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ABSTRACT

Objective: To determine the association between *Plasmodium falciparum* malaria and non-typhi Salmonella in children.

Design: Cross-sectional hospital based study.

Setting: Kilifi District Hospital (KDH) between January 1997 and June 2001.

Subjects: Children aged between three months to 123 months (mean age 28.28 months) and who had been admitted to the paediatric or High Dependency Research Ward (HDRW) of the KDH.

Methods: A total of 19, 118 blood cultures routinely obtained for all admissions and 1,820 clinically indicated stools samples were obtained from 9,147 children admitted with malaria. The specimens were cultured and antibiotic sensitivity done using standard laboratory procedures with stringent internal and external quality control in place.

Results: The total bacterial pathogens isolated from blood and stool were 1,395/19,118 (7.3%) and 342/1,820 (19%) respectively. Non-typhi salmonella consisted of 260/1,395 (18.6%) of the positive blood cultures and 92/324 (28.4%) of the stool cultures out of which a total of 101 NTS occurred in children with severe malaria. Out of the 9,147 malaria cases admitted, 101/9,147 (1.10%) had concomitant NTS infection. NTS with severe malaria as a proportion of all malaria admissions for the period varied between 0.8% and 1.5%. There was a significant association (p-value=0.032) between clinical outcome of death and female sex of the patient. The NTS isolates which occurred with severe malaria showed various levels of antibiotic resistance. They were resistant to ampicillin (35%), chloramphenicol (18%), gentamicin (22%), cefuroxime (29%), sulphamethoxazole-trimethoprim (39%), ciprofloxacin (3%), cefotaxime (14%), amoxicillin-clavulanic acid (26%) and tobramycin (18.0%). Multidrug resistance (MDR) was seen in 34 (33.6%) of the isolates.

Conclusions: NTS and severe malaria occurring together are a problem in this area and that a large number of the isolates are MDR. An elaborate case-controlled study is required to elucidate the chain of events of both NTS and malaria parasite co-existence.

INTRODUCTION

Non-typhi salmonellae are a major cause of septicaemia and bacteraemia. They are responsible for approximately 1.4 million cases annually in the United States alone (1). In sub-Saharan Africa, NTS are amongst the most common causes of invasive bacterial childhood disease (2-4). Infections caused by both typhoid salmonellae, and NTS species cause major health problems including acute gastro-enteritis, typhoid fever, severe bacteraemia and septicaemia that result in high morbidity and mortality.

Globally malaria is a major cause of morbidity and mortality and may be responsible for between one to two million childhood deaths each year in sub-Saharan Africa (6). In a study conducted in Kilifi, Kenya, a mortality rate of 3.5% was observed in children admitted with a primary diagnosis of malaria(7). Association between malaria and NTS septicaemia was first noted in British Guyana(8). Salmonella septicaemia was found to be more common and more severe during outbreaks of malaria than at other times. Bacteremia complicating severe malaria has also been observed in Kilifi, Kenya, however, NTS was not the focus of the study((9).

Infection with multidrug resistant *S.typhimurium* and other NTS is associated with high mortality(10,11). Even though several investigators discourage the use of antibiotics in salmonella gastroenteritis since they prolong the carrier state(10), the antibiotics are sometimes given during severe infection and in the absence of culture results. This is normally the case in most resource poor countries where there are no laboratory facilities for culture and sensitivity of clinical specimens. The problem is exacerbated by the emergence of multidrug resistant strains (MDR) of NTS, which can lead to therapy failure and hence high mortality rates in children.

This study sought to determine and characterise NTS isolated from the blood and stool of children with severe malaria who were admitted to the High Dependency Research Ward (HRDW) and the paediatric wards of the Kilifi District Hospital (KDH) with a view to understanding the interaction between these two important diseases.

MATERIALS AND METHODS

Site: The study was carried out at the Kenya Medical Research Institute (KEMRI), Centre for Geographic Medicine-Coast/Wellcome Trust Research Laboratories situated within the Kilifi District Hospital (KDH). KDH is situated in Kilifi town, 60km north of Mombasa town. The hospital serves a rural population of about 150,000 people. Most of the population comprises the Miji-kenda community with a majority of them being of the Giriama sub-tribe. KDH has a 35-bed Paediatric ward and a 5-bed High Dependency Research Ward (HDRW), which serves approximately 4,000 in-patients a year.

Study patients: These were children between the ages of 3-123 months who were admitted to either the paediatric ward or the HDRW of the KDH. The mean age of the children was 28.28 months (SD=25.28 months). The criterion for inclusion into the study was a diagnosis of severe malaria with the following clinical definition: a blood slide positive for *Plasmodium falciparum*, recurrent convulsions, metabolic dysfunctions such as, hypoglycaemia, lactic acidosis or severe anaemia(12). Informed consent was obtained from the children's mothers/caretakers.

Bacterial isolates: Between 1 to 3ml of blood was routinely obtained for culture and sensitivity from all admissions. However, only those patients with a primary diagnosis of malaria were included in this study. Stool samples for culture and sensitivity were collected when clinically indicated. Non-typhi Salmonella (NTS) were isolated from the blood or stool of children admitted with a primary diagnosis of malaria from January 1997 to June 2001. Bacterial isolation was done using standard microbiological procedures and the isolates were stored at -70°C in trypticase soy broth with 15% glycerol until retrieved for analysis. Commercial salmonella agglutinating antisera (Murex Diagnostics, Dartford, UK, and Denka Seiken, Tokyo, Japan) were used to serotype the Salmonella isolates according to the Kauffman-White schema(13).

Antibiotic sensitivity profiles: The Kirby-Bauer single disk diffusion technique(14) was used to test 101 NTS isolates for sensitivity against ampicillin (amp 10µg), chloramphenicol

(chl, 30µg), gentamicin (cn, 10µg), co-trimoxazole (sxt, 25µg), cefuroxime (cxm, 30 µg), ciprofloxacin (cip, 1 µg), cefotaxime (ctx, 10 µg), amoxicillin-clavulanic acid (amc, 30 µg) and tobramycin (tob, 10 µg) commercially available disks (OXOID, Unipath Ltd, Basingstoke, Hampshire, UK). In addition minimum inhibitory concentrations of the same antibiotics was determined using the agar dilution technique as described by National Committee for Clinical Laboratory Standards(15). Pure antimicrobial powders of ampicillin, chloramphenicol, gentamicin, cefuroxime, ciprofloxacin and amoxicillin-clavulanic acid (Waki pure chemicals, Tokyo, Japan) were used to prepare doubling dilutions of the antibiotics in Mueller-Hinton agar(15). *E.coli* ATCC 25922 was used as quality control strain. Antimicrobial susceptibility data were interpreted according to the National Committee for Clinical Laboratory Standards(15).

RESULTS

Prevalence of non-typhi salmonellae associated with severe malaria: Results of blood and stool cultures are shown in Table 1. There were 9147 malaria cases admitted during the same time period of which 101/9147 (1.1%) had concomitant NTS infections (Table 2). The prevalence of NTS in the admitted population was found to be 1.68%(352/20938) and was 20.48% of all the pathogens isolated. The prevalence of NTS with severe malaria as a proportion of all NTS isolates varied between 0.8% and 1.5% between January 1997 and June 2001 (Figure 1). A seasonal variation in the occurrence of NTS was seen with an increased isolation rate immediately after the long rains of March to May and with a peak occurring from May to October. In 1999 during the El Nino rains, a peak was seen in January, which coincided with the abnormally heavy rains of that year.

Serotypes: Out of 352 salmonella that were isolated, 101 were from patients with severe malaria. Of the 101 NTS serotyped the most common serotypes were *S. typhimurium* 30/101(29.7%) and *S. enteritidis* 39/101 (38.6%).The other serotypes were seven isolates of *S. braenderup*, single isolates each of *S. blegdarm*, *S. bradford*, *S. heidelberg*, *S. hannover*, *S. lovelace*, *S. mkamba*, *S. rissen*, *S. ruzizi*, *S. seremban*, *S. subgenus II* and 15 isolates that could not be completely serotyped, designated as *Salmonella species*.

Age distribution of patients with NTS: The ages of children admitted to the paediatric or HDRW at KDH ranged between three months to 123 months of age with a median age of 21 months (IQR=10 to 35 months). Between the ages of 3-24 months there were 25 patients with *S.enteritidis*, 19 with *S. typhimurium* and 14 with other *Salmonella species*. The other age groups had between two and five isolates each of the three groups of serotypes isolated. Children between the ages of three months to 123 months were infected with both NTS and malaria. The most affected ages were between 3 to 24 months who represented 49/87 (56.32%) of all the patients. There were only six patients over 60 months of age.

Table 1

Number of paediatric samples cultured at the KDH (Kenya) during 1997-2001, positive samples, non-typhi salmonella (NTS) isolates and salmonella serotypes, identified by source

Source	No	No. positive	NTS	NTS + malaria	S. enteritidis(%)	S. typhimurium(%)	Other Salmonellae(%)
Blood	19,118	1395/19118 (7.3%)	260/1395	67	35(52)	23(34)	9(13)
Stool	1820	324/1820 (19%)	92/324	34	4(12)	7(21)	23(67)
Total	20938	1719/20938 (8.2%)	352/1719	101	39(39)	30(30)	32(32)

Table 2

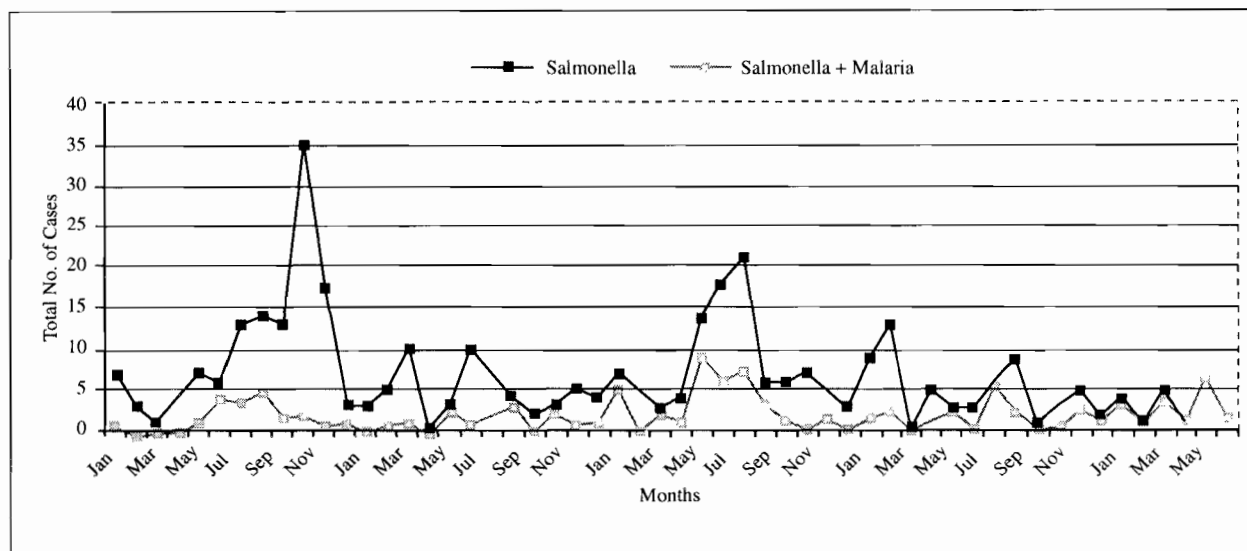
Number of malaria cases, salmonella cases and malaria with concomitant salmonella infection from children admitted to the paediatric and HDRW at KDH(Kenya) during 1997-2001

Infection type	1997	1998	1999	2000	2001	Total
Malaria	1769	1841	2398	2098	1041	9147
Salmonella and malaria	21(1.2%)*	14(0.8%)*	35(1.5%)*	16(0.8%)*	15(1.4%)*	101(1.1%)
Salmonella	131	66	76	57	22	352

* Salmonella and malaria as a percentage of all malaria admissions

Figure 1

Total cases of NTS and NTS with severe malaria from January 1997 to June 2001



Antimicrobial resistance and minimum inhibitory concentration profiles: Antibiotic resistance profiles of the NTS isolates associated with malaria (Table 3). Multidrug resistance (MDR) (isolates resistant to three or more drugs) was seen in 34(33.6%) of the isolates. There were 20 resistance types (resistypes) with the most common resistance type being Amp, cn, cxm, sxt,

ctx, amc, and tob with nine isolates showing this type of resistance. Forty-eight (47.5%) isolates were sensitive to all the antimicrobials tested. *S.typhimurium* showed consistently higher resistance than *S. enteritidis* for all the antibiotics tested except for chloramphenicol and ciprofloxacin (Table 4). The MIC ranges were , however the same for both serotypes.

Table 3

Antimicrobial resistance profiles of the NTS isolated from children with concomitant NTS and malaria infections admitted to the paediatric and HDRW at KDH (Kenya) during 1997-2001

Antimicrobial agent	No. and (% resistant) disc diffusion	MIC Range (g/mL)	MIC ₅₀	No. and (% resistant) MIC method
Ampicillin	35 (35.0)	1.0->256.0	16	35 (39.8)
Chloramphenicol	18 (18.0)	0.5->256.0	16	18 (20.4)
Gentamicin	22 (22.0)	0.125-16.0	2	20 (22.7)
Cefuroxime	29 (29.0)	16.0-32.0	16	23 (26.1)
Co-trimoxazole	39 (39.0)	0.032>32.0	0.047	43 (48.9)
Ciprofloxacin	3 (3.0)	2.0-8.0	2	1 (1.1)
Cefotaxime	14 (14.0)	8.0-64.0	16	12 (13.6)
Amoxycillin-clavulanic acid	26 (26.0)	8.0->32.0	8	26 (29.5)
Tobramycin	18 (18.0)	Not done	-	Not done

Table 4

Comparison of the antimicrobial resistance rates for the two major NTS serotypes isolated from patients with malaria

Antimicrobial	<i>S. typhimurium</i> % n=30	<i>S. typhimurium</i> MIC range	<i>S. enteritidis</i> (%) n=39	<i>S. enteritidis</i> MIC range
Ampicillin	70.0	16.0->256.0	20.5	1.0-256.0
Chloramphenicol	16.7	16.0->256.0	20.5	0.5->256.0
Gentamicin	60.0	0.190-4.00	0.0	0.125-4.0
Cefuroxime	56.7	16.0-32.0	20.5	16.0-32.0
Co-trimoxazole	73.3	0.032->32	30.8	0.032->32.0
Ciprofloxacin	0.0	2.0	2.6	2.0-8.0
Cefotaxime	30.0	8.0-64.0	7.7	8.0-64.0
Amoxycillin-clavulanic acid	56.7	8.0-64.0	15.4	8.0-16.0
Tobramycin	51.7	Not done	0.0	Not done

Clinical outcome: Analysis was done for 86 children (30 females and 56 males) whose data were complete. The overall mortality rate due to NTS occurring together with severe malaria was 13/86 (15.12%). Eight of the 30(27%) females died while 5 out of 56 males (9%) died. The relative risk for a female patient being discharged alive was 0.49 (OR=0.27, p-value=0.054). an association between sex of patient and NTS serotypes was sought but no statistical significance was observed (p-value=0.602). There was also no statistically significant association between clinical outcome, sex of patient and NTS serotype isolated in association with malaria (p-value=0.762).

DISCUSSION

During the period of this study, a prevalence of NTS in children admitted to KDH was found to be 1.68% (352 out of 1719). It was also found that up to 1.5% of all malaria patients had NTS. Conversely

about 29% of all the NTS patients had malaria while in Malawi(3). Thirty one point four percent of all NTS cases had malaria. Comparatively malaria was found to be present in 42% of all children with NTS in the Gambia(16). Even though results of this study indicate a slightly lower rate than these two locations there is a general trend indicating a rate of over 25% of all NTS cases having malaria. The isolation cases according to source was 67 out of 260 (25.8%) for blood isolates and 34/92 (36.96%) from stool cultures. These figures are similar to what was observed by Mabey *et al* (16) in the Gambia and by Dougle *et al* (17) in Mumias, Kenya.

Across all age groups, the main serotypes of NTS were *S. typhimurium* (29.7%) and *S. enteritidis* (38.6%). These results also agree with the observations of other workers(2,6,11,17). These two serotypes are the main causes of human salmonellosis worldwide(1). There was no association between any particular NTS serotype and malaria. A study is currently being carried out to determine the distribution of NTS serotypes and risk

factors for invasive NTS in this community.

In the developed world salmonellae are uncommon blood culture isolates with a frequency of under 10% (18,19). In the developing countries, however, NTS are a very common blood culture pathogen in children. Our results indicate a much higher isolation rate of 18.64% of NTS from blood cultures. Our figures compare with those from other regions of the developing world where rates from 11.3% to 50% have been reported (2,3,11,20,21).

Most of the children affected by severe malaria and NTS were below the age of five years. There was no significant association between the age of patient and NTS serotype, in accordance with observations of other workers(3,4) or between any particular NTS serotype and malaria. The age groups of three months to 24 months were mainly affected by *S. typhimurium* 16 out of 101 (15.84%) and by *S. enteritidis* 20 out of 101 (19.80%), which were also the main serotypes isolated during the study period. This situation was also true for the other age groups but in smaller numbers. The sex ratio of the patients was 1:1.9 for female:male. Other studies have found a consistently similar ratio of more males being affected than females(2,6,10). There is a need to seek an explanation for this phenomenon.

It has been observed that blood and stool cultures are inherently insensitive and that they could only be detecting up to 50% of all salmonella infections(2). If this figure of 50% is taken as the upper limit of isolation of NTS, it therefore, means that the NTS occurring with malaria is currently possibly underestimated by as much as 50%. The effect of this is that between 1.6% and 3.0 % of all malaria cases could be having salmonella infections. Malaria has been estimated to cause up to two million childhood deaths in sub-Saharan Africa each year. It could, therefore, be submitted that almost 60,000 or more of these deaths could possibly be due to the effect of infection by both NTS and severe malaria.

Antimicrobial sensitivity profiles of the 101 isolates against the nine antimicrobials tested showed a varied resistance profile. Previous studies have shown that the antibiotic resistance rates of salmonella species in Africa are alarmingly high(11,21,22). This high rate of MDR can translate to therapy failure especially when using the drugs of choice chloramphenicol and ampicillin. Some authors have argued against the antibiotic therapy for salmonellosis(10), suggesting that it caused no improvement in terms of duration of fever and severity and duration of diarrhoea(23). Sirinavin *et al* (24) have argued that because severe complications of extraintestinal infection due to NTS can occur, it is sometimes difficult to decide whether to give antimicrobial drugs to patients with suspected or proven NTS diarrhoea. Another study by Elliot *et al*, (25) indicated that antibiotic treatment of uncomplicated

salmonella gastroenteritis might prolong the carrier state and increase the incidence of relapse. treatment is not recommended unless there is accompanying septicaemia or metastatic infection, when choice of antibiotic is based on sensitivity testing (25). Chloramphenicol has been the drug of choice for the enteric fevers caused by sensitive organisms (25) but this is now debatable as evidenced by the level of resistance observed in this study. This situation is different from that of Malawi(3) where a resistance rate of chloramphenicol of 0.3% was observed.

The presence of high levels of multidrug resistance in this area of Kenya and elsewhere is cause of concern in the choice of therapy. The problem is compounded by the ease of transfer of resistance between enterobacteriaceae(20). The children involved in this study were sick enough to require admission; and therefore, antibiotic treatment were justified. From the antimicrobial resistance profiles, however, the real possibility of therapy failure has been demonstrated by the high rates of resistance to chloramphenicol observed. Antibiotic sensitivity testing and surveillance for changes in resistance profiles is still important.

Clinical outcome for those 101 children with both malaria and NTS was analysed and showed overall mortality rate of 13 out of 86 (15.12%). Mortality rates for females (27%) were higher than for males (9%). This association between clinical outcome and sex of child was statistically significant (p-value =0.032). Females have a poor prognosis as more males get ill but more females die. A larger case-controlled study is desirable to answer this question. The reported mortality rate for malaria in this area is about 3.5%(7). Mortality of NTS and malaria combined is about three times higher than for malaria alone. The combination of these two conditions could lead to a rapidly evolving severe illness with a higher mortality rate than for either condition alone(9). NTS have been associated with higher mortality rates than for other infections. The mortality figures we observed are comparable to those reported from other areas of the developing world(3,24). There is a need to investigate if the occurrence of severe malaria in combination with NTS and for which high mortality rate has been observed is coincidental or there is a demonstrable association.

There is no information on the mechanism of interaction between NTS and malaria parasites *in vivo*. Several studies have tried to postulate on the mechanisms of association between NTS and malaria (9,26-31). Although the above studies have indicated several possibilities, it is still not clear which event takes place first. From this study, we conclude that NTS and severe malaria occurring together are a problem in this area and that a large number of the isolates are MDR. A high mortality rate has also been associated with these diseases in this area with a significant association being female. Two Salmonella serotypes are responsible for

the majority of these infections namely, *S.typhimurim* and *S. enteriditis*. The NTS affect mainly children under the age of five years and with no significant association between age of child and any particular NTS serotype. This could be due to their immature immunological response.

We propose that during sequestration, in mesenteric vessels *Plasmodium* parasites make these vessels porous and hence open them up to invasion by salmonella from the gut. The salmonella finds a medium rich in iron, which it needs both for growth and virulence. This may explain why an occurrence of both NTS and *Plasmodium* leads to a severe illness and high mortality. A more elaborate case-case-control study is required to elucidate the chain of events of both NTS and malaria parasite co-existence.

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