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Malaria parasite positivity among febrile neonates

DOI:<http://dx.doi.org/10.4314/njp.v41i4.6>

Accepted: 3rd May 2014

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Abstract Background: Malaria, earlier considered rare in neonates, has been reported with increasing frequency in the last decade. Neonatal malaria diagnosis is challenging because the clinical features are non-specific, variable and also overlap with bacterial infection.

Aim: To determine the prevalence of neonatal malaria and the associated clinical features in newborn babies with fever.

Patients and methods: One hundred and fifty neonates with fever admitted into the Newborn unit of the University of Calabar Teaching Hospital, over a six month period, were recruited consecutively. Symptoms and signs for each neonate were documented. Blood film for malaria parasites and investigation for sepsis work-up were done before commencement of drugs.

Results: One hundred and fifty babies were recruited. Most (85.3%) of the babies were aged ≤ 7 days. One hundred and thirty six (90.7%) of the mothers were

booked for antenatal care (ANC). Most of the babies were from primiparous women (54.7%).

Six babies (4%) had malaria parasitaemia with four (2.7%) being congenital malaria and two (1.3%) acquired malaria. *Plasmodium falciparum* was the only species identified. All six with malaria were from the 136 booked mothers. Four of the affected six neonates also had septicaemia.

The clinical features in babies with malaria only were, fever, fast breathing and jaundice while those with malaria and bacterial co-infection had, in addition, poor suck.

Conclusion: Malaria infection and septicemia can coexist in some Nigerian newborns and since the clinical presentation of each of these conditions are closely similar, it is recommended that malaria parasite investigation be included as part of the investigation in the newborns with fever. This approach can help to avoid a delay in applying the appropriate therapeutic intervention

Introduction

Malaria remains a major global problem, exacting an unacceptably high toll on the health and economic welfare of the world's poorest communities¹. *P. falciparum* causes about 95% of malaria infection, and 18% of all causes of mortality in children less than five years¹⁻³. There are reports of an increasing but variable incidence of newborn malaria from many parts of the world, initially considered very rare in this age-group²⁻⁴. Reasons for the reported rarity include that the malaria prophylaxis taken by mothers during antenatal care lowers anti-malarial immunoglobulin production in some mothers and consequently lowers the acquisition of passive immunity to malaria in their newborns⁵. Drug resistance of *P. falciparum* to common antimalarial drugs and resistance of the malaria vector, *Anopheles* mosquitoes, to

insecticides have however developed, contributing to the increasing incidence⁵.

Diagnosis of newborns with malaria can be quite challenging because the clinical features are non-specific, variable and also overlap with those of bacterial infection. These neonates are subjected to sepsis screening and empirically commenced on antibiotics pending blood culture result. In some of these cases, even when fever persists despite the use of different antibiotic regimens, malaria infection is rarely considered⁶. It becomes imperative to undertake further evaluation of the prevalence and clinical features that may be attributed to malaria among newborns with fever. This would increase the index of suspicion and avert delays in early laboratory diagnosis and treatment. This study was therefore conducted to determine the prevalence of neonatal malaria and the associated clinical features in newborns

with fever.

Materials and Methods

This prospective, cross sectional, analytical hospital-based study was conducted among neonates admitted into the Newborn Unit of the University of Calabar Teaching Hospital (UCTH) from the 3rd of November 2010 to the 8th of May 2011. The Unit which had earlier been described by Udo et al,⁷ has undergone much improvement over time in terms of structural and manpower development.

Inclusion criteria were neonates with temperature $\geq 37.5^{\circ}\text{C}$ or recent history of fever, who had not received anti-malarials or antibiotics at least two weeks prior to enrolment into the study and whose parents or guardians had given consent.

Ethical clearance was obtained from the Ethics Review Committee of the University of Calabar Teaching hospital before commencement of the study.

The study was explained to the parents to understand what the study entailed and a signed informed consent was obtained from the parents or guardians who gave consent.

All consecutive babies (0-28 days) who met the inclusion criteria were recruited until the desired sample size was obtained. Detailed clinical history (presenting complaints, drug history, immunization history, nutritional history, pregnancy history that includes investigations done, compliance with chemoprophylaxis/ folic acid, tetanus immunization, fever, blood film for MP in pregnancy, drug treatment for malaria if taken. Others were delivery history, family and social history which includes the parents age, marital status and mothers parity, level of education attained and occupation) was obtained and anthropometric measurements performed on the babies. The social classes of the babies were arrived at based on the objective criteria of the father's occupation and level of maternal education, as suggested by Olu-sanya O et al.⁸

Two blood films (thick and thin film) for malaria parasite (MP) and samples for sepsis work-up (full blood count, blood culture, urine microscopy/culture/sensitivity via suprapubic tap, cerebrospinal fluid protein, sugar, microscopy, culture and sensitivity) were taken before commencement of treatment. Both thick and thin blood films were prepared and stained with 2% freshly prepared Giemsa stain. Thereafter, they were read using $\times 100$ objective lens with oil immersion within 24 hours of collection of blood⁹ by the investigator, assisted by the laboratory scientist. The slides were validated independently by the microscopist with Institute of Tropical Disease Research and Prevention and a World Health Organisation certified laboratory scientist attached to Department of Paediatrics research laboratory. Asexual forms of the parasite (trophozoites or ring forms) and the sexual forms (gametocytes) were counted in each field along with the leucocytes. Parasite count was discontinued when 200 leucocytes had been

counted or if 500 parasites had been reached before counting up to 200 leucocytes. A slide was declared negative if after examining a minimum of 200 fields for at least 15 minutes no malaria parasite was found, according to standardized protocols.⁹

All the babies were commenced on intravenous Ceftriaxone and Gentamycin (if urinary output was established to be adequate). The babies whose blood film results were positive for malaria parasite were in addition, started on oral quinine at a dose of 10mg/kg/dose, eight hourly for seven days in line with the National Malaria Treatment Policy for newborns.¹⁰ Gentamycin was replaced with Ampiclox injection if a particular baby was to receive Quinine. This was to reduce the risk of ototoxicity.

On retrieval of laboratory results, (full blood count (FBC), cerebrospinal fluid (CSF), blood and urine cultures), antibiotics were discontinued if results were found to be normal. At the completion of the anti-malarial drug in babies with positive MP result, peripheral blood films for malaria parasite were repeated to ascertain response to treatment.

Findings were collated with the aid of the case record form designed for the study. Data was analysed using SPSS version 14 statistical software. Frequency, sample means, and percentages were calculated as necessary. Statistical significance of difference was determined using Chi square (X^2) for dichotomous variables, t-test for continuous variables and Wilcoxin rank-sum test was used to test the non parametric variables. The level of significance was set at $p \leq 0.05$.

Results

A total of 150 subjects were recruited. The study population was made of 87 (58.0%) males and 63 (42.0%) females with M:F ratio of 1.4:1. The age category 0-7 days represented 128 (85.3%) of the subjects. The study population was not normally distributed. It had a mean age of 4.2 ± 5.9 days, with a median of 2.0 days. The difference in ages between the male and female population was not statistically significant ($p=0.71$). (Table 1)

Table 1: Anthropometric and clinical characteristics of the study population

Patients characteristics	Mean \pm SD		Total N=150	p-value*
	Male(n=87)	Female(n=63)		
Age (days)	4.4 \pm 6.2	4.0 \pm 5.5	4.2 \pm 5.9	0.71
Examining Temperature ($^{\circ}\text{C}$)	38.1 \pm 0.6	38.1 \pm 0.6	38.1 \pm 0.8	0.88
Weight (Kg)	3.1 \pm 0.8	3.0 \pm 0.7	3.1 \pm 0.8	0.39
Length (cm)	49.3 \pm 3.6	49.2 \pm 3.3	49.3 \pm 3.5	0.80
Occipito Frontal Circumference (cm)	34.4 \pm 2.0	34.0 \pm 2.0	34.2 \pm 2.0	0.17
Heart rate (bpm)	144.7 \pm 13.3	142.6 \pm 19.3	143.8 \pm 118	0.29
Respiratory Rate (cpm)	54.8 \pm 14.1	54.4 \pm 13.3	54.6 \pm 13.7	0.85

*Statistical test= Wilcoxin rank-sum test; characteristics similar in males and females

The average age of the mothers was 28.1±4.9 years. Ninety three percent of the mothers had at least, secondary school education. The social class⁸ distribution showed that 19(12.7%) babies were of the lower social class, 75 (50.0%) were of the middle social class and 56 (37.3%) were of the upper social class.

One hundred and thirty six (90.7%) mothers booked for antenatal care (ANC) either in UCTH or at other health facilities. One baby was adopted and so the ANC status was not known. Primiparous mothers constituted 54.7% of the maternal population.

Interview of the mothers revealed that 21(14.0%) of them had malaria or symptoms suggestive of malaria during pregnancy. Only three of these mothers had laboratory confirmation; the rest were treated presumptively. Twelve of the 21 cases of suspected malaria (57%) occurred during the second trimester while nine (43%) were in the third trimester. Out of these 21 mothers, 19 were booked for ANC and two were not. Eighteen (85.7%) of the mothers used Lumefantrine/Artemeter combination, an Artemisinin based Combination Therapy (ACT).

Six (4.0%) of the newborn population had malaria parasitaemia, and all were from the 136 mothers that booked for ANC. *Plasmodium falciparum* was the only species identified. Four (66.6%) of the six babies with malaria parasitaemia were aged under seven days, indicating that that they were congenital infections. The other two babies were aged 14 and 23 days respectively.

A total of 92(61.3%) babies had septicemia: 54(58.7%) blood samples yielded *Staphylococcus aureus* and 38 (41.3%) grew unclassified *Coliform species*. Four neonates had malaria and bacterial co-infection. Two of these had *Staphylococcus aureus* while the other two had unclassified *Coliforms* septicemia infections. The two babies that had malaria alone were a day old female, and a 14 day old male. Fifty eight (38.7%) febrile newborns had no growth in their blood cultures

Fever (100.0%), fast breathing (100.0%) and yellowness of the skin (25.0%) were the commonest clinical features presented by the newborns with malaria parasitaemia only. None in the study had hepatosplenomegaly. The differences in the symptoms and signs between newborns with malaria alone and those with septicaemia were not statistically significant, except for fast breathing ($p<0.05$). (Table 2a and 2b)

Table 2a: Presenting symptoms among the study populations

Symptoms	Mal.only (N=2)		Mal+Sep (N=4)		Sep. only (N=84)		Nil mal/ Nil Sep (N=56)		P-value
	n	%	n	%	n	%	n	%	
Fever	2	100.0	4	100.0	87	98.9	54	96.4	0.212
Fast breathing	2	100.0	1	25.0	13	14.8	11	19.6	0.043*
Yellow skin	1	50.0	1	25.0	41	46.6	24	42.9	0.847
Seizures	0	0.0	0	0.0	5	5.7	4	7.1	0.819
Poor suck	0	0.0	1	25.0	14	15.9	5	8.9	0.458
Excessive cry	0	0.0	0	0.0	5	5.7	2	3.6	0.780

*Proportion with fast breathing differ significantly across groups

Table 2b: Common clinical signs elicited in the study population

Clinical signs	Malaria only (N=2)		Malaria + Sepsis (N=4)		Sepsis only (N=88)		No Malaria/No sepsis (N=56)		P-value
	n	%	n	%	n	%	n	%	
Low Birth Weight	0	0.0	0	0.0	19	21.0	13	23.3	0.841*
Abdominal distension	0	0.0	0	0.0	3	3.4	2	3.6	1.000*
Jaundice	1	50.0	1	25.0	41	46.6	24	42.9	0.847*
Pallor	0	0.0	0	0.0	4	4.5	0	0.0	0.289*
Tachypnoea	2	100.0	1	25.0	12	13.6	14	25.0	0.015*
Dyspnoea	0	0.0	0	0.0	4	4.5	1	1.8	0.714*
Crepitation	0	0.0	0	0.0	2	2.3	0	0.0	0.559*
Murmur	0	0.0	0	0.0	1	1.1	1	1.8	1.000*
Lethargy	0	0.0	0	0.0	4	4.6	0	0.0	0.285*

*Fisher's exact

One hundred and twenty eight (85.3%) mothers were aged 20-35 years and four of their newborns had malaria parasitaemia. Sixteen (10.7%) of the mothers were 35 years and above, two of their babies had malaria parasitaemia. Six (4%) of the mothers were teenagers and none of their babies had malaria parasitaemia.

There were 31 (20.7%) low birth weight newborns, none of whom had malaria parasite identified in their blood film. Five of the 99 (66.0%) term adequate for gestational age babies compared to one of 20 (13.3%) macro-somic neonates had malaria parasitaemia.

All the 150 newborns recruited were followed-up at the Newborn outpatient clinic as scheduled. None of six with parasitaemia had malaria in the repeat peripheral thick blood smear. None of the babies died during the period of study and follow-up.

Discussion

The present study has revealed a prevalence of 4% for neonatal malaria among newborns with fever, consisting of 2.7% and 1.3% of congenital and probably acquired malaria, respectively. None of the newborns had transfusional malaria since none had received blood transfusion. The prevalence of congenital malaria of 2.7% in this study is similar to earlier report of 2% prevalence of congenital malaria by Oduwole et al¹¹ using PCR and 3% reported by Bassey et al¹² both in Calabar. The lower prevalence rates observed in the current study compared to 8% reported by Ibhanesebor² in Benin, 8.25% reported by Orogade¹³ in Zaria, 24.8% reported by Runsewe-Abiodun et al¹⁴ in Sagamu, 33.3% by Ojukwu et al¹⁵ in Ebonyi may be explained by the recent improvements in malaria control practices in pregnancy,¹⁶ differences in the methodology and expertise of the laboratory scientist¹⁷. Microscopy in the present study was validated by two independent research laboratories.

The prevalence from this study is higher than a prevalence of 0.35% found in the newborns in a Kenyan study¹⁸ and 0.98% in Cote d' Ivoire.¹⁹ These differences may still be a reflection of differences in malaria trans-

mission pattern and local control efforts²⁰. This study documented co-existence of malaria infection with septicemia in some Nigerian newborns. This suggests that in high malaria transmission areas such as ours, a number of newborns with confirmed bacterial sepsis may also have malaria co-infection. Furthermore, there is clearly an overlap in clinical features between the infants with isolated malaria infection, septicemia alone, or co-infection. This underscores the need to screen for malaria in every febrile newborn infant in malaria endemic areas. The combined clinical and therapeutic implication of this is that if bacterial sepsis is the tentative diagnosis and malaria is confirmed to coexist, antibiotics and anti-malarial are commenced simultaneously to achieve optimum clinical response. Also if after commencing empirical antimicrobials, laboratory reports later confirm that all body fluids are sterile except for malaria, the antibiotics maybe discontinued early enough to avoid wastage.

In the current study, fever, jaundice and fast breathing were more prevalent in newborns with malaria parasitaemia compared to those with septicemia alone or co-infection. The limitation of our study is that the number of newborns with malaria parasitaemia only was too small to make generalization on the clinical features that are specific to neonatal malaria. Further large scale studies will be necessary to specifically look for the specific features.

Conclusions

The prevalence of neonatal malaria in febrile newborns presenting in the University of Calabar Teaching Hospi-

tal is 4% with *P. falciparum* being the only species implicated. It appears the clinical features in neonates with malaria parasitaemia cannot be differentiated from the presentation of neonates with septicemia. It is therefore recommend that in malaria endemic areas, malaria screening be made part of sepsis work-up in every ill newborns. This approach will help to avoid a delay in applying the appropriate therapeutic intervention.

Authors' contributions

Enyuma COA: Lead investigator, manuscript preparation

Meremikwu MM: Study design, investigation, editing and correction of manuscript.

Udo JJ: Reviewed all the neonates and corroborated the findings.

Anah MU: Cross checked the results, editing and correction of manuscript.

Asindi AA: Editing and correction of manuscript.

Conflict of interest: None

Funding: None

Acknowledgement

We gratefully acknowledge Prof Emmanuel E Ekanem for assisting in preparing and correcting the manuscript, Dr Udeme Ekrikpo for his contribution to data analysis and all the Residents in department of Paediatrics for their assistance in data collection.

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