

Effect of malaria on the outcomes of sickle cell phenotypes in a semi-nomadic population

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Abstract

Studies have shown that malaria contribute significantly to mortality among infants and children with Sickle Cell Anemia (SCA). The nomadic lifestyle of the Fulanis make access to health care difficult and exposure to malaria high. We conducted a cross sectional study among consenting members of a semi-nomadic Fulani population in Nigeria to determine the impact of malaria on the outcome of SCA. On-the-spot malaria rapid diagnostic test (RDT) and hemoglobin electrophoresis were done. A total of 229 subjects participated, 100 (43.7%) females. Median age was 35 years (yrs) with range of 15-80 yrs. Hemoglobin AS phenotype was found among 53 (23.1%) subjects; none had hemoglobin SS. A positive malaria RDT was found among 24 (10.5%) individuals. The FGD revealed that majority of the respondents considered malaria as an important cause of ill-health but were not aware of SCA as an important disease. The high prevalences of malaria, hemoglobin AS phenotype, and absent of hemoglobin SS in the community implies the potentially fatal effect of malaria on individuals with hemoglobin SS. A comprehensive intervention to reach this vulnerable population is thus recommended.

Introduction

Malaria is an important cause of morbidity and mortality in sub-Saharan Africa (SSA) and Nigeria has failed to reach the 1998 Abuja Roll Back Malaria (RBM) declaration targets.¹ The very young, the pregnant and those with chronic hemolytic anemias notably sickle cell anemia (SCA) are among the worst affected by malaria. The close geographic association between the distribution of malaria and sickle cell gene in Africa provides an insightful association. Having the birth of 230,000 children annu-

ally with SCA, Nigeria accounts for approximately 80% of the global burden.² Another report put the estimated birth at 300,000 with Nigeria accounting for roughly 40% of all SCA births.³ More than 50% of these children die annually, with malaria making a major contribution in African children.⁴⁻⁶

Earlier works in Nigeria revealed a prevalence of 21-25% for sickle cell trait and 1-3% for SCA.⁷ The mechanism for the survival advantage in malaria of hemoglobin AS phenotype (HbAS) compared with hemoglobin AA phenotype (HbAA) and SCA (HbSS) as explained by the law of balanced polymorphism remained poorly understood. Possible explanations include selective sickling and removal of parasitized RBCs by the reticulo-endothelial system, inhibition of parasite growth by the greater potassium loss and low pH of the sickled red cells, greater endothelial adherence of parasitized red cells, reduced ability of *Plasmodium falciparum* parasites to grow and multiply in HbAS erythrocytes as well as accelerated acquisition of malaria-specific immunity.^{8,9} On the other hand, HbSS individuals are at increased life-threatening crises and increased susceptibility to infections because of hyposplenism, inadequate opsonization and diminished cell mediated immunity.¹⁰ This is further buttressed by the fact that daily oral penicillin prophylaxis reduces the risk of pneumococcal infections in children with SCA.¹¹ Furthermore, some local studies have shown the contribution of malaria to mortality in infants and children with SCA and the value of prophylaxis and other quality of care measures in reducing same.^{12,13} Thus, in rural Nigeria, where malaria is endemic, infections common, and access to qualitative health care is sub-optimal, HbSS individuals hardly live to adult age.

The Fulanis in northern-Nigeria have cattle rearing and farming as their major occupation. Thus, they contribute significantly to meat and milk production. Regardless of whether they are fully nomadic or semi-nomadic, their settlement in a malaria endemic area and the practice of polygamy and consanguineous marriage could result in high incidence of malaria and SCA respectively. This is because genetic diseases with recessive modes of inheritance have shown higher predilection to consanguineous marriages^{14,15} and it has been reported that consanguineous marriages and polygamy tend to be the prevailing predisposing epidemiological factors in the transmission of SCA.¹⁶

Through landmark projects in developed countries, the common causes of morbidity and mortality in children with SCA

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have been well established.¹⁷ However, with the high burden of both malaria and SCA in Nigeria, surprisingly little research has been conducted to ascertain malaria is a major cause of death among children with SCA. Perhaps the old Garki project, conducted in North Western Nigeria during the 1970s is the only study in this part of the country which provided some evidence of high mortality among SCA children attributable to malaria.^{18,19} Additionally, there are studies especially from East Africa that have suggested that malaria is not a major cause of death in children with SCA.²⁰⁻²²

There has been remarkable ecological and population dynamics changes since the publication of the Garki study in Kano state, thus this study aims to elucidate the current demographic dynamics and assess the impact of malaria incidence in the area. Furthermore, the Garki study was done among domesticated rural Hausa population, we thus aim to study a nomadic Fulani population. Determining the true association between malaria and mortality in SCA

would provide strong justification for SCA newborn screening program and malaria prophylaxis. The nomadic lifestyle of the Fulanis exposes them more to malaria and at risk of being overlooked in micro-planning by national disease control programs, malaria inclusive. The dual combination of malaria and SCA in the setting of poor access to health care could lead to low survival rate among SCA infants and children.

Materials and Methods

Study design

Using a cross sectional study design, we conducted a community survey in a semi-nomadic Fulani setting in Kano state, North Western Nigeria to determine the burden and effect of malaria on outcomes of Sick Cell Disease (SCD). During a community health outreach, a community survey was conducted to determine the incidence of Sick Cell Disease (SCD) and malaria. Interviews were conducted with consenting adults that agree to provide blood samples for genotype, packed cell volume (PCV) and malaria rapid diagnostic tests (RDT). This was complemented by ethnographic methods (focus group discussions [FGD]) to identify perceived common illnesses and felt needs of the community.

Ethical approvals for this survey were obtained from the ethical committee of Aminu Kano Teaching Hospital (AKTH), Kano state Ministry of Health and Kano Local government Council of Kano state.

Interviews

We administered a structured questionnaire to consenting individuals 15 years and above to obtain information on age, gender, income, marital status, consanguinity and symptoms of malaria. Further information was obtained to determine knowledge, attitude and preventive practices against malaria and SCA. A 12-month verbal autopsy was conducted to identify recognized causes of death within the community. Questionnaires were administered by staff of the Department of Medicine, AKTH Kano, Nigeria. They were trained for a period of two days to ensure uniformity and consistency of the collected data.

Laboratory methods

Three milliliters (3 mls) of venous blood were collected from a prominent superficial arm vein of consenting participants using aseptic venepuncture technique. The blood sample was then carefully transferred into an EDTA container and mixed properly.

Hemoglobin phenotyping and (PCV)

were performed by an experienced laboratory hematologist using the cellulose acetate electrophoresis at alkaline pH of 8.4-8.6 and the microhematocrit method respectively with appropriate controls as described in Dacie and Lewis.²³

On-the-spot malaria rapid diagnostic test (RDT) was conducted using SD-bioline RDT kit. The test was conducted by an experienced laboratory technologist in conformity with the manufacturer's instructions.

Qualitative methods

FGDs were conducted with selected members of the community to determine knowledge, attitude and preventive practices against malaria and SCA. Three FGDs were conducted: young men (15-44 yrs), middle-elderly aged (45 above yrs), and women of reproductive age (15-45 yrs). Each group had 15-20 participants and the sessions lasted 60-90 minutes. The FGD guide was developed using key thematic areas aimed at determining awareness of and preventive measures against development of common communicable and non-communicable diseases. Each session was conducted by 2 interviewers with experience in conducting qualitative research. One of the interviewers moderated the interview while the other documented the proceedings. The data collected was grouped into various thematic areas to enable identification of the most recurrent themes.

Data analysis

Data was collated and entered by 2 individual clerks (double entry) to ensure accuracy and consistency. In the event there was disparity between the 2 entries the questionnaire was recalled for adjunction. We compared prevalence of malaria, consanguinity and hemoglobin phenotypes within the community. We summarized categorical data as proportions and continuous data were presented as median with inter quartile range. We compared proportions using the χ^2 test or student's t test as appropriate. All analyses were conducted using STATA, Version 10.0. A P value of 0.05 or less is taken as statistically significant.

Results

A total of 229 subjects were interviewed of which 100 (43.7%) are females and 129 (56.3%) males. Median age (Inter Quartile Range) was 35 yrs (25-50 yrs). Among the 194 married respondents, 100 (51.5%) were in consanguineous marriages. More than two-thirds of the women 73 (73.0%) were of reproductive age. Cattle rearing is the

most common occupation among 71 (31%) respondents. Symptoms of malaria and positive RDT were found among 97 (42.4%) and 24 (10.5%) subjects respectively. Hb AS was found among 53 (23.1%) of the subjects; none had Hb SS (Table 1). The median PCV (Inter Quartile Range) was 36% (33-46%). As shown in Table 2, a statistically significant relation was found between hemoglobin phenotype and age (P=0.01). However, no statistically significant relation was observed between hemoglobin phenotype and PCV (P=0.35); Malaria symptoms (P=0.89); RDT (P=0.31); gender (P=0.51); occupation (P=0.32); marital status (P=0.34); consanguinity (P=0.65); and family history of SCD (P=0.71). Similarly, no relation was found when RDT and PCV were compared (P=0.58).

Table 3 shows that among those with positive RDT, 13 (54.2%) were women of reproductive age.

Perceived causes of death among respondents based on 12 months verbal autopsy revealed that of 90 respondents that lost a relation within their household, 36 (40%) were as a result of an infectious cause. A similar proportion [37 (41%)]

Table 1. Socio-demographic, clinical and diagnostic parameters of study subjects (N=229).

Characteristic	N. of Patients (%)
Female Sex	100 (43.7)
Median age (range)(yrs)	36.5 (15.0 -80.0)
Occupation	
Farming	142 (62.0)
Cattle rearing	71 (31.0)
Others	16 (7.0)
Marital status	
Married	194 (84.7)
Single	19 (8.3)
Widowed	14 (6.1)
Divorced	2 (0.9)
Marriage type	
Consanguineous	100 (51.5)
Non-consanguineous	94 (48.5)
Malaria symptoms	
Present	156 (97.5)
Absent	4 (2.5)
Malaria RDT	
RDT positive	24 (10.5)
RDT negative	205 (89.5)
Median PCV (IQR)	36 (33-40)
Hb electrophoresis	
AA	176 (76.9)
AS	53 (23.1)
Others (SS, AC)	0 (0.0)

AA= Hemoglobin AA, AC= Hemoglobin AC, AS= Hemoglobin AS, SS= Hemoglobin SS, Hb= Hemoglobin, IQR= inter quartile range, RDT= rapid detection test.

where due to other non-communicable diseases; more than half of which [24 (26.6%)] were due to either recognized chronic non-infectious diseases or sudden, unexplained deaths. Only one death was due to a known case of SCA (Table 4).

FGD

The FGD revealed that respondents considered malaria an important cause of ill-health but lack knowledge of appropriate preventive measures against it. None of the participants was aware of SCA as a disease not to talk of how to prevent it. Majority of

the participants consider potable water supply, access roads and a health care facility as their felt needs in order of priority. According to a 24yr old mother of two: *Mosquitoes are a major problem for us. They disturb our sleep and cause 'janta' (fever). We simply close our doors early in the evening to reduce the number that enter our rooms.* An elderly man who never heard of SCA responded thus: *We don't know any disease like that. I don't believe marriage to a close relation (consanguinity) causes any disease. Just provide us with water, roads, and health center and God will bless you.* A teenager had a different perspective: *I am*

married to my cousin for 5 years and we are fine. We have three children and lost only one at the age of two. We don't think our being close relations have anything to do with this. My main concern is how to take care of my family. Get a borehole for us and we are fine"

Table 2. Comparison of bio-demographic/ laboratory findings and hemoglobin phenotype.

Variable	Frequency	Phenotype		P value
		AA	AS	
Age (Mean±SD)		36.49±14.32	44.87±16.43	0.01#
PCV(Mean±SD)		35.61±6.63	34.64±6.58	0.35#
Gender				0.51*
Male	130	102	28	
Female	99	74	25	
Occupation				0.32**
Cattle Rearer	71	52	19	
Farmer	142	111	31	
Trader	6	5	1	
Others	10	8	2	
Marital status				0.34**
Married	194	150	44	
Single	19	16	3	
Divorced	14	9	5	
Widowed	2	1	1	
Consanguinity				0.65*
Yes	100	76	24	
No	94	74	20	
Education				0.13**
Primary	13	10	3	
Secondary	22	21	1	
Tertiary	10	8	2	
Non-formal	166	122	44	
Malaria symptoms				0.89*
Yes	97	75	22	
No	132	101	31	
RDT				0.31**
Positive	24	21	3	
Negative	205	155	50	
FH of SCD				0.71**
Yes	12	10	2	
No	217	166	51	

#Student t test, *Pearson's Chi squared test, **Fisher exact test, RDT = Rapid Detection Test, FH of SCD = Family History of Sickle Cell Disease.

Table 3. Malaria RDT positivity by age group and gender (N=24).

Age group	Females (%)	Males (%)	Total (%)
15-49	13 (54.20)	4 (16.65)	17 (70.85)
50-64	3 (12.50)	4 (16.65)	7 (29.15)
65 and above	0 (0)	0 (0)	0 (0)
Total	16 (66.70)	8 (33.30)	24 (100)

Discussion

Our study reveals the absence of HbSS among adults in this semi nomadic population despite high number of HbAS and more than 50% of the married individuals engaged in consanguineous marriages. In the setting of the high prevalence of malarial symptoms and 10.5% RDT positivity found in this study population, this may suggest the effect of natural selection by common infections especially malaria preventing the survival of individuals with HbSS and at the same time protecting HbAS in the population. This is because in HbAS, Plasmodium falciparum-infected red cells sickle preferentially and get eliminated from the circulation by macrophages.²⁴ Also, symptomatic malaria infection is prevalent in individuals with sickle cell traits which confirms the protection of this genetic disorder against severe malaria.²⁵ Conversely, HbSS individuals are highly susceptible to the lethal effects of malaria because malaria worsens the anemia of SCA and is a major trigger of crises. Hyposplenism which is a positive adaptation in SCA also reduces parasite clearance.¹⁹ Though there was no statistically significant relation established in this study between phenotypes and symptoms of malaria and also with RDT, these mechanisms may partly explain our finding of a statistically significant difference in age in the study population (P=0.01) with HbAS individuals having a higher mean age of

Table 4. Distribution of common causes of death based on verbal autopsy (N = 90).

Cause of death	Frequency (%)
Childbirth (maternal)	5 (5.6)
SCA	1 (1.1)
Chronic non-infectious diseases	11 (12.2)
Sudden death	13 (14.4)
Cancers	4 (4.4)
Injuries/accidents	5 (5.6)
Infectious diseases	36 (40.0)
Neonatal/infant mortality	7 (7.8)
Unclear cause	8 (8.9)
Total	90 (100)

44.89±16.43 years compared to HbAA with an average age of 36.49±14.32 years.

Thus, it is reasonable to hypothesize that HbSS adult could not be found in the community because the children die before reaching adulthood due to rudimentary health services that will ensure their protection against malaria and other common infectious diseases highly prevalent in the area. Our findings reflect those of the Garki project wherein less than 2% of those with SCA survived beyond the age of 4 years.¹⁹ The study provides the crude mortality from SCD in settings without health interventions. However, in a different report of the same study it was concluded that malaria infection in HbSS is less intense but more lethal than in HbAS and HbAA and anti-malarial intervention did not lead to a significant decrease in HbSS mortality.¹⁸ Many other recent studies are suggesting that malaria is not a major cause of mortality among children with SCA.²⁰⁻²² In contrast, a survival of 75% among HbSS at the age of 5 years from Kenya showed how much could be achieved with appropriate interventions.²⁶ Also in the Cooperative Study of Sickle Cell Disease (CSSCD), approximately 85 percent of children and adolescents with SCA survived up to 20 years of age which was attributed to an integrated clinical approach to the management of SCA.²⁷ Additionally a study by Kudnik *et al.* established the cost effectiveness of early screening plus administration of prophylactic interventions like use of Insecticide Treated Nets (ITN) in SCD in SSA.²⁸ Thus, a cost-effective approach to malaria control which has been reported can be achieved by providing appropriate prevention and treatment for malaria to these neglected communities.²⁹

The finding that majority of those with malaria RDT positivity were women of reproductive age is worrisome given the risk associated with malaria in pregnancy in terms of poor outcomes and congenital malaria. It implies poor availability, accessibility or utilization of ante-natal care services among nomads. This further support the findings of the FGD establishing lack of access to preventive and curative care as a major problem among nomads. There should be customized approach by disease control programs to addressing challenges faced by nomads. This has been shown to be useful in other programs like the National Stop Transmission of Poliomyelitis (NSTOP), nomadic education, and tuberculosis control programs, among others.³⁰

Considering the advances made in management of SCD, malaria, and other infectious diseases, it is baffling to see existence

of communities that were so underserved to the extent that their mortality from SCD is similar to that documented in past studies.^{6,19} Access to basic health care to this community is thus a matter of equity. In fact, high quality of care to SCD patients require the establishment and integration into the sickle cell comprehensive clinics that encompasses vaccinations, prophylactic therapy, nutritional and social support. This will ensure that in addition to providing care for common infections, better health maintenance could prevent frequent crisis thereby reducing the need for frequent transfusion that exposes Africans with sickle cell disease to HIV/AIDS, another common cause of mortality among Africans.

The finding of low level of awareness about prevention and treatment of malaria is similar to Akogun *et al.*'s studies of febrile illness in similar settings of Northern Nigeria in which he was able to show in a separate study, the cost-effectiveness and acceptability of the *feverkit*, a solar-powered device programmed with user-interactive capabilities that guide Nomads to distinguish malaria from non-malaria-induced fevers thereby selectively treating them.³¹ This and other universally accepted conventions like the home treatment of malaria, use of ITN, and indoor residual spraying under the Roll Back Malaria (RBM) initiative could go a long way in providing more access to care for malaria and other infectious diseases.

The high prevalence of malaria in our study subjects was unlikely to have been affected by the timing of the study given that it was conducted in an area of stable malaria transmission. Thus, the results are not likely to change if the study was conducted at other times of the year.

Our study is limited by the fact that it wasn't a longitudinal study and as such, a clear cause-effect could only be extrapolated. However, the similarities of our findings with previously conducted longitudinal studies means more attention should be paid to this neglected population with lack of access to basic amenities and proven health interventions.

Conclusions

Lack of access to basic health care still expose vulnerable populations like the nomads to the devastating effects of malaria and SCA. Furthermore, despite the high prevalence of AS heterozygotes in our setting, the people most affected lack the basic awareness of SCD and how to prevent or access care for it which needs to be addressed with more awareness campaigns.

Disease control programs should have customized approaches to special populations like the nomads in program planning and implementation. Further studies should be conducted to evaluate the efficacy and utility of other proven initiatives like the seasonal malaria chemoprevention (SMC), daily oral penicillin and pneumococcal conjugate vaccines use in SCA in special populations like the nomads.

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