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Asymptomatic Malaria Parasitemia Amongst Patients with Steady-State Sickle Cell Anaemia and The Influence of Proguanil Prophylaxis

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ABSTRACT

Background: *Majority of sickle cell anaemia (SCA) patients reside in sub-Saharan Africa where malaria is also endemic and a frequent cause of hospitalization and poor outcome. Although commonly practiced, the value of life-long antimalaria prophylaxis for SCA patients residing in endemic region has been a subject of concern and academic discourse.*

Aims: *To determine the prevalence of malaria parasitemia in asymptomatic SCA patients and the impact of proguanil prophylaxis.*

Methods: *Patients with steady-state homozygous sickle cell anaemia (i.e HbSS) were studied at the haematology clinic of the University of Maiduguri Teaching Hospital (North Eastern Nigeria) from November to December 2018. Malaria parasite density was determined using Giemsa-stained thick blood film adhering to standard quality control procedure.*

Results: *Seventy-two HbSS patients and 50 HbAA controls were studied. The prevalence of malaria parasitemia was similar between the HbSS patients (53.4%) and controls (44%) (p=0.472). Presence of malaria parasitemia was not related to frequency of antimalaria prophylaxis amongst the HbSS subjects (p=0.392). The intensity of malaria parasitemia amongst HbSS patients' was similar.*

Conclusion: *Malaria parasitemia did not differ between patient with steady-state HbSS receiving proguanil prophylaxis and healthy control. Malaria prophylaxis with proguanil did not significantly affect the intensity of malaria parasitemia in patients with HbSS.*

Keywords

Sickle-cell, Malaria, Proguanil, Prophylaxis.

Introduction

Majority of sickle cell disease (SCD) patients reside in sub-Saharan Africa, where malaria is also endemic. The heterozygous form of the sickle cell gene (HbAS) confers protection against malaria [1,2], while individuals with homozygous form of the gene (HbSS) are at greater risk [3]. Malaria infection is a common precipitating factor for both vaso-occlusive and haemolytic crisis; and a frequent cause of hospitalization and poor outcome among children with SCD residing in endemic region [4]. Earlier studies showed malaria was associated with higher mortality in hospitalized children and adults with SCD compared to non-SCD patients [5,6]. WHO recommends antimalaria prophylaxis for high risk individuals residing in endemic region, therefore, prophylaxis is given routinely to SCD patients [7]. However, there is no consensus on the optimal chemotherapeutic agent that is suitable for SCD patients across the region [8-12].

The preventive value of proguanil for malaria prophylaxis was first demonstrated in a small study by Malik et al. in 1948 [13]. Subsequently, other reports have shown beneficial effect of its prophylaxis action in endemic region [14]. Although commonly practiced, the value of life-long antimalaria prophylaxis for SCD patients residing in endemic region has been a subject of concern.

We aimed to determine the prevalence of malaria parasitemia in asymptomatic SCA patients and the influence of malaria prophylaxis.

Methods

Steady-state SCA (HbSS) patients on routine follow-up were studied at the haematology clinic of the University of Maiduguri Teaching Hospital (UMTH, North Eastern Nigeria) over two months. Apparently healthy hospital staff working at the UMTH voluntarily served as controls (HbAA). Information on demographics, use of antimalaria prophylaxis, hospitalization, last diagnosis of malaria and blood transfusion were obtained using a semi-structured questionnaire. Malaria parasite density was determined using Giemsa-stained thick blood film adhering to standard quality control procedure, and reported as follows:

+ (1+) ……1-10 parasites per high power fields
++ (2+) ……11-100 parasites per high power fields
+++ (3+) ……...1-10 parasites in every high-power field
++++ (4+) ……. More than 10 parasites in every high power field

Results

General characteristics of the study population

A total of 122 subjects, comprising 72 HbSS (41 females and 31 males) patients and 50 HbAA (20 females and 30 females) controls were studied. The mean age of the subjects and controls were 25.25 and 32.14 (p=0.001) respectively. Fifty-six (77.8%) of the HbSS patients were on regular antimalaria prophylaxis with proguanil, while eighteen of the remaining HbSS patients and all the HbAA controls were not prophylaxis (Table 1).

Prevalence of malaria parasitemia

The prevalence of malaria parasitemia in samples taken from all participants was not significantly different between the HbSS group on regular prophylaxis (53%), HbSS not on prophylaxis (38.9%) and HbAA control (44%) (p=0.472) (Table 1). The intensity of the parasite load was similar across all groups (p=0.397).

Variables		HbSS on prophylaxis	HbSS not on prophylaxis	HbAA	P value
Malaria Parasitemia	Absent	25 (46.3%)	11 (61.1%)	28 (56%)	0.472
	Present	29 (53.7%)	7 (38.9%)	22 (44%)	
Parasite density	+ (1+)	20 (69%)	6 (85.7%)	19 (86.4%)	0.397
	++ (2+)	9 (31%)	1 (14.3%)	3 (13.6%)	

Table 1: Distribution of malaria parasitemia and density across various groups.

P value: Fisher's exact test.

Efficacy of proguanil and clinical parameters amongst the HbSS group

Acute malaria episodes were recorded in 28 of the HbSS patients in the recent period (less than a month) prior to the study. The incidence was significantly higher in those regular on proguanil prophylaxis compared with those not on prophylaxes (50% vs 16.7%) (Table 2). Majority of patients not on prophylaxis (83.4%) reported higher incidence of malaria in months before the study (more than one 1 month) (p=0.024). The frequency of blood transfusion and level of haematocrit was similar between the two groups (p=0.290 and p=0.513 respectively). The distribution of malaria parasitemia amongst gender was not influenced by status of prophylaxis intake (p=0.101).

Variables		HbSS on prophylaxis	HbSS not on prophylaxis	P value
Gender	Male	20 (37%)	11 (61.1%)	0.101
	Female	34 (63%)	7 (38.9%)	
Haematocrit	< 20%	14 (33.3%)	3 (21.4%)	0.513
	> 20%	28 (66.7%)	11 (78.6%)	
Acute malaria	< one month	25 (50%)	3 (16.7%)	0.024*
	> one month	25 (50%)	15 (83.3%)	
Hx of transfusion	< one month	10 (20.4%)	3 (16.7%)	0.290
	> one month	33 (67.3%)	15 (83.3%)	
	Never	6 (12.3%)	0 (0%)	

Table 2: Influence of malaria prophylaxis on some clinical parameters.

Discussion

The current report found no significant difference in malaria parasitemia and density amongst HbSS patients' regular on proguanil prophylaxis compared with their counterpart not on any intervention and HbAA controls. Twenty-nine (53.7%) of the HbSS patients regular on prophylaxis had detectable malaria parasitemia. This finding is in sharp contrast to the reported rates of 24% and 83% from studies conducted in the South West [15] and South Eastern [16] part of Nigeria respectively. This disparity may be due to geographical variation which plays an important role in the distribution of the parasite. Factors that affect the distribution of the parasite across regions include pattern and duration of rainy season and the pattern of rural urban migration. The long rainy season in the South East could therefore explain the higher rate reported.

In a recent systematic review and meta-analysis on the safety and effectiveness of antimalaria chemoprophylaxis use in SCD patients, the report showed that antimalaria prophylaxis provided protection against parasitemia and clinical malaria episodes in children with SCD [17]. However, the analysis revealed that all the three studies included from Nigeria, used proguanil as prophylaxis and all reported positive malaria parasitemia [17]. Therefore, the finding from the current study may suggest two things. First, the presence of malaria parasitemia amongst all the groups may imply presence of immunity amongst these individuals due to chronic exposure to the parasite. This suggestion can be supported by previous report which demonstrated high level of antimalaria IgG level amongst SCD patients in Nigeria [18]. Also, the symptomless presence of parasites in immune Africans was a common finding in children and in adults in earlier studies and did not necessarily indicate an overt clinically important infection [14].

Secondly, the similarity in malaria parasite density between HbSS on chemoprophylaxis and those not on prophylaxis raises questions

about the efficacy of proguanil in eliminating the parasite. The effectiveness of a chemoprophylactic agent depends on its ability to decrease detectable parasitemia, and reduce the frequency of clinical malaria episodes [17]. Our report showed no clear advantage of proguanil usage and clinical events. The incidence of acute malaria was significantly high in the prophylactic group. This finding was unexpected, and it was not clear why the HbSS patients on regular doses of proguanil had more episodes of malaria infection. Could this be due to sub-optimal dosing and compliance; or to individual differences in the pharmacokinetics of the drug such as the transformation of the active principle into a non-active compound [19]. Resistance to the drug by the parasite has been documented; occasional failure of prophylactic proguanil was documented as far back as the 1940s during it usage as the main form of antimalaria prophylaxis in the non-African and non –immune population residing in Nigeria [14]. However, these studies are old, and new studies are required to determine this.

In Nigeria, the recommended antimalaria prophylaxis is proguanil for both adults and children alike [20]. In terms of side effects proguanil is associated with low toxicity when used at recommended dose for prophylaxis, nevertheless, earlier report have reported the occurrence of pancytopenia in some individuals [21,22]. In addition, about 70% of proguanil is excreted via the kidneys, and there are reports of life threatening toxicity following its usage in patients with end stage renal disease [22,23]. Increasing awareness about this potential side effect is important in patients with SCD patients giving that the drug needs to be taken lifelong, and considering that chronic kidney disease (CKD) is a common problem in SCD. A common dosing may not be applicable to all the patients, therefore, a strict policy on prescribing and dose reduction in SCD patients with CKD, or alternative form of malaria prophylaxis may need to be considered.

Conclusion

The presence of asymptomatic parasitemia in all the three groups studied in this report may suggests the presence of immunity to the parasite. However, this finding also raises the question about the efficacy of proguanil as the ideal prophylaxis agent against malaria SCD patients residing in endemic regions.

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