[3]

1.Department of Paediatrics, Federal Teaching Hospital Gombe, Gombe State Nigeria. 2. Department of Child Health, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria. 3. Department of Medical Microbiology, University of Maiduguri Teaching Hospital, Borno State

Corresponding author: Yasangra Rabo Adeniji, Department of Paediatrics, Federal Teaching Hospital Gombe, Gombe State Nigeria. yasangra@yahoo.com

ABSTRACT

Introduction: Malaria is a cause of fever in the neonatal period especially in malaria-endemic regions and it is important to recognize and treat it early. We set out to document the risk factors, clinical features and outcome in subjects with neonatal malaria in our setting

Methods: We conducted a prospective, cross-sectional study in which 131 newborns with fever were recruited. Malaria diagnosis was by use of direct microscopy following Giemsa staining. Maternal and newborn characteristics were documented. Data analysis was done using SPSS version 24 and p-value was considered significant when less than 0.05.

Results: A history of malaria in the mother regardless of the gestational age of occurrence, prematurity, Packed cell volume(PCV) less than 45, jaundice and a history of transfusion were significantly associated with malaria in the newborn. More deaths were recorded in newborns with malaria however the difference was not statistically significant.

Conclusion: Clinicians should have a heightened index of suspicion for malaria in neonates who present with fever and the features mentioned above in malaria-endemic regions.

KEYWORDS: Perinatal, Maternal, Mortality, Neonatal

INTRODUCTION

The burden of neonatal malaria was thought to be low previously however emerging evidence points to the contrary[1–3]. Studies in Kenya[4] and Ghana[5] reported congenital malaria prevalence of 0.35% and 2.2% respectively[5,6]. In Nigeria values range from 5.1% to 58.5%.[7–14] Neonatal death attributable to malaria has also been documented to be as high as 25% [15]. Therefore it is important to detect and treat malaria in the newborn early enough to prevent morbidity and mortality.

Prevalence rates for malaria parasitaemia in neonates appear to be higher in those with fever (as high as 80%) and in studies that include both term and pre-terms [7,9]. Some risk factors have been documented in the literature such as maternal and placental parasitaemia specifically for congenital malaria[2,14]. Runsewe-Abiodun *et al* documented that sex, place of delivery or gestational age at delivery did not affect occurrence however a history of malaria/febrile illness in the mother within the two weeks before delivery was noted as an important factor[12].

Malaria in the neonate has no specific features, however fever has been said to be the characteristic manifestation of neonatal malaria and can be seen in as high as 100% [2,3]. While some authors have documented low birth weights, others did not find a significant difference in weight when comparing neonates with and those without congenital malaria [2,16]. Anaemia is a common feature of malaria in neonates and ranges from 15.7%-100% [17, 15,18]. Jaundice appears to have a relatively consistent frequency (22-27%) regardless of the form of

neonatal malaria [15,17,19] Other features include poor suck, irritability, respiratory difficulty, diarrhoea and seizures. Less common features are disseminated intravascular coagulopathy and cyanosis[12,15,17,19]. Mortality in neonates with malaria was found to be as high as 25% by Hyacinth et al in Jos [15] and a similar rate of 27% by Mwaniki in Kenya.[5] However, Khichi et al mortality rates for congenital and acquired neonatal malaria were 16.66% and 13.33% respectively [16].

There is paucity of data on neonatal malaria in the North East sub-region and prevalence rates in other regions may not be applicable due to geographic variations and endemicity. Therefore, we set out to document the risk factors, clinical features of malaria amongst newborns with fever in our facility, and the clinical outcome.

MATERIALS AND METHODS

Setting

We conducted this study in the neonatal unit of Federal Teaching Hospital Gombe (FTHG) from March to June 2020. The hospital is a tertiary facility that offers postgraduate training in Paediatrics as well as other specialities. The newborn Unit is manned by consultant paediatricians, resident doctors, interns, nurses as well as support staff. It is a 32-bed unit with an average admission rate of 60 babies every month.

Study Design

This cross-sectional descriptive study determined its sample size using the Fischer formula for minimum sample size estimation in cross-sectional studies. The prevalence rate of neonatal malaria in sick neonates (8.25%) as reported by Orogade et al. was utilized, given the similarity in facility type, newborn age range, and geographic location. The study applied a confidence limit of 95%, and a margin of error of 5%. We added 10% of the minimum sample size to account for incomplete/missing data; the total number was 128.

Study Population

This comprised neonates from the first to twenty-eight days of life with fever (an axillary temperature ≥ 37.5 degrees Celsius using a digital thermometer).

Inclusion Criteria: Newborns with fever whose parents consented to the study*:*

Exclusion Criteria: Those who had received antimalaria treatment before presentation.

Data Collection Methods

All newborns who met the inclusion criteria were recruited consecutively until the desired sample size was met. A proforma designed for the study was used to document sociodemographic /clinical parameters of the subjects. We collected blood samples using standard technique within 30 minutes of subject recruitment[20] from which thick and thin blood films were made, Giemsa staining was done according to WHO standard.[20] The slides were viewed using the LEICA DM500® microscope manufactured by Leica Microsystems Switzerland. The thin film was used to identify the species while the thick film was used to calculate the parasite density. We assumed a white blood cell count of 8000/l and the number of parasites per 200 white blood cells was used to calculate the parasite density per microlitre. Slides were considered negative when no parasite was seen after viewing 100 high-power fields[21] We noted the absolute number of parasites and subsequently used the plus system of grading parasite density.[22]

Data Analysis

This was done using SPSS version 24. Chi-square test was used to test the relationship between categorical variables. A p-value less than 0.05 was considered to be statistically significant. Results were presented in tables and charts.

Ethical Consideration

Ethical approval was obtained from the ethics and research review committee of the hospital. The researchers bore all financial costs. Subjects who had malaria were treated and those who did not were evaluated and managed based on their clinical presentation. No identifying information was used to ensure confidentiality.

RESULTS

We studied 131 newborns, from the first to the 28th day of life. There was a male preponderance with a male-to-female ratio of 1.9:1. Most neonates, 81 (61.8%), were born within the facility (inborn) while the remaining were referrals. The median age was 4.0 days, with an interquartile range of 4 days. The prevalence of malaria in the study population was 59.5% (78/131) and all cases were due to *Plasmodium falciparum*.

Table 1: Relationship Between Sociodemographic Characteristics with Malaria Parasitaemia

Variable	Mp+ n=78 Frequency (%)	Mp – n=53 Frequency (%)	p value
Age(days)			
1-7	67(67.0)	33(33.0)	0.078
>7	11(35.5)	20(64.5)	
Gender			
Male	51(58.6)	36(41.4)	0.763
Female	27(61.4)	17(38.6)	
Place of birth			
FTHG	49(60.5)	32(39.5)	0.393
SSHG	2(33.3)	4(66.7)	
PHC	20(60.6)	13(39.4)	
Private facility	3(100)	0(0.00)	
Home	4(50.0)	4(50.0)	
Ethnic group			
Fulani	24(63.2)	14(36.8)	0.810
Hausa	17(65.4)	9(34.6)	
Tera	7(63.6)	4(36.4)	
Tangale	5(50.0)	5(50.0)	
Igbo	4(50.0)	4(50.0)	
Waja	3(42.9)	4(57.1)	
Others[α]	16(55.2)	13(48.4)	
Religion			
Islam	54(58.7)	38(41.3)	0.762
Christianity	24(61.5)	15(38.5)	
Social class			
Low	20(55.6)	16(44.4)	0.072
Middle	18(47.4)	20(52.6)	
High	40(70.2)	17(29.8)	

α (Yoruba, Tula, Idoma, Kamu, Kilba, Pero, Yandan, Babur, Dadiya, Mbula, Higgi, Margi,)

Congenital malaria accounted for the largest burden at 75.6 %, acquired malaria was 12.8% and transfusion-related malaria was 11.6%. We have published the sociodemographics, forms of neonatal malaria and parasite density in a prior article(23) .There was no statistically significant relationship between malaria parasitaemia and sociodemographic characteristics as shown in Table 1

The only maternal characteristic that had a significant association with malaria parasitaemia is a history of malaria in pregnancy (p = 0.001) regardless of the gestational age at which it occurred (trimester).

Table 2: Relationship Between Mothers' antenatal Characteristics and Malaria Parasitaemia

Characteristic	Mp+ n=78 Frequency (%)	Mp- n=53 Frequency (%)	p value
Age of mother			
<20	10(58.8)	7(41.2)	0.938
21-30	42(57.5)	31(42.5)	
31-40	22(62.9)	13(37.1)	
41-50	4(66.7)	2(33.3)	
Parity			
Primipara	25(55.6)	20(44.4)	0.606
Para 2	9(50.0)	9(50.0)	
Para 3	15(65.2)	8(38.4)	
Para 4	10(55.6)	8(44.4)	
Grand multi para	19(70.4)	8(29.6)	
Booking status			
Booked	76(59.4)	52(40.6)	0.799
Unbooked	2(66.7)	1(33.3)	
Use of ITN			
Yes	20(50)	20(50)	0.140
No	58(63.7)	33(36.3)	
Doses of SP			
None	21(70.7)	9(30.0)	0.074
1	20(60.6)	13(39.4)	
2	24(72.7)	9(27.3)	
3	11(39.3)	17(60.7)	
4	2(66.7)	1(33.3)	
Missing			
malaria in pregnancy			
Yes	34(81.0)	8(19.0)	**0.001**
No	44(49.4)	45(50.6)	

Table 3: Relationship between newborn characteristics and malaria parasitaemia

Parameter	Mp+ n-78 Frequency (%)	Mp- n=53 Frequency (%)	p value
Gestational Age			**0.049**
Pre-term	27(72.9)	10(27.1)	
Term	51(54.2)	43(45.8)	
Weight(g)			0.361
<1000	0(0.0)	0(0.0)	
1000-1499	8(72.7)	3(27.3)	
1500-2499	25(67.6)	12(32.4)	
2500-3999	43(55.1)	35(44.9)	
>4000	2(40.0)	3(60.0)	
Length(cm)			**0.027***
<45	23(76.7)	7(23.3)	
45-55	55(33.3)	44(69.7)	
>55	0(0.00)	0(0.00)	
OFC (cm)			**0.014***
<33	24(68.6)	11(31.4)	
33-37	54(59.3)	37(40.7)	
>37	0(00.0)	5(100.0)	
PCV(n=125)			**0.027***
<45%	29(74.3%)	10(25.7%)	
>45%	46(53.5%)	40(46.5%)	
No PCV	3(50.0%)	3(50.0%)	
History of transfusion	9(90.0)	1(10.0)	**0.040**
Yes	69(57.0)	52(43.0)	
No			

*Fisher's exact test

Table 4: Relationship Between Clinical Symptoms/Signs and Malaria Parasitaemia

9.5	Mp+ n=78 Frequency (%)	Mp- n=53 Frequency (%)	P value
Symptom/sign			
Poor suck			0.636
Yes	15(55.6)	12(44.4)	
No	63(60.6)	41(39.4)	
Seizures			0.468
Yes	15(53.6)	13(46.4)	
no	63(61.2)	40(38.8)	
Jaundice			**0.010**
Yes	53(68.8)	24(31.2)	
No	25(46.3)	29(53.7)	
Irritability			0.383
Yes	5(50.0)	5(50.0)	
no	72(60.0)	48(40.0)	
Respiratory difficulty			0.855
Yes	37(41.3)	26(58.7)	
No	41(60.3)	27(39.7)	
Hepatomegaly			0.630
Yes	19(63.3)	11(36.7)	
No	59(58.4)	42(41.6)	
Tachycardia			0.086
Yes	12(80.0)	3(20.0)	
No	66(56.9)	50(43.1)	
Tachypnea			0.244
Yes	37(64.9)	20(35.1)	
No	40(54.8)	33(45.2)	

Of the physical characteristics of the newborn as well as clinical signs, there was a statistically significant relationship between malaria parasitaemia and prematurity, anaemia, low length/occipitofrontal circumference and jaundice. Ten babies developed fever following transfusion and ninety percent of them tested positive for malaria. This is shown in table 3 and 4

Death rate was higher in those with parasitaemia (5.1%) which accounted for 80% of mortality among subjects as compared with 1.9% in those without parasitaemia. However, this difference is not statistically significant (p= 0.323). This is shown in figure 1

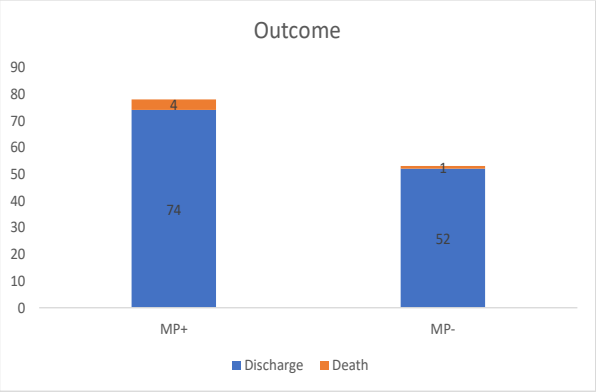

Figure 1: Outcome in malaria positive versus malaria negative patients

DISCUSSION

We found a high prevalence of malaria (59.5%) among the study population similar to other Nigerian studies carried out among term and pre-term sick newborns in the neonatal unit.

Malaria parasitaemia was significantly associated with prematurity and low birth weight in this study. This is not surprising as malaria in pregnancy is a known cause of pre-term delivery with attendant low birth weight.[24] Sotimehim et al and Falade *et al* reported a similar finding of malaria parasitaemia being significantly higher among pre-terms and babies with lower anthropometry. [25,26] A study by Ojukwu *et al* also documented lower mean weights in neonates with malaria as compared to those without malaria.[8] This contrasts what was reported by Runsewe *et al* who did not find a difference between term and pre-term babies possibly due to it being a retrospective study and maturity/gestational age was not documented for 11(19%) babies with malaria. The prevalence of malaria in this study showed no relationship with sex, place of delivery and social class as previously documented in the literature. [12,26] .

A history of febrile illness/malaria in the mother was the only maternal characteristic significantly associated with malaria parasitaemia in the newborn in this study. This finding is consistent with reports by Sotimehin *et al* and Price *et al* likely due to congenital malaria being a direct consequence of malaria in pregnancy. [25,27] Booking status, use of insecticide-treated net, and use of sulphadoxin Pyrimethamine rates were similar in mothers of babies with and without parasitaemia which was the same as the findings reported by Sotimehin *et al*.[25] Okechuckwu *et al* in Abuja also reported that the use of antimalaria prophylaxis did not affect the development of congenital malaria.[28] This could be due to the resistance of Plasmodium spp to sulphadoxine-pyrimethamine following point mutations as has been documented by Emrah *et al*[29]. The use of treated insecticide-treated nets has also shown inconsistent results in the prevention of malaria in pregnancy and subsequently congenital malaria.[30] This could also be due to social desirability as mothers are more likely to report adhering to malaria preventive strategies when asked within a hospital setting. A history of malaria in pregnancy is not stigmatized in our environment and therefore mothers are more likely to volunteer accurate history.

Neonatal anaemia was commoner in subjects with malaria as more than half of them had anaemia as against a quarter of those without malaria which is an important finding in this study. This is similar to the findings by Thapa *et al* who studied both congenital and transfusional neonatal malaria[17] and Mwaniki *et al* studied congenital and acquired neonatal malaria in India

and Kenya[5]. This is however different from findings by Lesi *et al* in Lagos where no case of anaemia was seen in the newborns with malaria parasitaemia.[19] This may be because babies were recruited at birth and screened for congenital malaria and bacteraemia, only babies with negative sepsis screening and malaria parasitaemia were considered to have malaria. This could have excluded those with co-infection (malaria with bacteraemia) as both can co-exist.[8,28] In this study, bacteraemia was not an exclusion criterion and other forms of neonatal malaria were included. We were not surprised that 90% of newborns who received blood transfusion and subsequently developed fever had malaria parasitaemia. This is because the study was conducted in a malaria endemic region where routine donor screening for malaria is not done.

Clinical Features of Neonatal Malaria

Jaundice was the most common clinical feature in the studied subjects as 58.7% had jaundice at recruitment regardless of their malaria test result. The majority of those with jaundice had malaria (68.8%) and the difference was statistically significant. Lesi *et al* reported jaundice as the commonest clinical feature of malaria with a statistically significant difference between those with/without malaria.[19] in the same study by Lesi *et al* the prevalence of jaundice was lower (27.9%) and this may be because only those with congenital malaria were studied.[19] Hepatomegaly was present in 24% of subjects with malaria in this study which is lower than 50% reported by Okechukwu *et al* but higher than 7.7% reported by Lesi *et al*.[19,28] Both studies were on congenital malaria however Okechukwu *et al* studied sick neonates as done in this study which could have accounted for higher rate of hepatomegaly reported while Lesi et al recruited babies at birth who were not sick.[19,28] Other clinical features did not show any statistically significant difference as clinical signs and symptoms in newborns are usually not sensitive nor specific.[19,28] Splenomegaly was not reported in this study which is similar to findings by Enyuma *et al* who also screened neonates with fever without excluding bacteraemia.[31] Other studies have documented splenomegaly ranging from a tipped spleen to palpation up to 3cm below the left coastal margin.[32,33] Poespoprodjo et al reported splenomegaly up to the umbilicus in a newborn with high parasite density (26,700 per microlitre) and was by far the highest parasite density they recorded in four years.

Majority of subjects were discharged (96.2%) with 5 mortalities recorded (3.8%). The death rate in newborns with malaria in our study was 5.1% which is less than the rate reported by Khichi et al (16.6%) and thought to be due to chloroquine resistance as documented in that study[16] Hyacinth et al recorded death in 25% of patients with malaria parasitaemia which is higher than the rate in this study possibly due to a different protocol of treatment used (predominantly amodiaquine) as against quinine in this study and other co-morbidities such as disseminated intravascular coagulopathy and neural tube defects in their study.[15] Okechukwu et al reported a death rate lower than all the studies mentioned above (1.6%) however only congenital malaria was studied and the drug used for treatment was not documented which could have affected the outcome.

CONCLUSION

A history of malaria in pregnancy, prematurity, anaemia, transfusion and jaundice were significantly associated with malaria parasitaemia while malaria preventive strategies such as the use of insecticide-treated nets, and malaria prophylaxis in pregnancy did not appear to affect the occurrence of malaria in the newborn. Clinicians should have a heightened index of suspicion for malaria in neonates with fever whose mothers had malaria in pregnancy, delivered pre-term, have jaundice and PCV less than 45% . Furthermore, donor screening for malaria should be done before transfusion in malaria endemic regions.

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