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PREVALENCE AND CLINICAL FORMS OF MALARIA AMONG FEBRILE HIV-INFECTED CHILDREN SEEN AT USMANU DANFODIYO UNIVERSITY TEACHING HOSPITAL, SOKOTO, NIGERIA

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Abstract

Background: Malaria and HIV infections are major health problems facing the world today. Sub-Saharan Africa with 10 percent of world's population harbors more than half the burden of the scourge. The present study determined the prevalence and clinical forms of malaria among febrile HIV-infected children aged 3months to 15years, seen in Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria.
Materials and Methods: Cross-sectional study among febrile HIV-infected children and their control cohort were carried out between May and October 2016. The participants had the following investigations: malarial parasite, packed cell volume, random blood sugar, retroviral test.
Results: A total of 140 febrile HIV-infected children aged 3 months to 15 years and 140 febrile HIV-negative age- and gender-matched children were recruited; 100 of the HIV-infected children were on ART and cotrimoxazole. The prevalence of malaria among the febrile HIV-infected children was 71.4% (100/140) which was significantly lower than the prevalence of 94.3% (132/140) among the control group (χ^2 27.72, p=0.001). Among the febrile HIV-infected children that had malaria, 54(54.0%) had uncomplicated malaria while 46(46.0%) had severe malaria. Of the 132 controls that had malaria, 48(36.4%) had uncomplicated malaria and 84(63.6%) had severe malaria (χ^2 =7.184, p=0.007).
Conclusion: Malaria is a problem in HIV-infected children. Since nearly half of the febrile HIV-infected children had severe form of malaria, it is recommended that health promotion, intermittent malaria prophylaxis, early diagnosis and prompt effective treatment should be instituted for HIV-infected children. This may prevent severe form of malaria and its attendant mortality.

Key words: Malaria; Prevalence and clinical forms of malaria; Febrile, HIV-infected, Sokoto state.

List of Abbreviations: Artemisinin-based combination therapy (ACT); Acquired immune-deficiency syndrome (AIDS); Antiretroviral therapy (ART); Ethylene diamine tetra acetate (EDTA); Enzyme-linked immunosorbent assay (ELISA); Emergency Paediatric Unit (EPU); Paediatric Outpatient Clinic (POPC); Human Immunodeficiency Virus (HIV); Polymerase Chain Reaction (PCR); Parasite density (PD); Paediatric Medical Ward (PMW); Parasitized red blood cells (PRBCS); Retroviral Screening (RVS); and Rapid Diagnostic Test (RDT); World Health Organization (WHO).

Introduction

Malaria is a major global health problem with 3.2 billion people at risk of developing malarial infection. About half a million people died from malaria in the year 2017, and more than 90% of malaria cases and deaths occurred in sub-Saharan Africa, including Nigeria (WHO, 2018). Malaria is still a major killer of under-5 children (WHO, 2018).

Human immunodeficiency virus (HIV) infection is also a major health problem facing the world today, with nearly 78 million people who have contracted HIV infection since the onset of HIV pandemic, and close to 39 million people have died from acquired immunodeficiency syndrome (AIDS) (UNAIDS, 2018 ; HIV/gov, 2019). In 2017, approximately 37 million people worldwide were living with HIV infection, 1.8 of these were children below 15 years (HIV/gov; WHO; 2019). Sub-Saharan Africa is home to 25.7 million of people living with HIV (HIV/gov, 2019).

The geographical occurrence of both malaria and HIV infections in sub-Saharan Africa may result in malaria/HIV co-infection among populations at risk of each infection. Yet, the interaction between these two infections has been little studied ((Hochmam and Kim 2009, Chandramohan and Greenwood 1998). Interaction may occur because infection with HIV causes cellular immunosupression and thus may result in impaired immune response to malaria, leading to reduced capacity to either prevent or suppress malarial parasitaemia and possible development of clinical disease. This may result in increased incidence of clinical malaria, severe form of malaria in HIV infected children compared to non-infected children. Such that, the negative effect of HIV on the disease course or outcome for malaria can increase malaria severity and mortality with significant impact on public health because of the large number of people at risk of co-infection in sub-Saharan Africa, including Nigeria (HIV/gov, 2019, UNAIDS, 2018).

Earlier studies in African children and adults only demonstrated malaria and HIV co-infection without any major interaction of clinical importance (Greenberget al., 1991; Kalyesubula et al., 1997; Müller and Moser 1990; Nguyen- Dinh et al., 1987; Simooya et al., 1988; Niyongabo et al., 1994). Recently, studies in sub-Saharan Africa have reported increased risk of malarial parasitaemia and clinical malaria in HIV-infected populations compared to HIV-negative groups (Francesconi et al., 2001; Patnaik et al., 2005; Whitworth et al., 2000). However, most of these studies were carried out among adult populations (Francesconi et al., 2001; Patnaik et al., 2005; Whitworth et al., 2000).

In Nigeria, despite the high occurrence of both malaria and HIV, and the vulnerability of children to both pathogens, there is paucity of data regarding the clinical implication of HIV and malaria co-infection, especially among children (Iroezindu et al., 2012). Although increased prevalence of malarial parasitaemia in HIV-infected population has been documented in a few studies (Onyenekwe et al., 2007; Akinbo et al., 2009; Uneke et al., 2005), clinical malaria was not investigated in most of the available reports (Onyenekwe et al., 2007; Akinbo et al., 2009; Uneke et al., 2005). Also, most of these studies were conducted in adults, thus making it difficult to generalize the findings to paediatric population (Onyenekwe et al.,2007; Akinbo et al., 2009; Uneke et al., 2005).

To the best of the investigators' knowledge, there is no study in Sokoto, North-Western Nigeria that investigated the prevalence and clinical forms of malaria among febrile HIV-infected children. This study was conducted to assess the prevalence and clinical forms of malaria among febrile HIV-infected children, compared with febrile non-HIV infected children as seen in the study area. These findings may provide evidence on the need to integrate malaria control programmes to the care and treatment of HIV-infected children at various levels of the health care system. Also, in the face of scarce resources for integrated health service delivery, this evidence may help to tailor such control programmes to communities with convincing evidence.

Materials and Methods

Study area

The study was carried out at the Paediatrics Outpatient Clinic (POPC), Paediatrics ART Clinic, Emergency Paediatrics Unit (EPU) and Paediatrics Medical Ward (PMW) of the Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto, Nigeria. The Hospital is a tertiary Health Facility in North-Western Nigeria, that serves as a referral centre for more than 10 million people from Sokoto, Zamfara, Niger, Kebbi and Katsina States, and the neighbouring Niger and Benin Republics in the West African sub-region.

Malaria occurs throughout the year in Sokoto, with the peak incidence (59.5%) in the month of August and lowest incidence in March (9.18%) (Abdullahi et al., 2010). Malaria is meso-endemic from January to August and hyper endemic from September to December (Jiya et al., 2010). The mean sporozoites rate in Sokoto is 0.4%.Patricia, 2011

Study design.

The study design was a comparative cross-sectional. The duration of the study was six months (May, 2016 to October, 2016).

Study population.

The study was conducted among two groups; the first group comprised of febrile HIV- infected children aged 3 months to 15 years presenting to Pediatrics Antiretroviral Therapy (ART) clinic of UDUTH Sokoto with complaint of fever or recorded temperature $\geq$ 37.5^{o}C (subject). The second group were the controls and comprised of age- and sex-matched

febrile non-HIV infected children attending the POPC, EPU and PMW with complaint of fever or with documented temperature $\geq$ 37.5^{o}C. Selection of control was by one-to-one matching with the age and gender of the subjects.

Sample size

The minimum sample size (n) was determined as follows (Araoye, 2004):

$N=z^2pq/d^2$

where N= minimum sample size.

Z = the standard normal deviation set at 1.96.

p = prevalence of malaria among HIV-infected children which was 9.1% (0.091) from previous study in Nigeria.(Okonko et al., (2012)).

The minimum sample size was 126; assuming an attrition rate of 10%, the investigator enrolled approximately 140 children (126+13 = 139) into each group as subjects and controls.

Sampling technique

All children presenting with fever and who met the eligibility criteria were recruited consecutively into the respective group until the required sample size was obtained over a six month period (1st May 2016 - 31st October 2016).

Inclusion Criteria

For Subjects: Confirmed HIV infected children, aged 3 months to 15 years with axillary temperature $\geq$37.5^{o}C or complaint of fever whose parents gave written informed consent, or those $\geq$ 7 years that gave assent (Waligora et al., 2014).

For Controls: Confirmed HIV infected children, aged 3 months to 15 years with axillary temperature $\geq$37.5^{o}C, or complaint of fever whose parents gave informed written consent or those $\geq$ 7 years that gave assent.

Exclusion criteria for both subjects and controls

Prior anti-malarial treatment (<2weeks) before presentation, patients with known background of chronic illnesses like sickle cell anaemia, malignancy, allergic disorders, severe malnutrition (not due to HIV infection) and children with obvious clinical features of alternative causes of fever other than malaria were also excluded.

Ethical clearance

Ethical approval was obtained from the Hospital's (UDUTH) Health Research and Ethics Committee (UDUTH/HREC/2015/No.341), while informed written consent was obtained from the parents or caregivers. Additionally, assent was obtained from children aged 7 years and above (Waligora et al., 2014).

The cost of tests of blood film for malarial parasite, HIV infection, CD4 count and malaria treatments was partly borne by the investigators and partly by the management of UDUTH.

Subjects and controls recruited were assigned identification numbers details of which were kept confidential by the investigators. The content of the consent form was read and interpreted in a language that the parent/caregiver understood. The consent form provided information on the importance of the study; the blood tests required for the study and need for anti-malarial treatment for those with malaria.

Data collection

A proforma was used to obtain information on socio-demographic characteristics, clinical parameters of participant, other symptoms that may present with fever and laboratory result of participants. Socio-economic class of the parents was determined using Oyedeji's classification (Oyedeji, (1985).

Laboratory Methods

Venipuncture technique was used to obtain 2.0 ml of blood into ethylene diamine tetra acetate (EDTA) vacuette container at presentation under aseptic condition. Universal precaution was assured by investigator in handling these highly infectious samples.

Investigations carried out include HIV serology tests; ELISA for HIV I and II to rule out HIV infection among controls, those < 18 months with positive serology further had HIV DNA PCR for confirmation of HIV infection. In both group (subjects and controls); blood film for malarial parasite, random blood sugar and packed cell volume were done to classify the form of malaria.

Microscopic diagnosis of malaria using thick blood film was used in this study.(Tangpukdee et al., 2009;Warhurst and Williams 1996).

The calculation for parasite density (number of parasites/microlitre) required total white blood cell count (WBC). However, in the absence of a complete blood count, a value of 8000 WBC was assumed.

Parasite density was calculated using the formula: (Pakistan, 2009).

$$\frac{\text{No of observed asexual parasites in microscopic fields}}{\text{Number of WBC counted.}} \times 8000 \text{ WBC} = \text{parasite/microlitre}$$

A negative result was assumed when no asexual parasites are found after counting 200 leucocytes under the microscopic fields, or viewing 100 fields through high power (100HPF). Negative slides were re-examined by the consultant microbiologist for validation of procedure.

Data Analysis

Data analysis was done using the IBM Statistical Package for Social Sciences (SPSS) version 23.0 software. At confidence interval of 95%, p-value of 0.05 or less was regarded as statistically significant.

Results

The Socio-Demographic Characteristics of the Participants

As shown in Table I, the mean age of the HIV-infected children was 5.46 ± 4.10 years (range: 3 months – 15 years), while the mean age for the non-HIV-infected children was 5.51± 4.05 years (range 3 months– 15 years). There was no statistically significant difference in the mean age (t=0.11, p=0.9.), age distribution (χ^{2*}= 0.0001, df=2, p =1) and sex distribution (χ^2=3.24, p=0.07) of the HIV-infected children and the non-HIV infected children. However, a statistically significant difference was found in the socio-economic distribution of the HIV-infected children compared with the non-HIV infected children (χ^2=62.4, p<0.0001).

One hundred (100/140=71.4%) of the HIV-infected group were on ART, while 40(40/140=28.6%) were newly diagnosed HIV-infected children who were not on ART, but were eventually commenced on ART.

Table 1: Socio-demographic characteristics of the participants

Variables	HIV-infected (n = 140) Frequency (%)	Non-HIV infected (n = 140) Frequency (%)	Test of significance
Age (in years)			
Minimum	0.25years	0.25years	t* = 0.11,
Maximum	15.00years	15.00 years	p = 0.90
Mean	5.46 ± 4.10	5.51 ± 4.05	
Age group (in years)			
0.25 – 5.0	69 (49.3)	69 (49.3)	χ^{2*}= 0.000
6.0 – 10.0	51 (36.4)	51 (36.4)	df=2
11.0 -15.0	20 (14.3)	20 (14.3)	p = 1
Sex			
Male	71 (50.7)	72 (51.4)	χ^{2*}= 3.24
Female	69 (49.3)	68 (48.6)	df=1
			p = 0.07
Socio-economic status			
Upper class	12 (8.6)	16 (11.4)	χ^{2*}= 62.4
Middle class	24 (17.1)	84 (60.0)	df=2
Lower class	104 (74.3)	40 (28.6)	p < 0.0001

t* = unpaired t test. χ^{2*} = Pearson`s chi-square

Prevalence of malaria among febrile HIV infected and non-HIV infected children

Among the (140) febrile HIV-infected children, 100 (71.4%) had malarial parasite, whereas, of the 140 non-HIV infected children recruited, 132 (94.3%) showed positive results for malarial parasites. This difference was statistically significant $p< 0.0001$, $\chi^2 = 27.73$ as shown in Table 2. Prevalence of malaria among the HIV-infected children was found to be significantly related to sex ($p<0.0001$), age ($p<0.0001$) and socio-economic class ($p<0.0001$), compared with the non-HIV infected children, where the prevalence of malaria was only significantly related to age ($p=0.013$), but not to sex or socio-economic class ($p=0.93$, $p=0.06$) - as shown in Table 3.

Table 2: Prevalence of malaria among the study participants

Group	**HIV-infected (n = 140)**	**Non-HIV infected (n = 140)**	**Total (n = 280)**	**Test of significance**
Malaria	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	
Malaria present	100 (71.4)	132 (94.3)	232 (82.9)	$\chi^{2*} = 27.72$
Malaria absent	40 (28.6)	8 (5.7)	48 (17.1)	df=1, OR=2
Total	140(100)	140(100)	280(100)	$p < 0.0001$.

χ^{2*} = **Pearson`s chi-square**.

Table 3: Frequency distribution of malaria among febrile HIV-infected and non-HIV infected children by gender, age and socio-economic class

Variables	**HIV infected (n = 140) Frequency %**		**Non HIV infected n = 140) Frequency %**	
	Malaria present	**Malaria absent**	**Malaria present**	**Malaria absent**
Gender				
Male	44 (44.0)	27(67.5)	68(51.5)	4(50.0)
Female	56(56.0)	13(32.5)	64(48.5)	4(50.0)
	$\chi^{2*} = 147.34$, df=1, $p < 0.0001$		$\chi^{2*} = 0.007$, df=1, $p = 0.93$	
Age group (in years)				
0.25 – 5.0	45(45.0)	24(60.0)	61(46.2)	8(100.0)
6.0 – 10.0	43(43.0)	8(20.0)	51(38.6)	0(0.0)
11.0 – 15.0	12(12.0)	8(20.0)	20(15.2)	0(0.0)
	$\chi^{2*} = 147.78$, df=2 $p < 0.0001$		$\chi^{2*} = 8.73$, df=2, $p = 0.013$	
Socio-economic class				
Upper class	4(4.0)	8(20.0)	16(12.1)	0(0.0)
Middle class	20(20.0)	4(10.0)	76(57.6)	8(100.0)
Lower class	76(76.0)	28(70.0)	40(30.3)	0(0.0)
	$\chi^{2*} = 151.41$,df=2, $p < 0.0001$		$\chi^{2*} = 5.66$,df=2, $p = 0.06$	

χ^{2*}**Pearson`s c**

Mean parasite density among febrile HIV infected and non-HIV infected children

The mean parasite density among the HIV-infected children was 66,000 ±48,786 compared with 123,951±68,538 among the non-HIV infected children. The difference was statistically significant ($p<0.0001$).

Clinical forms of malaria

Majority of the HIV-infected children with malaria had the uncomplicated forms of malaria (54/100=52.9%), while more than half of the non-HIV infected children had the severe forms of malaria (84/132=63.8%) (Table 4). The difference in the prevalence and pattern of clinical forms of malaria was statistically significant (χ^2 =7.18, p=0.007, OR=2).

Table 4: Distribution of Clinical Forms of Malaria among the study participants

Group	**HIV-infected (n = 100)**	**Non-HIV infected (n = 132)**	**Total (n = 232)**	**Test-of-significance**
Variables	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	
Clinical forms of malaria				
Uncomplicated	54 (54.0)	48 (36.4)	102 (44.0)	χ^{2*} = 7.184, df=1, OR=2
Severe malaria	46(46.0)	84 (63.6)	130(56.0)	p < 0.007

χ^{2*} **Pearson`s chi-square**

Discussion

The high prevalence of malaria in both the HIV-infected and non-HIV infected children in this study maybe because the study was carried out during the raining season (May- October), which is a period that favours increased vegetation and stagnant water collection that favour mosquito breeding and increased malaria transmission. The significantly lower prevalence of malaria among HIV-infected children compared with the non-HIV infected children may be related to the low mean serum level of glucose in HIV-infected children since glucose is needed for parasite growth and survival.(Fanget al., 2004). The observed lower prevalence in the HIV-infected group may also imply be that ART which majority of the subject were on had some impact on malaria.

Similar to the finding in this study, Omoti in Benin (Omoti et al., 2013) reported malaria prevalence of 74% in HIV-infected subjects; their patients had fever (clinical malaria). Okonko in Ibadan, Nigeria (Okonko et al., 2012), reported a significantly lower prevalence of malaria among HIV-infected children, compared to non-HIV infected children (9.1% vs 90.9%) aged 3days to 15years. The authors, however, did not employ HIV DNA PCR to confirm HIV- infection among children who were less than 18 months, implying that the HIV-infected group might have been under-represented resulting in the lower prevalence of malaria among them. Ahmed in Abuja, Nigeria (Ahmed et al., 2016), found a prevalence of malarial parasitaemia of 13.3% among HIV-infected children, compared with 25.0% in non-HIV infected children, aged 3-15 years. However, children of less than 3 years that constitute part of under 5 years with the highest risk for malaria as documented in this study, were not included in the study, and may have contributed to the low prevalence in both HIV-infected and non-HIV infected children. Also cases of clinical malaria were not identified, thus contributing to the low prevalence of malaria reported.

The malaria prevalence of 94.3% among the non-HIV infected children corroborates the 90% reported in Ibadan, Nigeria (Okonko et al., 2012), 81.5% reported in Abeokuta, Nigeria by Okonko et al. (2009) and 81.9% reported in western Kenya (Marete et al., 2014). These studies involved clinical malaria (fever) which may be responsible for the high prevalence reported. However, a lower prevalence of 59.5% (Abdullahi et al., 2010) was reported earlier in Sokoto, Nigeria. This study did not include clinical malaria, which may have accounted for the lower prevalence. This may mean that fever is a possible sensitive clinical case definition for malaria. Singh in Sokoto also reported a lower prevalence of 56% (Singh et al., 2014) during the dry season which corresponded to period of low malaria transmission.

The lower mean parasite density among the HIV-infected children may also be because of their low level of blood glucose, since glucose is needed for parasite growth and survival (Fang et al., 2004). The lower parasite density also raises the possibility of ART serving some protective role against malarial parasite. Most studies on malaria and HIV co-infection

in children tended to focus only on prevalence of malaria than on malarial parasite density. Kyeyune in Malawi (Kyeyune et al., 2014), in a study of febrile children ≤ 5 years who were severely anaemic (Hb ≤ 5mg/dl), similarly reported lower mean malarial parasite density among febrile HIV-infected children (6903) compared to non-HIV infected children (12417, p=0.18). The much lower mean parasite reported in both groups may be because the children were severely anaemic, and this may have affected the erythrocytic phase of *Plasmodium* life cycle.

The significantly lower prevalence of severe malaria among the HIV-infected children compared to the non-HIV infected children can be attributed to the suspected protective role of ART in reducing malarial prevalence, parasite density, and consequently, reduced episodes of severe malaria according to the mechanical hypothesis of severe malaria.(Newton and Krishna 1998). It may also be attributed to the lower random blood sugar in the subject which militates against parasite growth and survival.(Fang et al.,(2004).

Conclusions

Although the prevalence of malaria and mean parasite density among febrile HIV-infected children is high, both parameters are significantly higher among the febrile non-HIV infected children. Uncomplicated form of malaria is commoner among the febrile HIV-infected children, compared to febrile non-HIV infected children.

Recommendations

Owing to the high prevalence of malaria among febrile HIV-infected children, there is need to intensify malaria preventive measures such as the use of insecticide-treated mosquito nets, and this strategy should be incorporated into routine counseling and care for HIV-infected children. There may also be need for intermittent prophylactic anti-malarial drugs use, particularly during the rainy season when malaria transmission is high. Early diagnosis and prompt treatment of malaria in HIV-infected children should be provided to prevent progression of uncomplicated malaria to severe form of malaria and reduce the risk of mortality.

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Declaration of Conflict of Interest

The authors declare that there are no conflicts of interest involved in this study.

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