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BACTERAEMIA, URINARY TRACT INFECTION AND MALARIA IN HOSPITALISED FEBRILE CHILDREN IN NAIROBI: IS THERE AN ASSOCIATION? F. N. Okwara, MBChB, (Nbi) MMed (Nbi), E. M. Obimbo, MBChB, (Nbi) MMed (Nbi), MPH (USA), E. M. Wafula, MBChB, (Nbi) MMed (Nbi) and F. V. Murila, MBChB, (Nbi) MMed (Nbi), Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi. P.O. Box 19676, Nairobi, Kenya

BACTERAEMIA, URINARY TRACT INFECTION AND MALARIA IN HOSPITALISED FEBRILE CHILDREN IN NAIROBI: IS THERE AN ASSOCIATION ?

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ABSTRACT

Background: **There is laboratory evidence of altered immune function in children with malaria. Bacterial infections have been documented to complicate severe forms of malaria. However, it remains unclear whether such infections are attributable to the malaria, other risk factors, or are coincidental.**

Objective: **To determine the prevalence of bacteraemia and urinary tract infections (UTI) in febrile hospitalised children with and without malaria.**

Design: **A cross-sectional survey.**

Setting: **General paediatric wards, Kenyatta National Hospital, Nairobi.**

Subjects: **Children aged between three months and 12 years admitted with an acute febrile illness, with no obvious focus of bacterial infection.**

Materials and Methods: **Using a standardised questionnaire, information on socio-demography, symptomatology, and nutritional status was obtained. Malaria slides, blood and urine cultures were performed on each child.**

Results: **Malaria parasitaemia was present in 158 (60%) of 264 children presenting with acute febrile illness with no obvious focus of bacterial infection. Bacteria were isolated from blood and/or urine of 62 (23%) of all enrolled children.**

Bacteraemia was prevalent among 11.4% of 158 children with malaria and among 13.2% of 106 without malaria. Gram- positive organisms comprised 28.1% of blood isolates, gram-negative 62.5%, and atypical bacteria 9.4%. UTI was prevalent among 13.3% of 158 children with malaria and 16.0% of 106 children without malaria. Gram- positive organisms comprised 18.4%, gram-negative 78.9%, and atypical bacteria 2.6% of the urine isolates. Presence of malaria parasitaemia was not associated with an increased risk of bacteraemia (OR 0.9, 95% CI [0.4-0.7], or UTI (OR 0.8 95% CI [0.4-1.6] in this study population.

Conclusion: **Among children hospitalised in Nairobi with fever and no obvious bacterial infective focus, there should be a high index of suspicion for malaria, followed by bacteraemia and UTI. Malaria parasitaemia does not appear to be associated with increased risk of bacterial co-infection.**

INTRODUCTION

An estimated 300 - 500 million cases of malaria are reported globally annually, 90% of which occur in African children below five years(1,2). Despite good understanding of disease mechanisms in malaria, and advances in malaria chemotherapy, malaria causes approximately 26,000 deaths in children under five in Kenya annually(1,3-5). The frequent presence of complicating pathology in relatively non-immune young children with malaria contributes to this high morbidity and mortality(6). There is laboratory evidence of impaired immune function in *Plasmodium falciparum* malaria. Opsonization and phagocyte killing by macrophages becomes impaired after ingestion of parasite-derived haemozoin(7,8). Deficient cell mediated cytotoxicity has been demonstrated even in patients with low-level parasitaemia(9). Patients with malaria have reduced circulating T-lymphocytes, impaired proliferative T-cell response, and have plasma anti-lymphocyte antibodies(9-12). Humoral immunity has also been shown to be impaired(12,13). The clinical features of malaria closely resemble those of other febrile illnesses, such as septicaemia and urinary tract infections. Failure to treat concurrent bacterial infection in a child with malaria may lead to severe morbidity and mortality. Local data on the prevalence of invasive bacterial infection in malaria among young children are limited. Such information is important to health workers on how frequently antibacterial therapy may be indicated in children presenting with non-focal febrile illness and malaria parasitaemia.

MATERIALS AND METHODS

The study was carried out at the University of Nairobi teaching hospital Kenyatta National Hospital, in Nairobi, Kenya. Study subjects were children aged between three months and 12 years admitted with an acute febrile illness (temp > 37.5° C), but no obvious focus of bacterial infection. Children with obvious focal infections, known chronic illnesses or severe malnutrition were excluded. Through interview, information on socio-demography and use of antimalarial or antibiotic drugs during the preceding week was obtained. Utilization of drugs was verified by examining a health record card or the bottle containing the drug. The children were examined for fever and their nutritional status assessed.

A thick blood film was prepared from a finger prick, stained by Field's stain, and examined for asexual forms of *Plasmodium falciparum.* Following iodine disinfection of the skin, a 2ml sample of blood was drawn from each child on admission. The blood was inoculated into brain heart infusion and incubated for three days. The bottles were examined daily for evidence of growth and sub-cultured on blood and chocolate agar after 48 hours, and 72 hours if there was no evidence of growth. The first urine passed after admission was collected by either the child passing a mid-stream specimen of urine directly into a sterile bottle or by swabbing the perineum with chlorhexidine then applying a sterile urine collector for the younger children who could not follow instructions. The urine was inoculated onto cystein lactose electrolyte deficient agar and incubated for 48 hours. Significant bacteriuria was defined as isolation of more than 10^5 bacteria/ ml from any patient or a pure colony growth of 10^3 bacteria /ml of urine in those who had previously been on antibiotics. Isolates were identified by standard bacteriological techniques.

Data entry and analysis were done using Statistical packages for Social Sciences software - version 9.0. Subjects were categorised according to the presence or absence of malaria parasites in their blood slide. Prevalence of bacteraemia and UTI were determined amongst malaria and non-malaria groups and compared using the Chi-square test. Effect of recent antibiotic use on prevalence of bacteraemia and of UTI was assessed using Chi-square test.

RESULTS

A total of 264 children were enrolled between January and March 2001, of whom 158 (60%) had malaria parasitaemia and 106 (40%) had no malaria parasites in blood. Bacteria were isolated from blood and/or urine of 62 (23%) of all enrolled children. The mean age was two years, eight months (range three months to eleven years) for malaria subjects, and three years, one month (six months to twelve years) for non-malaria subjects. Males comprised 62% and 55% of malaria and non-malaria subjects respectively. Seventy-eight percent of malaria subjects and 74% of non-malaria subjects reside in low-income neighbourhoods. Malnutrition (underweight) was present among 18% of malaria subjects, and 22% of non-malaria cases. (Table 1)

Use of antimicrobials during the previous week was reported among 26% of malaria subjects and 17% of non-malaria subjects. Recent use of antimalarial drugs was reported among 23% of malaria subjects and 18% of non-malaria subjects. (Table 1)

Table 1

Descriptive characteristics of the study population

Characteristic	Malaria present N= 158 Number (%)	Malaria absent N= 106 Number (%)
Age in years		
0-1 years	32 (21)	30 (19)
1- 5 years	113 (71)	66 (62)
> 5 years	13 (8)	10 (9)
Male	98 (62)	58 (55)
Underweight	28 (18)	23 (22)
Reside in low income area	123 (78)	78 (74)
Household with > 4 people/room	33 (21)	31 (29)
Mother has ≤ primary education	91 (58)	48 (45)
Use of antimalarials previous week	34 (23)	18 (18)
Use of antimicrobials previous week	37 (26)	16 (17)

Table 2

Association between bacteraemia, urinary tract infection and malaria

	Malaria present N=l58 Number (%)	Malaria absent N=106 Number (%)	OR (95% CI)	p-value
Bacteraemia	18 (1 1.4)	14 (13.2)	0.9 (0.4 -1.9)	0.7
UTI	21 (13.3)	17 (16.0)	0.8 (0.4- 1.7)	0.5

Table 3

Microbial aetiology of bacteraemia and UTI in study population

Organism	Blood isolate	Urine isolate
Staphylococcus aureus	4	-
Coagulase negative *staphylococcus*	-	5
Streptococcus pneumoniae	1	-
Enterocoeeus sp.	4	2
Total Gram positive	**9**	**7**
Salmonella typhi	1	-
Salmonella typhimurium	11	-
Citrobaeter sp.	5	6
Proteus sp.	-	1
Klebsiella sp.	1	4
Escherichia coli	1	18
Pseudomonas sp.	1	1
Total gram negative	**20**	**30**
Acinetobaeter sp.	3	-
Candida albicans	-	*1*
Total atypical	**3**	**1**
Total bacterial isolates	**32**	**38**

*Numbers represent frequency of isolation of a specific type of bacteria

Table 4

Prevalence of baceteraemia and UTI by density of malaria parasitaemia

Malaria parasites	Bacteraemia Number[a] (%)	UTI Number[b](%)	Total Number of subject[c]
+	4 (12.5)	4 (12.5)	32
++	5 (8.1)	9 (14.5)	62
+++	9 (14.0)	8 (12.5)	64
Total	18 (11.4)	21 (13.3)	158

a - number of subjects with bacteraemia in malaria parasite density sub-category.
b - number of subjects with UTI in malaria parasite density sub-category.
c - total number of subjects within malaria parasite density sub-category.

Prevalence of bacteraemia - Pathogenic bacteria were isolated from blood of 18 (11.4%) of 158 children with malaria, and from 14 (13.2%) of 106 children without malaria. Prevalence of bacteraemia was similar between children with and without malaria (OR=0.9, 95% CI [0.4-1.8], P=0.7). (Table 2). Bacterial contaminants were isolated in the blood cultures of 16 children, specifically coagulase negative *staphylococcus* (11), *diphtheroid species* and *micrococcus*.

Prevalence of UTI - Significant bacteriuria was present in 21 (13.3%) of the 158 children with malaria, and in 17 (16.0%) of 106 children without malaria. Prevalence of bacteriuria was similar between children with and without malaria (OR 0.8, 95% CI [0.4 -1.6], p=0.5) (Table 2).

Overall, bacteria were isolated from blood and/or urine of 35 (22.2%) of the 158 malaria cases, and from 27 (25.5%) of the 106 non-malaria cases. Concurrent bacteraemia and UTI was present in four (2.5%) malaria cases and four (3.8%) non-malaria cases. All children with concurrent bacteraemia and UTI were less than three years old.

Microbial aetiology of bacteraemia and UTI - Specific microbial etiology of bacteraemia and of UTI is shown in Table 3. Gram-positive organisms comprised 28.1% of all blood isolates, gram-negatives 62.5%, and atypical bacteria 9.4%. *Salmonella typhimurium* and *enterococcus* were the commonest pathogenic blood isolates. Gram- positive organisms comprised 18.4%, gram-negative 78.9%, and atypical organisms 2.6% of the urine isolates. *Escherichia coli* was the most frequent urine isolate.

Neither bacteraemia nor UTI showed association with malaria parasite density in blood in this study population. (Table 4) Similarly, age and recent antibiotic use showed no association with prevalence of bacteraemia or of UTI in this population ($p > 0.05$).

DISCUSSION

We have shown that malaria, bacteraemia and UTI are prevalent among febrile hospitalised children presenting with no obvious infective focus. The bacteraemia prevalence that we observed was similar to that reported in other African studies(14,19-20). In Nigeria 7.8 and 12.2% of malaria and non-malaria subjects had bacteraemia(14). Prevalence of bacteraemia of 7.8 and 16% have been reported among children with severe malaria in Kenya and Nigeria respectively(19, 20).

In industrialised counties, bacteraemia appears less frequent among children without obvious infective focus, with prevalence ranging from 3 to 8% reported(6,15). Possible explanations for higher prevalence of invasive bacterial infection in resource-poor settings include malaria, malnutrition, HIV/AlDS, and young age of our study population. Most of the children studied were aged below five years, a period during which their immune systems are immature and have limited capability to resist and control infection. Other studies have demonstrated bacteraemia prevalence as high as 31% in malnourished children(16). One fifth of the children in this study were malnourished. With an estimated 220,000 children in Kenya living with HIV/AIDS, the disease is thought to contribute to more than one third of paediatric hospitalisation(20,21). HIV/ AIDS may contribute to the relatively high prevalence or bacteraemia observed in this study.

The presence of malaria parasites does not appear to show association with invasive bacterial infection in this population. This finding is unexpected given that malaria infection is known to depress immunity, and needs further validation. We also found that bacteraemia prevalence did not change significantly with increasing malaria parasite density, however we had limited power to examine such association due to small numbers of patients with high density parasitaemia. Other Nigerian and Kenyan studies have reported no association between presence versus absence of bacteraemia, and malaria parasite density (14, 20).

Gram-negative bacteraemia appeared more frequent than gram-positive bacteraemia in this population, with a predominance of *salmonella* species as has been reported in other parts of Africa(19,22,23). Several hypotheses have been advanced to explain this trend. Salmonellosis and malaria both exhibit seasonal variation, and both conditions peak at the same time. An association has also been observed between HIV infection and salmonellosis. Haemolysis, complement abnormalities, and defective opsonization by macrophages present in malaria infection have been associated with higher risk of salmonellosis(22). In contrast, in industrialised countries, gram-positive organisms are the more common cause of bacteraemia in children with fever of unknown origin(6).

To the authors' knowledge, the prevalence of UTI in children with malaria has not been previously studied in this region. Our findings suggest that UTI frequently complicates malaria in African children. *Escherichia coli* was the commonest organism isolated from urine. Many investigators have demonstrated similar findings(24). *Escherichia coli* has been shown to account for up to 75% of UTI in all paediatric age groups, followed by other enterobacteria especially *Klebsiella, Proteus* and *Pseudomonas* species. Gram-positive organisms are rare except *Staphylococcus saprophyticus,* which occurs in adolescent girls.

The high malaria prevalence of 60% in this study population appears high for Nairobi, which is categorised as non-endemic for malaria. Kipmutai and others(25), in a recent study found malaria parasitaemia in 11% of febrile children presenting to outpatient government clinics in Nairobi, and found that one-third of those with malaria had not travelled in the previous three months, suggesting that their malaria was acquired within Nairobi. This suggests changing ecology in Nairobi, and requires further investigation.

Our findings suggest that up to two-thirds of children hospitalised with fever without obvious infective focus have malaria, and that up to one-fifth have either bacteraemia or significant bacteriuria. Bacterial co-infection appears to be similarly present among children with and without malaria parasitaemia. We conclude that among children hospitalised in Nairobi with fever and no obvious bacterial infective focus, there should be a high index of suspicion for malaria, followed by bacteraemia and UTI.

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