East African Medical Journal Vol. 95 No. 2 February 2018
CHARACTERISTICS OF FEBRILE CHILDREN IN A MALARIA/HIV CO-ENDEMIC REGION OF WESTERN KENYA
Irene K. Marete, MBChB, MMed (Paeds), MPH, PhD Department of Child Health and Paediatrics, School of Medicine Moi University. Peter W. Saula, MBChB, MMed (Gen.Surg), MMed (Paed.Surg) Department of Surgery and Anaesthesiology, School of Medicine, Moi University. Justus M. Simba; MBChB, MMed (Paeds) Department of Child Health and Paediatrics, School of Medicine, Jomo Kenyatta University of Agriculture and Technology.

Corresponding author; Irene Marete, MBChB, MMed (Paeds), MPH, PhD, Moi University P.O. BOX 1998 -30100 Eldoret, Kenya Email address; mareteirene07@yahoo.com

CHARACTERISTICS OF FEBRILE CHILDREN IN A MALARIA/HIV CO-ENDEMIC REGION OF WESTERN KENYA

I. K. Marete, P. W. Saula and J. M. Simba

ABSTRACT

Background: **Fever is still a priority health problem in the paediatric population. The cause of fever in children in resource-limited settings is not always investigated and thus clinical characteristics are relied on to make presumptive diagnosis especially for malaria.**
Objectives: **To determine the demographic, clinical and haematological characteristics of febrile children in the context of their HIV and malaria parasitemia status.**
Design: **A cross-sectional comparative hospital based study was carried out on febrile children seeking care in the ambulatory clinics.**
Setting: **Webuye Sub-County Hospital in western Kenya.**
Main Outcomes: **Demographic and clinical characteristics for those who met the inclusion criteria. Malaria parasitemia using blood slide and haematological characteristics based on complete blood count.**
Results: **A total of 282 febrile HIV-infected and 332 Non-HIV-infected were recruited into the study. Prevalence of malaria parasitemia was 84% and 51.2% among HIV-infected and the non-HIV-infected febrile children respectively. Of the HIV-infected, 97% were on cotrimoxazole. The HIV-infected were significantly older than the non-infected with a median age of 59 (IQR43, 89) and 48(IQR36, 60) months respectively. Splenomegaly, hepatomegaly and anaemia were more common among the HIV-infected (p-value 0.000, 0.0001 and 0.000 respectively). However, these HIV-infected children had generally more favourable haematological parameters (haemoglobin & MCV) compared to the HIV-non- infected (p-value≤0.0001).**
Conclusion: **HIV infected children with malaria parasitemia were significantly older than non-HIV infected in western Kenya. The HIV infected children however had better haematological parameters compared to the non-HIV infected. There is need to intensify other preventive measures for malaria in**

this community as it appears cotrimoxazole prophylaxis does not confer additional benefit to those with HIV.

INTRODUCTION

Fever is still a priority health problem in the paediatric population, accounting for 30-40% of all the outpatient visits in our health facilities. Malaria is an important cause of fever in the tropics and subtropics. It was responsible for the deaths of 438,000 people in 2015 mostly among African children(1).

Several guidelines are in place on the approach of a febrile child. However all these are based on the geographical region and the already documented disease epidemiology in the region. In the last decade, there has been an epidemiological transition especially in the tropic and subtropics where malaria is thought to be the commonest cause of paediatric fever. This transition has seen a reduction in malaria transmission.The HIV pandemic however has further complicated the diagnosis of fever among children in the malaria endemic regions where malaria and HIV usually coexist. Apart from predisposing children to other common infections presenting with fever, the medications used in prophylaxis of opportunistic infections (OI) in these children is also known to prevent malaria. However, the extent to which it does this is still not known especially in this region where anti-folate resistance by malaria parasites is widespread. Other malaria and HIV interactions have not been well documented among children as various studies done on this are not conclusive.

We sought to document the demographic and clinical characteristics in two cohorts of children: one infected with HIV; and the other not infected in a malaria endemic region where close follow up for the HIV children has been done. This study therefore determined the demographic, clinical and haematological characteristics of febrile children in the context of their HIV and malaria parasitemia.

METHODS

A cross-sectional comparative study involving two cohorts of febrile HIV infected and non- HIV infected children was conducted at Webuye Sub-County Hospital, Bungoma County. This is located in western part of Kenya, which is a malaria endemic area. Recruitment of study participants was done at the pediatric ambulatory clinics (general pediatric clinic and the pediatric HIV clinic). Further details of this clinic as well as the study methods were provided in a related publication (2).

A minimum sample size of 217 for each cohort was calculated. A systematic sampling technique was applied for these two groups of participants. Eligibility criteria were assessed and axillary temperature was obtained using a clinical digital thermometer BK4301Models.

Informed consent was obtained. An interviewer-administered questionnaire was then administered. Blood samples were obtained for blood slide for malaria parasite as well as for complete blood count, which was analyzed using an automated blood analyzer.

Data was analysed using STATA version 10. It was presented as descriptive statistics of measures of central tendency and those of dispersion. Chi square and Kruskal Wallis test were used to test associations between the dependent and independent variable. Fischer's exact test was used where values in the cells were less than five. A P-value of 0.05 or less was considered significant. All ethical requirements were met (2).

RESULTS

Two hundred and eighty two febrile HIV infected and 332 non-HIV infected children were recruited into the study during the study period (November 2011 to January 2013).

The prevalence of malaria parasitemia was found to be 84.4% among the HIV infected febrile children while the HIV non- infected had a parasitemia prevalence of 51.2%. 97% of the HIV infected children were on cotrimoxazole prophylaxis**.**

Median age was significantly higher in the HIV infected group compared to the non-HIV-infected group. Other clinical characteristics are as shown in Table 1.

Table 1

Comparison of socio-demographic and anthropometric characteristics of febrile HIV infected and Non -infected children

	Frequency (%)		
Variable	**HIV+**	**HIV-**	**p-value**
Age in months	N=282	N=308	0.0001
Mean(STD*)	52.18(25.95)	52.18(25.95)	
Median (IQR#)	59(43, 89)	48(36, 60)	
Height (cm)	N=58	N=321	0.0001
Mean(STD)	83.81(48.2)	64.9(43.45)	
Median (IQR)	97.5(19, 123)	85(12, 96)	
Weight (Kg)	N=281	N=330	0.0001
Mean(STD)	18.91(13.1)	15.74(19.34)	
Median (IQR)	16(14, 23)	14(12, 16)	

**STD- standard deviation; #IQR- Interquartile range*

The age distribution of the study participants was skewed toward the ages above 1year with very few infants being recruited into the study. More than 47% were above 5 years in the HIV infected group (Table 2).

Table 2

Age distribution of the febrile children in the context of their HIV status

Age Categories	HIV Infected	Non-HIV Infected
< 6 months	11	3
6-12 months	7	0
1-5 years	131	238
> 5-14 Years	133	67

Clinical symptoms: Running nose and abdominal pain were the commonest symptoms in the HIV infected while headache and joint pains were the commonest among the HIV non-infected, as shown in Table 3.

Table 3
Clinical symptoms of the participants in the context of their HIV status

	Frequency (%)		
Symptoms	**HIV+**	**HIV-**	**p-value**
Vomiting	96(34)	123(37)	0.438
Diarrhoea	75(26.6)	55(16.6)	0.002
Chills	39(13.8)	48(14.5)	0.824
Sweating	13 (4.6%)	124 (37.3%)	0.000
Anorexia	13(4.6)	124(37.3)	0.296
Headache	198(70.2)	220(66.3)	0.000
Abdominal pains	250(88.7)	133(40.1)	0.000
Convulsions	236(83.7)	134(40.4)	0.179
Cough	26(9.2)	21(6.3)	0.003
Joint pains	139(49.3)	203(61.1)	0.000
General Malaise	220(78)	25(7.5)	0.000
Runny nose	248(87.9)	148(44.6)	0.000
Difficulties breathing	20(7.1)	141(42.5)	0.002

Clinical signs: Splenomegaly, hepatomegaly and anaemia were significantly more common among the HIV infected compared to the non-infected (P-value 0.000). (Table 4)

Table 4
Clinical signs among the febrile children in the context of their HIV status

	Frequency (%)		
Signs	**HIV+**	**HIV-**	**p-value**
Splenomegaly	39(13.8)	4(1.2)	0.000
Hepatomegaly	14(5)	2(0.6)	0.001
Anaemia	76(27)	30(9)	0.000
Skin rash	28(9.9)	33(9.9)	0.996
Drowsiness	7(2.5)	61(18.4)	0.000
Reduced skin turgor	89(31.6)	1(0.3)	0.000
Prolonged capillary refill	62(22)	3(0.9)	0.000
Sweating	25(8.9)	29(8.7)	0.995
Kussmauls breathing	17(6)	1(0.3)	0.000
Tachypnea	249(88.3)	22(6.6)	0.000
Tachycardia	232(82.3)	31(9.3)	0.000
Coma	0(0)	2(0.6)	0.192

Haematological characteristics: Mean platelet counts, mean haemoglobin level and mean MCV levels were found to be significantly higher in the HIV infected group. (Table 5)

Table 5

Comparisons of haematological characteristics of febrile HIV infected and non-infected children

Variable	Frequency (%) HIV+ve	HIV-ve	p-value
WBC (x 10^3/µl)	N=282	N=332	0.6328
Mean(STD)	8.64(6.54)	8.24(6.74)	
Median (IQR)	6.6(4.9, 10.4)	7.25(1, 11.25)	
Platelets (x 10^3/µl	N=282	N=332	0.0075
Mean(STD)	370.75(352.91)	293.75(329.76)	
Median (IQR)	280.5(130, 490)	275.5(1, 425)	
Hb (g/dl)	N=282	N=332	0.0001
Mean(STD)	10.62(3.96)	8.13(4.77)	
Median (IQR)	11.05(7.9, 13.1)	10.3(1, 11.9)	
MCV (fl)	N=282	N=332	0.0001
Mean(STD)	77.05(15.45)	53.36(32.11)	
Median (IQR)	76.5(66.6, 87.1)	66.25(1, 76.1)	

Ref. values WBC 4-9 MCV 80-100 PLT 120-380 Hb 12-18

Correlation coefficient (r) of < 1 was found for the correlation between age and various haematological characteristics.

Clinicians approach to the management of febrile children based on their HIV status: The clinical diagnosis, investigations and treatment were more likely to include malaria if a febrile child was Non –HIV infected compared to an HIV infected child. However, a febrile HIV infected child is more likely to have positive malaria parasitemia as compared to a non-HIV infected child at 84.4% and 51.2% respectively. These are shown in more details in Table 6.

Table 6

Clinical decisions in the management of febrile children in the context of HIV status

Signs	Frequency (%) HIV+N=282	HIV- N=332	p-value
Diagnosis			
Includes malaria	263(93.3)	324 (97.6)	0.009
Investigation			
Includes BS for MPS	273 (96.8)	329 (99.1)	0.041
Treatment			
Includes anti-malarial	231 (81.9)	302 (91.0)	0.001
Blood slide for malaria Positive	239 (84.4)	170 (51.2)	0.000

DISCUSSION

Malaria parasitemia prevalence was found to be high (52%) among febrile non-HIV infected but even higher (84.4%) among the HIV infected febrile children. The question emerging from this study is whether we are already losing the gains made in the fight against malaria while we are supposed to be working towards total malaria elimination. The emerging infections such as HIV in this study setting could be causing the reversal in the gains. Our finding of a positive association between HIV-positive status and malaria incidence is consistent with reported findings among adults in Malawi and

Uganda (3,4) and corroborates findings from other previous studies that reported higher malaria morbidity and mortality for HIV-positive compared to HIV-negative Kenyan and Ugandan children(5,6). High asymptomatic parasitemia have been reported in several studies hence the fever may be due to other bacterial infections or even drug reactions (7) as high as 39% carrier states have been reported in some parts of Africa(8). Among infants in the same region asymptomatic prevalence has been reported to be as high as 61% (9). Other common causes of fever include bacteraemia, urinary tract infections, and pneumonia with increased risk of serious disease in the more immunosuppressed (5). Some drugs used by the HIV infected children such as Abacavir have occasionally been reported to cause hypersensitivity reactions that manifests with fever.

We found a higher prevalence of malaria parasitemia in older children for the HIV infected cohort. This different has been found elsewhere where febrile children with HIV was more likely among those less than 2 years in a Nigerian study (10). The shift in age of malaria may be partially attributed to the initiatives which focus more in under 5s and pregnant women. Although in that set up only 49.1% of pregnant women used nets (11). This preposition doesn't seem to hold for the HIV non-infected. We postulate therefore, the diminishing immunity among the HIV infected children may affect their protection against malaria as they become older as has been documented before (12).

Clinical characteristics of febrile children:

In the HIV and non HIV infected groups, vomiting, headache, joint pains and running nose were the top common symptoms while convulsions and abdominal pain were found to be more prevalent in the HIV infected group. Sweating and difficulty in breathing were significantly higher in the non HIV infected group. Drowsiness was common in the HIV non infected group while splenomegaly, hepatomegaly, anemia, reduced skin turgor, prolonged capillary refill, tachypnea and tachycardia were common in the HIV infected group. It appears that among the HIV non-infected, malaria is likely to present typically while in the HIV infected atypical presentation is common with presentation of chronic disease characteristics such as splenomegaly and severe disease manifestations such as coma and convulsions. Some of the findings such as reduced skin turgor and reduced capillary refill may be manifestations of other concurrent diseases such opportunistic infections which present with diarrhoea and dehydration. HIV infection increases the incidence and severity of clinical malaria.

Clinical overlap between malaria and other common childhood illnesses e.g. pneumonia exists and should be noted with important implication for case management strategies and evaluation of disease. In our study running nose and difficulty in breathing were commonly cited symptoms. The rates of occurrence of these symptoms may vary with season and malaria transmission rates. (13).

Clinical presentation will vary with age and malaria endemicity in the region. However fever is a common finding even in those with severe forms of malaria such as cerebral malaria (14). Headache has also been found in 89.5 % of those with cerebral malaria (14). In our study headache was a common finding however all our patients had uncomplicated malaria.

Haematological parameters that were assessed were found to be within normal for the HIV infected group while haemoglobin level and MCV were found to be low in the non HIV infected group. This is consistent with findings from other studies conducted in malaria endemic regions. Acute and repeated malaria infections can lead to anaemia among children living in a malaria endemic region like the sub-Saharan African children (15,16). However, the connection

between malaria and anaemia is difficult to define because some people experience parasitemia in the absence of malarial disease (16).Whereas others become anaemic as parasites are cleared (17). Unfortunately this anaemia has been associated with poor treatment outcomes in our set up (18-19).

It was however of interest to note that these findings were not present in the HIV infected group of febrile children. In this study the HIV infected children were recruited from a comprehensive HIV care clinic where children are seen regularly in the clinic for check-up. During these appointments haemoglobin level among other tests are done regularly. In case a child is found to have anaemia they are treated immediately.

In conclusion, HIV infected children with malaria parasitemia are more likely to be older than non-HIV infected with malaria parasitemia. Haematological parameter were however better in the HIV infected group with malaria parasitemia. There is need to intensify other preventive measures for malaria in this community as it appears cotrimoxazole prophylaxis does not confer additional benefit to those with HIV.

REFERENCES:

1. WHO. World malaria report 2015. Geneva: 2015.
2. Marete, I., Mutugi, M., Lagat, Z., Obala, A., Simba, J., Mwangi, A., et al. Malaria Parasitaemia among Febrile Children Infected with Human Immunodeficiency Virus in the Context of Prophylactic Cotrimoxazole as Standard of Care: A Cross-Sectional Survey in Western Kenya. *East Afri Med J.* 2014;**91(1)**:21-8.
3. Mundy, C., Ngwira, M., Kadewele, G., Bates, I., Squire, S.B., and Gilks, C.F. Evaluation of microscope condition in Malawi. *Trans R Soc Trop Med Hyg.* 2000;**94**:583-4.
4. Kalyesubula, I., Musoke-Mudido, P., Marum, L., Bagenda, D. Aceng, E., Ndugwa, C, et.al. Effects of malaria infection in human immunodeficiency virus type 1-infected Ugandan children. *Pediatr. Infect. Dis. J.* 1997;**16(9**):876-81.
5. Kirinyet, J.K. Falciparum malaria and response to anti malarial therapy (Coartem and quinine) in HIV patients in western Kenya (Kisumu). Jomo Kenyatta University of Agriculture and Technology, Nairobi; 2011. *Unpublished PhD Thesis*
6. Sandison, T.G., Homsy, J., Arinaitwe, E., Wanzira, H., Kakuru, A, Bigira V, et al. Protective efficacy of co- tromoxazoe prophylaxis against malaria in HIV exposed children in rural Uganda; a randomised clinical trial. *BMJ.* 2011;**342**:1617.
7. Okiro, E.A., Alegana, V.A., Noor, A.M., and Snow, R.W. Changing malaria intervention coverage, transmission and hospitalization in Kenya. *Malar J.* 2010;**15(9)**::285.
8. Mabunda, S., Aponte, J.J., Tiago, A., and Alonso, P. A country-wide malaria survey in Mozambique. II. Malaria attributable proportion of fever and establishment of malaria case definition in children across different epidemiological settings. *Malar J.* 2009;**8**:74.
9. Marete, I.K., Koskei, P., Koskei, A., and Nyandiko, W.. Malaria parasitemia among asymptomatic Infants Seen in a Malaria Endemic Region of Western Kenya. *East Afr Med J.* 2016; **93(4)**: 135-140.
10. Pondei, K., Kunke-Oluwu, O.E., and Peterside, O. Patterns of acute febrile illness in children in a tertiary health institution in Niger region of Nigeria. *J Med and Med. Sci.* 2012;**3(11**): 743 - 740.
11. Wasike, E.W. The prevalence of malaria anaemia and the use of insecticide treared nets among expectant women during high transmission season in Bungoma District, Kenya. Jomo Kenyatta University of Agriculture and Technology, Nairobi. 2007 *Unpublished Master of Science Thesis.*
12. Muema, D.K.M., Ndungu, F.M., Kinyanjui, S.M., and Barkely, J.A. Effects of HIV infection on the acute antibody response to malaria antigen in children: An Observational Study. *Malar. J.* 2011; **10**:55
13. O'Dempsey, T.J., McArdle, T.F., Laurence, B.E., Lamont, A.C., Todd, J.E., and Greenwood, B.M. Overlap in the clinical features of pneumonia and malaria in African children. . *Trans R Soc Trop Med Hyg.* 1993;**87(6):**662-5.

14. Esamai, F., Nabakwe,E., Mining, S., Forsberg, P., and Lewis, D.H. Clinical presentation and diagnosis of cerebral malaria in children in the highlands of western Kenya. *East Afr Med J.* 1999;**76(2)**:89-92.

15. Newton, C.R., Kirkham, F.J., Winstanley, P.A., Pasvol, G., Peshu, N., Warrell, D.A., et al. Intracranial Pressure in African Children with Cerebral Malaria. *Lancet.* 1991;**337**:573-6.

16 Newton, C.R., Taylor, T.E., and Whitten, R.O.. Pathophysiology of fatal falciparum malaria in African children. *Am J Trop Med and Hyg.* 1998;**58**:673–83.

17. Marsh, K., Forster, D., Waruiru, C., Mwangi, I., Winstanley, M., Marsh, V., et al. Indicators of life-threatening malaria in African children. *N Engl J Med.* 1995;**332**:1399–404. 18 Crawley, J. Burden of clinical management and anemia in African children. *Am J Trop Med Hyg.* 2004;**71(2)**:25–34.

19 Murphy, S.C. and Breman, J.G. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurologic sequelae, anemia, respiratory distress, hypoglycemia and complications of pregnancy. *Am J Trop Med Hyg.* 2001;**64(12)**:57–67.