Features and outcomes of malaria infection in glucose-6-phosphate-dehydrogenase normal and deficient Nigerian children

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ABSTRACT

Background & objectives: Malaria and G6PD deficiency-related haemolyses are known causes of hospital admissions in Nigeria and pose great danger to child survival but data on interactions of these two pathologies are scarce. This study was carried out to determine the association between features of *Plasmodium falciparum* infection and G6PD status.

Methods: G6PD and haemoglobin were typed by fluorescent spot test and electrophoresis respectively, in 1120 children with microscopically-proven falciparum malaria. Clinical features of malaria were compared between G6PD normal and deficient children.

Results: There were 558 males and 562 females with median age of 35 months (range, 6 months–12 yr). In males, prevalence of G6PD-deficiency in patients with uncomplicated malaria (UM), severe malarial anaemia (SMA) and cerebral malaria (CM) was 23.4, 7 and 16.7%, respectively compared with 11.1, 7.3 and 4.4%, respectively among females. In both males and females, convulsion and rectal temperature above 38°C were less likely presentations among G6PD-deficient compared with G6PD-normal children ($p < 0.05$). The proportions of children with pallor, convulsion and impaired consciousness were significantly lower among G6PD-deficient than normal males ($p < 0.05$) but these features were not different between deficient and normal females ($p > 0.05$).

Interpretation & conclusion: Convulsions, pallor and elevated temperature were more frequent features of malaria in G6PD normal than deficient children. G6PD-deficient male children are protected against impaired consciousness. These differences may offer useful hints in malaria treatment and researches in endemic regions.

Key words   Clinical features; glucose-6-phosphate dehydrogenase; *Plasmodium falciparum* malaria

INTRODUCTION

The contributions of malaria to disease and socio-economic burdens of the world are well documented[1]. In spite of the currently increasing attention given to and resources aimed at malaria control, including initiatives such as Roll Back Malaria, the multilateral initiative on malaria and the introduction of artemisinin-based combination therapy, it remains a threat to the life of children in sub-Saharan Africa[1–2]. *Plasmodium falciparum* infection is the major cause of morbidity and mortality among children in Nigeria where malaria constitutes 25–40% of all outpatient clinic visits and 21% of hospital admissions[3]. It is one of the five leading causes of mortality in children under-5 years of age[4].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency on the other hand is the most common enzymopathy of humans[5]. G6PD status is considered to be one of the major determinants of host resistance to childhood malaria infection[6–8]. It is a known cause of haemolysis and suspected to significantly alter endemicity of malaria in the tropics[9]. The similarity of the geographical distribution of G6PD-deficiency and falciparum malaria was pointed out by Allison[10] and Motulsky[11] in 1960. Since then many authors have reviewed the hypothesis that G6PD-deficiency confers resistance to falciparum malaria[12–15]. A recent study in Nigeria showed that the prevalence of G6PD-deficiency among male (16.4%) and female (8.1%) malaria patients were lower than the general population[16]. The study also revealed that G6PD-deficient male but not female children were significantly less likely to develop severe malarial anaemia[16].

In situations where malaria eradication is not an option in the near future in Nigeria, emphasis must be given on the control of morbidity and mortality due to malaria. Under such circumstances making a distinction between malarial parasitisation and malarial disease as well as recognizing factors that may contribute to malaria severity are important. However, there is paucity of data on

whether or not there are differences in the manifestations of malaria between individuals with either homozygous or heterozygous G6PD-deficiency and those with normal G6PD activity. The knowledge of any peculiarity in the manifestation of falciparum malaria in children with respect to their G6PD status may be useful to shed more light on the importance of checking G6PD status in children who are known to be at higher risk of severe malaria than adults. It may also help to identify the potential areas of priority in research. Therefore, this study was carried out to describe the differences in the manifestations of falciparum malaria among G6PD-deficient and G6PD-normal children in Ibadan, in order to provide data that may help to improve the management and reduce morbidity and mortality due to malaria.

MATERIAL & METHODS

Study design and setting

Consecutive patients with symptomatic *P. falciparum* malaria were screened for G6PD-deficiency over a study period of 24 months (April 2005 to March 2007) at the outpatient and emergency unit of the University College Hospital, Ibadan, Nigeria. The hospital is located in Ibadan North Local Government Area. Ibadan is an urban city in the southwest of Nigeria, an area of malaria hyperendemicity. Ibadan has an estimated population of 2,550,393 and annual growth rate of 2.83% (2006 census). Majority of the inhabitants of Ibadan are mainly Yoruba speaking people. All the children with severe malaria were first admitted into the emergency ward which has side laboratory where simple ancillary investigations including microscopy and haematocrit are carried out.

Inclusion and exclusion criteria

Children who presented with fever had peripheral blood film examination for *P. falciparum*[17]. Those who had malaria parasitaemia were recruited provided there was no other obvious cause for the fever such as respiratory infections. Patients who were later found to have sickle-cell anaemia with haemoglobin genotype "SS" or "SC"and those who had blood transfusion within three months before enrolment were excluded from the study.

Data collection

History was obtained from the care givers and the children. Complete physical examination was carried out on each patient. All the findings including the results of G6PD test, packed cell volume (PCV), parasite counts,

blood groups and haemoglobin types were recorded by the investigators into a case record form. Cases of severe malaria were defined according to WHO criteria[18].

Laboratory procedures

Thick and thin films were made on the same slide for each patient. The thin film was fixed with methanol immediately and the slide was allowed to dry, then flooded with Giemsa stain already diluted (1 in 10) with phosphate buffer (pH 6.8). The stain was washed off with distilled water, after allowing it to stay for about 10 min, and air-dried. The stained films were then examined microscopically for malaria parasites. The parasites were counted against 200 white blood cells (WBC) and parasite density was calculated for each patient based on total WBC of 8000/μl of blood. Haematocrit, haemoglobin types and ABO blood groups were determined using capillary tube plus centrifugation, electrophoresis on cellulose acetate and agglutination tile[19] methods respectively. G6PD status was determined by fluorescent spot test according to the method of Beutler and Mitchell[20]. This test is based on the principle that NADPH generated in red cells in the presence of G6PD, fluoresces under long wavelength ultraviolet (UV) light. The drawback of this method is that it does not distinguish between heterozygote and homozygote G6PD normal females.

Quality controls

There was no attempt to distinguish clinical features between G6PD normal and deficient children until screening was done in order to minimize selection bias. A parallel G6PD screening test of some of the patients in each batch was carried out in the Paediatric Research Laboratory. This laboratory has been running G6PD screening for over 15 yr. All children with severe anaemia (PCV < 15%) had repeat G6PD screening three months after blood transfusion. There was over 98% agreement rate in the results obtained (Kappa = 0.9874).

Data analysis

Data were analyzed using SPSS 15.0 for Windows (SPSS Inc., Chicago, USA). Stratified analysis of the various manifestations of malaria infection by gender was carried out in order to control for its confounding effect. Categorical variables were compared using either the uncorrected chi-square test or Fisher's exact test while continuous variables were analyzed using the Student *t*-test or analysis of variance (ANOVA). Data not normally distributed were compared using Mann-Whitney U-test. The statistical significance level was set at $p < 0.05$.

Ethical consideration

Written informed consent was obtained from the care-givers and the protocol was approved by the University of Ibadan/University College Hospital Ethical Review Committee (IRC Protocol No.: UI/IRC/O4/0001).

RESULTS

The age of the patients who participated in this study ranged from 6 months to 12 yr with a mean of 41.4 ± 1.2 months. The mean age of the G6PD-deficient group of 45.2 months was not significantly different from 37.8 months in the G6PD-normal ($p = 0.060$). Infants (6 to 11 months) constituted 11.8% of all the study patients. Children who were 12 to 23, 24 to 35, 36 to 47 and 48 to 59 months old were 23.1, 15.3, 13.7 and 13.4%, respectively. Thus, under-5 children constituted 77.3% of all the study patients while those >5 yr were 27.7%. Study patients were 451 (251 males) uncomplicated malaria (UM), 428 (252 males) severe malarial anaemia and 241 (155 males) cerebral malaria. Prevalence of G6PD-deficiency in patients with UM, SMA, and CM was 18.1, 7.2 and 9.3%, respectively. The prevalence of G6PD-deficiency in male patients with UM, SMA and CM was 23.4, 7 and 16.7%, respectively. However, in the females category, prevalence of G6PD-deficiency among patients with UM, SMA and CM was 11.1, 7.3 and 4.4%, respectively. Of the 1120 study patients, there were 19 deaths giving an overall mortality rate of 1.7%. Other demographic characteristics of the study patients are shown in Table 1. Overall, the prevalence of G6PD-deficiency was significantly higher among males (16.7%) than females (8.3%); p <0.001. The patients' weight ranged from 5.5 to 32 kg with an overall mean weight of 13.4 ± 5.3 kg. The G6PD-deficient and G6PD-normal patients had a mean weight of 14.3 ± 5.6 and 12.9 ± 4.9 kg, respectively ($p = 0.057$).

All the 1120 patients had Hb type A. The proportion of G6PD-deficient patients with blood group O, A, B and AB was 57.1, 23.4, 15.6 and 3.9%, respectively. This pattern of distribution did not significantly differ from 58.7, 19.2, 18.9 and 3.1% for blood group O, A, B and AB, respectively among the G6PD-normal group ($p = 0.681$). The haematocrit of all the patients ranged from 6 to 45% and the mean PCV was 21%. The mean haematocrit of the G6PD-normal (22.8%) was not significantly different from G6PD-deficient children (21%); $p = 0.092$. The mean parasite counts of 15,477.5/µl (range = 5340 to 860,000) in G6PD-deficient patients was significantly lower than (19,784.4/µl, range = 2112 to 1824,400) in the G6PD-normal group ($p = 0.013$). However, in the male children, the mean parasite count was 15397/µl (range = 4240 to 880,000) in G6PD-deficient patients. This estimate was significantly lower than (24,662.8/µl; range = 3140 –1,824,400) in the G6PD-normal group ($p = 0.041$). Conversely, in the females category, though the G6PD-deficient group had a lower mean parasite counts (12,840.4/µl; range = 2960–860,000), but it was not significantly different from (15,548.6/µl; range=2102–969,882) estimated for the G6PD-normal group ($p = 0.419$).

The comparisons of the clinical features of malaria in G6PD-deficient and normal male patients are shown in Table 2. In the male category, more of those with normal G6PD status than G6PD-deficient presented with pallor (68.8% *vs* 45.2%), convulsions (30.3% *vs* 14%), impaired consciousness (30.8% *vs* 16.1%) and temperature above 37.5°C (77.4% *vs* 99.8%). On the others hand, more of those with G6PD-deficiency than G6PD-normal patients passed dark urine (35.5% *vs* 18.1%) and had pal-

Table 1. Comparison of gender, age and weight of 1120 malaria patients based on G6PD status

Characteristics	G6PD status		Total (n = 1120)	p = value
	Deficient (n = 139)	Normal (n = 981)		
Gender				
Male	93 (66.9)	465 (47.4)	558 (49.8)	<0.001*
Female	46 (33.1)	516 (55.7)	562 (50.2)	
Age (Months)				
Range	6–144	6–138	6–144	0.060**
Mean	45.2	37.8	41.4	
SD	1.8	1.6	1.2	
Weight (kg)				
Range	5.5–32	5.7–32	5.5–32	0.022+
Mean	14.3	12.9	13.4	
SD	5.6	4.9	5.3	

*Chi-square test; **Student *t*-test; +Mann-Whitney U-test (M-W U); SD = Standard deviation; Values in parentheses are percentages.

Table 2. Clinical features of malaria among glucose-6-phosphate dehydrogenase normal and deficient male patients

Presenting complaints	G6PD status				OR	95% CI	*p*-value[*]
	Deficient (n = 93)		Normal (n = 465)				
	No.	%	No.	%			
Pallor	42	45.2	320	68.8	0.37	0.24–0.59	<0.001
Dark urine	33	35.5	84	18.1	2.49	1.53–4.06	<0.001
Convulsion	13	14	141	30.3	0.37	0.20–0.69	0.002
Impaired consciousness	15	16.1	143	30.8	0.43	0.24–0.78	0.006
Fever	91	97.8	463	99.6	0.20	0.03–1.41	0.262
Vomiting	44	47.3	185	39.8	1.20	0.55–2.62	0.801
Cough	4	4.3	27	5.8	0.73	0.25–2.14	0.741
Diarrhoea	4	4.3	22	4.7	0.91	0.30–2.69	0.928
Difficulty in breathing	11	11.8	53	11.4	1.04	0.52–2.08	0.952
Temperature (>37.5ºC)	72	77.4	464	99.8	0.12	0.01–0.06	<0.001
Palpable spleen	62	66.7	238	51.2	1.90	1.19–3.05	0.006
Jaundice	6	6.5	18	3.9	1.67	0.68–4.09	0.264
Liver enlargement (>2 cm)	67	72	286	61.5	1.61	0.99–2.63	0.055
Respiratory distress	18	19.4	92	19.8	0.97	0.55–1.71	0.924

[*]Chi-square test used; OR – Obtained from 2 × 2 table for each clinical feature.

Table 3. Clinical features of malaria among glucose-6-phosphate dehydrogenase normal and deficient female patients

Clinical features	G6PD status				OR	95% CI	*p*-value[*]
	Deficient (n = 46)		Normal (n = 516)				
	No.	%	No.	%			
Pallor	10	21.8	109	21.1	1.04	0.50–2.16	0.927
Dark urine	4	8.7	179	34.7	0.18	0.06–0.51	<0.001
Convulsion	4	8.7	114	22.1	0.39	0.21–0.73	<0.001
Impaired consciousness	8	17.4	91	17.6	0.98	0.44–2.18	0.872
Fever	45	97.8	516	100	0	0–1.69	0.163
Vomiting	7	15.2	125	24.2	0.56	0.24–1.29	0.230
Cough	5	10.9	48	9.3	1.19	0.45–3.15	0.932
Diarrhoea	32	69.6	356	69	1.03	0.53–1.98	0.931
Difficulty in breathing	2	4.3	32	6.2	0.69	0.16–2.96	0.855
Temperature (>38ºC)	35	54.7	509	98.6	0.02	0.01–0.04	<0.001
Palpable spleen	25	39.1	147	28.5	1.61	0.94–2.75	0.109
Jaundice	4	8.7	11	2.1	3.06	0.94–9.91	0.072
Liver size (>2 cm)	4	8.7	77	14.9	0.38	0.13–1.08	0.825
Respiratory distress	28	43.8	170	32.9	1.58	0.93–2.68	0.094

[*]Chi-square test used; OR – Obtained from 2 × 2 table for each clinical feature.

pable spleen (66.7% *vs* 51.2%). However, there was no significant difference in the proportions of G6PD-deficient and normal patients who presented with fever, vomiting, cough, diar-rhoea, difficulty in breathing, jaundice, liver enlargement (>2 cm below the right costal margin) and respiratory distress.

Table 3 shows the comparisons of the clinical features of malaria in G6PD-deficient and normal female patients. The proportions of patients who presented with dark urine (8.7%), convulsions (8.7%) and temperature >38°C (54.7%) in G6PD-deficient group were significantly lower than 34.7, 22.7 and 98.6%, respectively in

the G6PD-normal group. There was no statistically significant difference in the proportions of patients who presented with pallor, fever, vomiting, cough, diarrhoea, difficulty in breathing, palpable spleen, jaundice, liver size >2 cm and respiratory distress in the G6PD-normal and deficient groups.

All the deaths were due to cerebral malaria, with a case fatality rate of 7.9% (19/241). Whereas, no death occurred among the G6PD-deficient patients in this study, all the dead patients were G6PD-normal. Visual and hearing impairment was documented at the time of discharge in four patients with cerebral malaria.

DISCUSSION

This study has shown that convulsions and elevated body temperature were more frequent features of malaria in G6PD-normal than deficient children in both males and females. The G6PD-deficient male, not female children showed protection against pallor and impaired consciousness as clinical signs during malarial illness. However, G6PD-deficient males were more likely to present with dark urine and enlarged spleen than G6PD-normal ones. These differences were not influenced by blood group and haemoglobin types. Also, there was male preponderance in all three types of malaria in this study and majority of affected children were <5 yr. The relative dominance of male children in the study population reflects the pattern of male to female ratio of malarial infection and admissions into the typical Nigeria tertiary hospitals that have been previously reported[4, 16, 21–22]. Globally, malaria affects more under-5 than older children in endemic regions mainly because of adaptive immunity against malaria which results from repeated malaria attacks is often not sufficiently strengthened until five years[18].

Fever was the most common presenting complaint among the study patients. This agrees with previous studies which showed that fever was the most common reason for which caregivers sought healthcare for children with malaria in endemic countries, particularly in Nigeria[21, 23]. However, fever could sometimes be under reported or exaggerated as in a recent study which showed that the sensitivity of tactile assessment for fever could be a as low as 23% among caregivers in emergency setting[24]. On the other hand, fever has been a useful index in monitoring recovery during treatment of malaria among children. In an earlier study of inpatients suffering from falciparum malaria, individuals with normal G6PD status had almost double the fever clearance time compared to those with G6PD-deficiency, an indication of a protective role conferred by low G6PD levels[25].

The present study showed no significant association between jaundice and G6PD status in both male and female malaria patients. This implies that jaundice may not be a good distinguishing feature of malaria between G6PD-normal and deficient children. There is a wide variation in the reports of jaundice in malaria among children. Massive intravascular haemolysis of parasitized red blood cells, malarial hepatitis, antimalarial drug induced haemolysis, coexisting acute viral hepatitis and underlying chronic hepatitis, are recognized mechanisms of jaundice in falciparum malaria[26]. While, G6PD-deficiency may confer protection against malaria, it may also be the cause of haemolysis and jaundice among the malaria patients. In a study of 35 children with G6PD-deficiency who presented with acute intravascular haemolysis, malaria was the incriminating factor responsible for haemolysis in four children[9]. Antimalarial drugs such as quinine and primaquine may also precipitate haemolysis in G6PD-deficient individuals[18]. However, the number of children who received these drugs before admission to the study centre was not documented in the present study since the drugs were only recommended for use in the hospital settings in Nigeria[27].

Liver enlargement (>2 cm below the right costal margin) was not associated with G6PD status among malaria patients in this study. The implication of this finding is that liver enlargement can not be a good discriminatory clinical feature of malaria between G6PD-normal and deficient children. Though, no previous study had elucidated the difference in presence of enlarged liver between G6PD-normal and deficient patients during malaria illness. A study[28] in the same hospital earlier showed that Nigerian children with acute falciparum malaria had complete resolution of hepatomegaly in 41% of children after recovery from the acute illness (by Days 7 or 14), and persistent hepatomegaly was common among children who failed to clear parasitaemia by Day 7 after appropriate treatments[28].

The proportions of G6PD-deficient children who presented with convulsions in male and female categories were lower than 69.6% that was earlier reported by Hendrickse et al[29], among malaria patients. Contrary to the findings of protection against occurrence of convulsions in the present study, Hendrickse et al[29] reported that convulsions were more frequent among G6PD-deficient patients than normal children. However, it is important to note that the present study included both children treated on outpatient and admission. Children studied by Hendrickse et al[29] were those admitted and were likely to be selectively biased, this may explain the high frequency of convulsions among the subjects. The present study, therefore, suggests that the cerebral involvement is less likely in G6PD-deficient children compared with normal children.

Our data also revealed no relationship between occurrence of respiratory distress and G6PD-deficiency in both male and female malaria patients. Respiratory distress being a summary description applied to children who have obviously abnormal breathing pattern involving the

use of more effort than usual could be an important risk factor for death among children with malaria[30]. Similarly, respiratory distress has been shown to adversely affect the outcome of childhood cerebral malaria among Nigerian children[22]. However, it is not clear from our data why a significantly less proportion of G6PD-deficient patients would have respiratory distress compared with normal children. The study did not investigate other possible causes of respiratory distress, such as acidosis, pneumonia and deep sequestration of parasites in the pulmonary vascular bed. None of the patients in the series had abnormal breath sounds.

In Nigeria, presumptive treatments of malaria based on the use of clinical signs and symptoms are recommended in settings where microscopy is not feasible and could cause delay in commencing antimalarial drugs[27]. Given this background, distinguishing between children who are likely to be G6PD-normal or deficient would be of value in a making safer choice of antimalarial. There is a drawback of the G6PD-deficiency screening test (fluorescent spot) used in this study. Fluorescent spot-test does not distinguish between heterozygote and homozygote G6PD-normal individuals and this limits the generalisability of the data to these categories of children. Nonetheless, this study suggests that malaria manifests different recognizable features in G6PD-normal and deficient children. Convulsion and elevated body temperature occurred more frequently in G6PD-normal than deficient in both males and females while pallor, impaired consciousness and enlarged spleen were more common features of malaria in G6PD-normal than deficient male but not female children. These differences may offer useful hints in the choice of antimalarial treatments and researches in endemic regions.

ACKNOWLEDGEMENTS

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