Original Article

Hemoglobin S and Glucose-6-Phosphate Dehydrogenase Deficiency Coinheritance in AS and SS Individuals in Malaria-Endemic Region: A Study in Calabar, Nigeria

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Abstract

Background: Malaria placed a huge burden on human life and has been reported to be a key health problem affecting developing countries. This study was designed to assay for glucose-6-phosphate dehydrogenase (G6PD) status and malaria parasite density of individuals with sickle cell gene in University of Calabar Teaching Hospital, Calabar. **Subjects and Methods:** The methemoglobin method was used to determine the G6PD status. Thick blood films were used to ascertain the malaria parasite density while hemoglobin genotype was determined using cellulose acetate paper electrophoresis with tris ethylenediaminetetracetic acid borate buffer (pH 8.6). Thirty hemoglobin SS (HbSS) and 30 hemoglobin AS (HbAS) individuals were recruited for the study while 30 hemoglobin AA (HbAA) individuals were recruited as control. **Results:** The study showed a high frequency of G6PD deficiency (17.78%) in the study area while G6PD deficiency was significantly ($P < 0.05$) higher in HbAA individuals (33.33%) when compared to HbSS (10.00%) and HbAS (10.00%) individuals. The prevalence of malaria parasitemia and parasite density was comparable in the three hemoglobin variants. The distribution of malaria parasitemia and parasite density in both gender among the various hemoglobin variants showed no association ($P > 0.05$). G6PD deficiency distribution in both gender were found to be comparable ($P > 0.05$). The distribution of malaria parasitemia in the various hemoglobin variants in the G6PD-deficient individuals showed no significant difference ($P > 0.5$). However, the parasite density of the HbAS (3100 ± 1828.48 µL) and HbSS (2400 ± 1687.06 µL) were significantly lower than that of HbAA (4040 ± 1529.44 µL). **Conclusion:** The result of this study supports the hypothesis that inheriting the G6PD deficiency gene and sickle cell gene (both in homozygous and heterozygous form) reduces the severity of malaria parasite infection and hence protects against severe acute malaria while having less effect on infection.

Keywords: Glucose-6-phosphate dehydrogenase, hemoglobin, hemoglobin SS, sickle cell, malaria parasite, G6PD

Introduction

Malaria, a tropical disease, is caused by the protozoa of the genus *plasmodium* species and is transmitted by the female anopheles mosquito.[1,2] Severe malaria is a multisystem disorder which may arise from multiple poorly understood processes including acute hemolysis of infected and uninfected red blood cells (RBCs) and dyserythropoiesis as well as through the interaction of malaria infection with other parasitic infections and with nutritional deficiency.[3,4] Immune processes and genetic traits have contributed in reducing the profligacy of the malaria parasite, and a wide range of genetic polymorphism has been developed to modify individual response to this lethal disease.[5] The high frequency of genetic defect such as the genes for glucose-6-phosphate dehydrogenase (G6PD) deficiency and sickle cell hemoglobin (HbS) in malaria-endemic regions is believed to be due to their advantage against severe malaria infection, especially HbS when in heterozygous form (hemoglobin AS [HbAS]).[6]

G6PD in human is an X-linked enzyme which plays an important role in the generation of reduced nicotinamide adenine phosphate, which is the only source of reducing power in RBC, where it is required to maintain the equilibrium and in particular

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to detoxify hydrogen peroxide and other compounds through reduced glutathione (GSH).[7] GSH also maintains hemoglobin and other red cells' protein in a reduced active form and possibly enhances the ability of the cells to withstand oxidative damage, particularly during infections and exposure to oxidant drugs.[8] Patients with G6PD deficiency develop hemolytic anemia during acute malaria infection and when treated with certain therapeutic agents such as antimalarial, antipyretics, and antibiotics which have oxidant properties. Increased oxidative stress in G6PD deficiency cell is well documented.[8]

Hemoglobinopathies are the most common monogenic disease and mutation. There are hundreds of hemoglobin variants identified, of which only three: HbS, HbC, and HbE have reached polymorphic frequencies.[9] HbS is due to point mutation in the genetic code in which thymine replaces adenine in the deoxyribonucleic acid encoding the beta globin gene; consequently, valine replaces glutamate at the 6th position in the beta globin product.[10] The gene for HbS is distributed widely throughout sub-Saharan Africa and countries with African immigration where a carrier frequency ranges from 5% to 40% or more.[6,9] This study was aimed at investigating the effect of inheritance of G6PD deficiency and hemoglobin SS (HbSS) in malaria parasitaemia and severity.

Subjects and Methods

Subjects and sample collection

This study was approved by Health Research Ethical Committee of the University of Calabar Teaching Hospital (UCTH). Informed consent was obtained from the participants. Thirty known sickle cell patients were recruited into the study from hematology day care unit of the UCTH, Calabar, Nigeria. They comprised of 13 females and 17 males all within the age range of 5–30 years of age and were not having any crisis and were in hospital for routine check. Sixty apparently healthy individuals comprising of 30 HbAS (used as part of the test individuals) and 30 hemoglobin AA (HbAA) individuals (used as control) from Calabar metropolis were also recruited. Three milliliters of venous blood was collected by venipuncture from each individual into ethylenediaminetetraacetic acid container. The methemoglobin reduction method by Brewer *et al*.[11] was used to screen for G6PD deficiency. Hemoglobin electrophoresis was done using cellulose acetate electrophoresis at pH 8.6. For the laboratory diagnosis of malaria parasite infection, thick blood films were prepared for each individual and stained using Giemsa staining method as described by Cheesbrough.[12] Malaria parasites were counted against white blood cells (WBCs). A minimum of 1000 WBCs were counted, and the number of malaria parasites counted per white cells were recorded. The parasite density was then converted to parasite per milliliter of blood according to the formula below:[13]

$$\frac{\text{Number of parasites counted} \times 8000}{\text{Number of leucocytes (WBC) counted}} = \text{Number of parasites counted per mm}^3\text{of blood.}$$

Statistical analysis

Data generated in this study were analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using frequency, percentages, and Chi-square while continuous variables were analyzed using descriptive statistics, *t*-test, and ANOVA. Chi-square was used to assess association among variables, while *t*-test and ANOVA were used to assess differences between two and multiple means, respectively. Alpha value was set at 0.05.

Results

The G6PD deficiency distribution among the HbAA, HbAS, and HbSS individuals were 33.33% (n = 10), 10.00% (n = 3), and 10.00% (n = 3), respectively. The distribution was statistically significant ($P < 0.05$). Malaria parasitemia in this study was found to be 17.78% (n = 16). Among these, 8 (26.67%), 5 (16.67%), and 3 (10.00%) were recorded in HbAA, HbAS, and HbSS variants, respectively. The malaria prevalence was comparable in the different hemoglobin variants ($P > 0.05$). The mean parasite density of the hemoglobin variants were comparable ($P > 0.05$) with HbAA, HbAS, and HbSS having mean values of 3725 ± 1888.1 μL, 4320 ± 2057.6 μL, and 2360 ± 981.4 μL, respectively [Table 1].

Gender distribution of malaria parasitemia and parasite density in the studied population showed comparable values for the males and the females ($P > 0.05$). Approximately 16.67% (n = 5%), 16.6% (n = 5), and 6.67% (n = 2) represented males with malaria parasitemia while 10.0% (n = 3), nil, and 3.33% (n = 1), respectively, represented females with malaria parasitemia. The mean parasite density of the male and female HbAA individuals were 4064 ± 1487 μL and 3168 ± 3011 μL, respectively, while the HbAS had mean values of 4320 ± 2057.6 μL and nil, respectively, for male and female individuals. The HbSS individuals had malaria parasite densities of 1740 ± 754 μL and 1374 ± 1309 μL for the male and female individuals, respectively [Table 2].

Table 3 shows the gender distribution of G6PD-deficient individuals in the studied population. Approximately 21.56% (n = 11) of the males were G6PD deficient while 12.82% (n = 5) of the females were G6PD deficient. The distribution of G6PD deficiency was found not to be associated with gender ($P > 0.05$).

The gender distribution of G6PD deficiency among the various hemoglobin variants was found to be comparable in all groups. Distribution of G6PD among the various hemoglobin variants was found not to be associated with gender ($P > 0.05$) [Table 4].

Table 5 shows the prevalence of malaria parasitemia and malaria parasite density of G6PD-deficient individuals according to the various hemoglobin variants. Approximately 50.0% (n = 5), 66.7% (n = 2), and 66.7% (n = 2) of the HbAA, HbAS, and HbSS G6PD-deficient individuals, respectively, had malaria parasitemia. However, this distribution is not statistically significant ($P > 0.05$).The

Table 1: Distribution of glucose-6-phosphate dehydrogenase deficiency, malaria parasitemia, and parasite density among the studied population

Parameters	Hb variant			Total (n=90)	P
	AA (n=30), n (%)	AS (n=30), n (%)	SS (n=30), n (%)		
Number of deficient for G6PD	10 (33.33)	3 (10.00)	3 (10.00)	16 (17.78)	0.0047
Number of positive for Mp	8 (26.67)	5 (16.67)	3 (10.00)	16 (17.78)	0.305
Mp density of individual (µL)	3725±1888.1	4320±2057.6	2360±981.4	3655±1998	0.430

Figures in parenthesis are percentages, P<0.05 represents significant difference, Mp reported as mean±SD. SD: Standard deviation, n: Number of individuals, Mp: Malaria parasite, G6PD: Glucose-6-phosphate dehydrogenase, Hb: Hemoglobin

Table 2: Frequency of malaria parasitemia and malaria parasite density of all individuals among the hemoglobin variants based on gender

Gender	Hb variants					
	HbAA (n=30), n (%)	Parasite density	HbAS (n=30), n (%)	Parasite density	HbSS (n=30), n (%)	Parasite density
Male	5 (16.67)	4064±1487	5 (16.67)	4320±2057.6	2 (6.67)	1740±754
Female	3 (10.0)	3168±3011	0 (0.00)	0.00±0.00	1 (3.33)	1374±1309
Total	8 (26.67)	3725±1888.1	5 (16.67)	4320±2057.6	3 (10.0)	2360±981.4
P		0.261		Nil		0.317

χ^2 (2, n=30)=2.444, P=0.295. Figures in parenthesis are percentages. Hb: Hemoglobin, HbAA: Hemoglobin AA, HbAS: Hemoglobin AS, HbSS: Hemoglobin SS

Table 3: Gender distribution of glucose-6-phosphate dehydrogenase-deficient individuals in all the individuals

Gender	Screened individuals	G6PD-deficient individuals, frequency (%)	χ^2	P
Male	51	11 (21.56)	0.817	0.366
Female	39	5 (12.82)		
Total	90	16 (17.78)		

G6PD: Glucose-6-phosphate dehydrogenase

mean parasite density of the HbAS (3100 ± 1828.48 µL) and HbSS (2400±1687.06 µL) were found to be significantly lower than that of HbAA (4040 ± 1529.44 µL) (P < 0.05).

Discussion

G6PD is very significant to red cell survival. Its deficiency deprives the red cell of the reducing power necessary for protection against oxidation. The malaria hypothesis maintains that the average people without G6PD deficiency and sickle cell gene died of malaria at higher frequency.[14]

This study had a malaria parasitemia prevalence of 17.78%. This value was quite lower than earlier report of 80% by Orok *et al*.[15] This large margin may be due to seasonal variation in malaria prevalence.

This study recorded 17.78% prevalence of G6PD deficiency among the studied population. This value is lower than 37.6% reported in previous study in Sokoto, Nigeria.[16] In contrast, lower values were documented in developed countries such as America and in Europe.[17] G6PD deficiency has been attributed to genetic adaptation to malaria in malaria-endemic regions[18,19] and seems to corroborate the malaria protection hypothesis and also the role malaria plays in the distribution of G6PD gene in most malaria-endemic areas in the world.[20] Although the electrophoretic mobility was not carried out to ascertain the G6PD variants, the common African variant G6PD A$^-$ was assumed.[21]

More so, the HbAS and HbSS hemoglobin variants had the least prevalence of malaria parasitemia. However, this variation was not statistically significant. This trend is consistent with earlier study by Bougouma *et al*.[22] and Carnevale *et al*.[23] Their result showed that incidence and premunition of malaria is comparable among individuals of different hemoglobinopathies going by the malaria prevalence and parasite density. Conversely, some studies[24,25] have reported protective effect of abnormal hemoglobin against clinical and subclinical malaria. Some researchers have proposed; decreased RBC invasion/poor growth under high oxygen tension,[26] accelerated acquisition of antibodies specific for *Plasmodium falciparum* erythrocyte membrane protein-1 and other variant surface antigens[27] as mechanisms of this protection.

The effect of G6PD deficiency on individuals with sickle cell trait and sickle cell anemia is controversial. Several reports have emphasized increased frequency of G6PD deficiency in patients with sickle cell disease. In these reports, there are contradictory views on the issue of the protective effect of the enzyme deficiency on the clinical manifestation of sickle cell anemia. Some reports claim that the combination is beneficial in sickle cell trait[28] while others have found no beneficial or adverse relationship.[29] In the present study, coinheritance of G6PD deficiency with HbAS and HbSS was both 10%. This finding is similar to 7% reported in previous study in Ghana.[30] Coinheritance of both the G6PD deficiency and the sickle cell gene has been reported to confer a better

Table 4: Distribution of glucose-6-phosphate dehydrogenase deficiency among hemoglobin variants based on gender

Gender	Hb variant			χ^2	*P*
	HbAA (*n*=30), *n* (%)	HbAS (*n*=30), *n* (%)	HbSS (*n*=30), *n* (%)		
Male	7 (23.33)	2 (6.67)	2 (6.67)	0.019	0.990
Female	3 (10.0)	1 (3.33)	1 (3.33)		
Total	10 (33.33)	3 (10.00)	3 (10.00)		

Figures in parenthesis are percentages. Hb: Hemoglobin, HbAA: Hemoglobin AA, HbAS: Hemoglobin AS, HbSS: Hemoglobin SS

Table 5: Malaria parasitemia and malaria parasite density of glucose-6-phosphate dehydrogenase-deficient individuals in different hemoglobin variants

Parameters	Hb variants deficient of G6PD			*P*
	AA (*n*=10)	AS (*n*=3)	SS (*n*=3)	
Number of positive for Mp, *n* (%)	5 (50.00)	2 (66.7)	2 (66.7)	0.367
Mp density (µL), mean±SD	4040±1529.44	3100±1828.48*	2400±1687.06*	0.000

*Means significantly lower when compared with that of HbAA ($P<0.05$). SD: Standard deviation, *n*: Number of individuals, Mp: Malaria parasite, Hb: Hemoglobin, G6PD: Glucose-6-phosphate dehydrogenase, HbAA: Hemoglobin AA

protection against malaria.[28,31] In this study, G6PD deficiency was associated with reduction in the risk of severe malaria for both G6PD-deficient HbAS and HbSS individuals as compared to HbAA individuals who were also G6PD deficient as seen in the significantly lower parasite density despite the fact that it did not show any association in preventing malaria parasitemia/incidence of malaria parasitemia. This observation is in agreement with the report of Awah and Uzoegwu.[28] Malaria parasite density provides information on the severity of infection.[32] The G6PD-deficient parasitized erythrocytes may have been phagocytized earlier thereby destroying the malaria parasite, hence keeping the parasite load low. This finding supports the premunition hypothesis of the protective effect of coinheritance of G6PD and HbS gene in malaria-endemic region. Premunition is not a sterile type of immunity, but it ensures that maximum parasite load is kept at low level.[33]

Gender distribution in G6PD deficiency is comparable in both males and females, though the proportion being higher in males (21.56%) than females (12.82%), showing male preponderance. However, this variation was not statistically significant (P = 0.366). This finding is in consonance with previous studies,[34,35] while same is in contrast with the findings of Jelani *et al*.[16] Some authors have argued that considering the fact that the abnormal gene responsible for G6PD deficiency is located on the X chromosome, and males are hemizygous while females are dizygous for X chromosomes, that the probability of finding two genes of G6PD mutation on chromosome X is lower in females.[36]

Conclusion

We conclude that G6PD coexistence with hemoglobin S gene (HBAS and HbSS) does not offer protective role in incidence of malaria infection, but, however, helps to adapt to low severity of the infection via low parasite density (premunition). However, there is still need for a collaborative study between scientists involving larger sectors of the population to be able to shed more light on the unresolved aspects of coinheritance of these two red cell genetic abnormalities and their interaction, especially in malaria-endemic regions.

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Conflicts of interest

There are no conflicts of interest.

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