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## Glucose-6-Phosphate Dehydrogenase Deficiency and Sickle Cell Disease in Burkina Faso

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**Abstract:** Where malaria is endemic, there is an unexpected association between haemoglobinopathies and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Their coexistence in a patient with sickle cell disease (SCD) can lead to hemolytic anemia, hemoglobinuria, sepsis, renal failure and vaso-occlusive attacks (VOA). The aim of this research was to determine the impact of G-6-PD deficiency in SCD patients. That is why, we screened haemoglobinopathies and G-6-PD deficiency in 7 villages and at 10 primary schools in Kadiogo Province, Burkina Faso. Hemoglobin electrophoresis was performed on blood from 18,383 people. From these results, we chose 342 subjects for a hemogram and the measure of the G-6-PD activity. The results were analyzed with EpiInfo-6 and Spss-10. Statistical significance was set at  $p < 0.05$ . We found a prevalence of 28.9% of Sickle Cell Trait (SCT), 1.3% of Major Sickle Cell Syndromes (MSCS), 12.3% of G-6-PD deficiency among women and 20.5% among men. We did not detect a statistically significant difference for counts of erythrocytes ( $p = 0.773$ ), leucocytes ( $p = 0.227$ ) and reticulocytes (0.292); hemoglobin levels ( $p = 0.998$ ); annual vaso-occlusive attacks ( $p = 0.869$ ) between persons with SCD having a G-6-PD deficiency and those with normal G-6-PD activity. According to this study, G-6-PD deficiency does not seem to increase the severity of SCD. However, these patients should know their G-6-PD genotype in order to avoid consuming oxidative drugs that might provoke oxidative stress.

**Key words:** G-6-PD, Sickle cell disease, HbS, malaria, hemoglobinuria, Burkina Faso

### INTRODUCTION

Burkina Faso, a country in Western Africa, is bordered on the north and the west by Mali, on the east by Niger and the south by Ivory Coast, Ghana, Togo and Benin. In tropical area, where malaria is endemic, there is a high prevalence of haemoglobinopathies and G-6-PD deficiency (Enevold *et al.*, 2005; Fleming *et al.*, 1979). The genes for sickle cell disease (SCD) and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency are located on chromosome 11 and chromosome X, respectively. During cell division, the genes normally assort independently (Bouanga *et al.*, 1998; Luzzatto *et al.*, 1968). Sickle cell patients experience vaso-occlusive attacks (VOA), bacterial infections, priapism and chronic visceral complications associated

with ischemia in different organs (Jacob *et al.*, 2005. Singh *et al.*, 2006. Rogers, 2005). Major Sickle Cell Syndromes (MSCS) are the most prevalent forms of genetic disease in the wider malaria area in tropical countries. Glucose-6-phosphate dehydrogenase deficiency also occurs with increased frequency throughout Africa, Asia, the Mediterranean and the Middle East. In G-6-PD deficient individuals, anemia is usually caused by fava beans (Laosombat *et al.*, 2006) and other oxidative drugs (Ciftci, 2005; Ozmen *et al.*, 2004): aspirin, primaquine and quinine that are used during malaria attacks. In addition to hemolytic anemia, G-6-PD deficient individuals are predisposed to prolonged neonatal jaundice, a result of neonatal hyperbilirubinemia (Muzaffer, 2005; Kaplan *et al.*, 2005). This is a potentially serious problem as neonatal hyperbilirubinemia can cause

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severe neurological complications and even death (Diop *et al.*, 2005). The high prevalence of hemoglobin S (HbS) and G-6-PD deficiency (A-type) in tropical areas is related to the selective advantage they provide against malaria (Williams *et al.*, 2005; Shimizu *et al.*, 2005). The reported prevalence of G-6-PD deficiency in SCD patients varies. According to some authors, the incidence of G-6-PD deficiency is higher in MSCS patients than the general population (Bouanga *et al.*, 1998; Lewis *et al.*, 1966; Samuel *et al.*, 1986). Other authors do not agree with this association believing rather that the mutated genes responsible for these states do not stay on the same chromosome, so they cannot be linked (Bouanga *et al.*, 1998; Luzzatto *et al.*, 1968). The potential influence of glucose-6-phosphates dehydrogenase deficiency upon the clinical manifestation of patients with SCD is a matter of contention as well (El-Hazmi *et al.*, 1987; Bienzle *et al.*, 1975). It is known, however, that G-6-PD deficiency in patients with SCT can express itself like symptomatic SCD. Screening of SCD patients who are carrying the G-6-PD deficiency gene will guide physicians in their care. Such measures allow sickle cell disease patients to enjoy a life expectancy beyond 50 years. This study has three aims: i) to estimate the prevalence of the association between the haemoglobinopathies and G-6-PD deficiency genes among the population, ii) to look at patients who carry this double mutation and to determine the evolution of any hematological parameters that might be therapeutically helpful, iii) finally, to see if this curious linkage of these two mutated genes causes more complications in the pathogenesis of SCD patients.

## MATERIALS AND METHODS

Blood samples were collected in 7 villages and at 10 primary schools of the Province of Kadiogo in Burkina Faso from May 25, 1999 to June 15, 2005. A total of 18,383 subjects, ages 7-32 years, average  $21.81 \pm 8.47$  years, were enrolled in the SCD study. From the electrophoresis of hemoglobin results, we chose 342 individuals for the following analyses: hemogram and G-6-PD test. All the SCD patients agreed to answer questions concerning their health status: number of annual transfusions, hospitalizations, vaso-occlusive attacks (VOA) and episodes of malaria. We compared the different evaluative elements of SCD patients who have G-6-PD deficiency with SCD patients who do not have a G-6-PD deficit. We calculated a severity index, a total equal to the sum of the scores obtained utilizing the following parameters:

**Number of hospitalizations in the year:** 0 times at score = 0; 1 to 2 times at score = 1; more than 2 times at score = 2

**Number of vaso-occlusive attacks (VOA) in the year:** 0 times at score = 0; 1 to 2 times at score = 1; more than 2 times at score = 2

**Number of transfusions in the year:** 0 times at score = 0; 1 to 2 times at score = 1; more than 2 times at score = 2

**Number of malaria attacks in the year:** 0 times at score = 0; 1 to 2 times at score = 1; more than 2 times at score = 2

**Number of suspensions of activity in the year:** 0 times at score = 0; 1 to 2 times at score = 1; more than 2 times at score = 2

**Ethical committee:** the Ethics Committee of Saint Camille Medical Center in Ouagadougou approved the admission of prospective participants into the study only after informed consent was obtained.

**Methods:** Ten milliliter of venous blood was drawn from each person and placed in two EDTA tubes. One blood tube was used soon thereafter for the hemoglobin electrophoresis and hematological parameters. Within 3 h of drawing blood, plasma was separated out by centrifugation at 3,000 rpm for 10 minutes in the 2nd tube to be used for the G-6-PD test. All subjects underwent hemoglobin electrophoresis using cellulose acetate plates (Helena Laboratories, Beaumont, TX, the USA) with a pH 8.6 buffer. A hemogram was carried out utilizing the Cell-dyn®1700 automat of Abbott House while reticulocytes were measured using new methylene blue dye. Glucose-6-phosphate dehydrogenase quantities were measured by Quantitative G-6-PD Diagnostic Real Time Systems Kit Test (Italy) using a spectrophotometer reader type Microlab 2000.

**Statistical analysis:** Demographic and clinical profiles were recorded on computer files and analyzed by standard software SPSS-10 and EpiInfo-6. Statistical significance was set at  $p < 0.05$ .

## RESULTS

Hemoglobin electrophoresis was performed on a sample of 18,383 individuals: 9,923 females (53,98%) and 8,460 males (46,00%). Table 1 presents allelic frequencies calculated utilizing the genotypes observed: p, q and r are respectively the frequency of  $\beta^A$ ,  $\beta^S$  and  $\beta^0$ . The formula of Hardy-Weinberg allowed us to calculate the genotypic and allelic frequencies:  $AA = Np^2$ ,  $AC = 2Npq$ ,  $AS = 2Npr$ ,  $CC = Nq^2$ ,  $SC = 2Nqr$ ,  $SS = Nr^2$ . N indicates the number of the sample. Table 2 presents the

G-6-PD genotypic frequencies according to age groups. The frequency of G-6-PD deficiency in the general population is 16.3%. This percentage increases with age: 6-9 years (8.4%), 10-19 years (20.9%) and 20-29 years (25.0%). Table 3 shows G-6-PD activity according to hemoglobin genotype after hemoglobin electrophoresis. The frequency of G-6-PD deficiency among SCT, MSCS and the control population with Hb AA are, respectively: 18.57%, 27.0% and 7.81%. It is important to note that the prevalence of the favism is higher in men (20.5%) than women (12.3%), with  $p = 0.041$ . Table 4 presents the results of the hemogram and the G-6-PD activity of AA, SCT and MSCS subjects. The t-TEST reveals a statistically significant difference ( $p < 0.001$ ) between the control population with Hb AA and MSCS patients for G-6-PD enzymatic activity, the number of red blood cells (RBCs), white blood cell (WBCs), reticulocytes, the concentration of hemoglobin and the mean corpuscular volume (MCV). Whereas the control population with Hb AA presents a normal hemogram, there is a severe anemia, increased amount of reticulocytes and leucocytes associated with MSCS subjects. The SCT subjects have a moderate anemia and reticulocytosis. Table 5 presents the influence of the G-6-PD deficiency on the pathogenesis of SCD. In our samples, we had 74 SCD patients: 37 hemoglobin homozygote SS and 37 hemoglobin double heterozygote SC. Among these patients, 54 had normal G-6-PD activity and 20 had

deficient G-6-PD activity. The subjects freely answered the questionnaire, the results of which are reflected in Table 5.

Table 1: Genotype and allelic frequencies observed and calculated

Genotypes frequencies	*Frequencies of genotypes	observed	**Frequencies of genotypes calculated
AA	12833	0.6981	12829 0.6979
AC	3513	0.1911	3541 0.1926
AS	1535	0.0835	1514 0.0824
CC	272	0.0148	245 0.0133
SC	184	0.0100	209 0.0114
SS	46	0.0025	45 0.0024
Total	18383		
Allelic frequencies			
$\beta^A$	$p = 0.8354$		
$\beta^C$	$q = 0.1153$		
$\beta^S$	$r = 0.0493$		

NS = Not significant.  $\chi^2$  \*--> \*\*:  $p = 0.659$  (NS)

Table 2: G-6-PD genotypic frequencies according to age group

No	Age groups	Frequencies	Normal G-6-PD activity	Deficient G-6-PD activity
1	X<10	83 (24.3%)	76 (91.57%)	7 (8.43%)
2	10<X<19	67 (19.6%)	53 (79.10%)	14 (20.90%)
3	20<X<29	96 (28.1%)	72 (75.00%)	24 (25.00%)
4	29<X	96 (28.1%)	85 (88.54%)	11 (11.46%)
Total		342	286 (83.63%)	56 (16.37%)

$\chi^2$  Test, 1-2:  $p = 0.029$ , 2-3:  $p = 0.542$  (NS), 1-3:  $p = 0.003$ , 2-4:  $p = 0.099$  (NS), 1-4:  $p = 0.502$  Not Significant (NS), 3-4:  $p = 0.015$

Table 3: G-6-PD frequencies and hemoglobin genotype distribution

N = 342 Frequencies	Control Population with HbAA	Sickle Cell Trait (SCT)	Major Sickle Cell Disease (MSCS)			
	128 (37.43%)	140 (40.93%)	74 (21.64%)	Females	Males	Total
Normal G-6-PD activity	118 (92.19%)	114 (81.43%)	54 (72.97%)	150 (87.7%)	136 (79.5%)	286 (83.63%)
Deficient G-6-PD activity	6-10 (7.81%)	26 (18.57%)	20 (27.03%)	21 (12.3%)	35 (20.5%)	56 (16.37%)
Total	128	140	74	171	171	342

$\chi^2$  Test: AA/G-6-PD \_ SCT/G-6-PD :  $p = 0.010$ ; AA/G-6-PD \_ MSCS/G-6-PD :  $p < 0.001$ ; SCT/G-6-PD \_ MSCS/G-6-PD :  $p < 0.152$  (NS), Not Significant

Table 4: G-6-PD activity and Hemogram parameter distribution

Parameters	G-6-PD	Age	GR	T Hb	HT	CCHB	VGM	T-Reti	GB
128 Control pop.									
AA Standard Dev.	133.69±10.02*	20.41±11.64	4.28±0.67*	12.31±1.98*	36.85±5.74*	33.18±1.34*	86.37±8.77*	10.88±1.88*	6.30±1.87*
140 SCT									
Standard Dev.	131.58±13.24	20.70±15.36	4.23±1.10	11.02±3.15	34.06±9.34	31.98±1.47	81.60±10.16	12.02±2.82	8.27±4.27
74 MSCS									
Standard Dev.	122.90±11.78**	17.96±14.16	3.85±0.74**	9.75±5.06**	30.11±5.91**	32.15±2.70	79.86±9.79**	14.28±6.06**	9.58±4.11**
MSCS/G-6-PD+	N = 54	19.11±7.36	3.82±1.03	10.07±2.74	31.06±7.66	31.97±2.35	82.78±9.31	14.33±4.82	8.92±3.49
MSCS/G-6-PD-	N = 20	17.85±10.07	4.34±0.51	10.08±1.29	30.55±3.64	33.00±1.12	70.62±5.84	12.10±1.65	10.14±4.62
t-test:		$p = 0.556$	$p = 0.773$	$p = 0.988$	$p = 0.776$	$p = 0.065$	$p < 0.001$	$p = 0.292$	$p = 0.227$

\* t-test:  $p < 0.001$ ; \*\* t-test:  $p < 0.04$

Table 5: G-6-PD deficit and SCD pathogenesis score

Number	MSCS/G-6-PD normal activity N = 54	MSCS/G-6-PD deficiency: N = 20	t-test
Vaso-occlusive attacks (VOA)	1.37±0.73	1.34±0.57	0.869(NS)
Malaria attacks	0.59±0.37	0.38±0.24	0.021
Hospitalization	1.21±0.64	1.19±0.52	0.901 (NS)
Transfusion	0.27±0.32	0.25±0.27	0.805 (NS)
Activity suspension	0.57±0.78	0.88±0.65	0.118(NS)

## DISCUSSION

For the 18,383 samples from the 10 schools of the town of Ouagadougou and the 7 surrounding villages of the capital, we found 5,320 (28,9%) SCT (HbAS, HbAC, HbCC) and 230 (1.3%) MSCS (HbSS and HbSC) (Table 1). We discovered 19.1% of the haemoglobinopathy AC. This frequency is higher than that identified in Mali (15.8%) (Diallo *et al.*, 1994) and in Nigeria (0.7%) (Storey *et al.*, 1979). According to Trabuchet (1991.) the epicenter of the HbC mutation could be in West Africa. Indeed, studying the haemoglobinopathies among the Mossi in Burkina Faso, Modiano *et al.* 2001a discovered that hemoglobin CC protected against severe malaria. In this research, we found AS in 8.4% of subjects. This prevalence is lower than that detected in Ghana 14,0% (Mockenhaupt *et al.*, 2000), Dhelki Kharia (India) 12.5% (Balgir, 2005), but very similar to that detected in Paik (India) 7.4% (Balgir, 2005), in Karachi (Pakistan) 5.1%, (Ghani *et al.*, 2002). Our result was quite higher than that found in Paraja (India) 0.9% (Balgir, 2005) and in Upper Volta 4.9% by Labie, (1984). The slight increase in the HbS percentage in our sample compared with that of Labie in (1984) is certainly due to the additional medical care provided in Burkina Faso since 1990 for SCD patients: vaccinations against pneumococcus, antimicrobial prophylaxis and improved medical care. Simpoire *et al.* (2002) with their haemoglobinopathy research, demonstrated that SCD patients are often sick and frequently go for medical consultation at Saint Camille Medical Centre in Ouagadougou: 660 HbSC (6.5%), 196 HbSS (1.9%) and 3400 SCT (33.4%). We detected 16.37% G-6-PD deficiency (Table 2). This prevalence is higher than that they found in Dakar in 2005 (12.3%) (Diop *et al.*, 2005), in Pakistan (1.8%) (Ali *et al.*, 2005) and lower than that detected in both Lome in 2001 (24,1%) (Gbadoe *et al.*, 2001) and Vataliya Prajapati community (India) (22,0%) (Gupte *et al.*, 2005). However, our G-6-PD deficiency frequency is almost the same as Modiano *et al.* (2001a) identified (14.9%) (Modiano *et al.*, 2001b). The prevalence of G-6-PD deficiency in male subjects (20.5%) differs significantly ( $p = 0.04$ ) from that found in women (12.3%) Table 3. That is due to the fact that the males are hemizygous and the females are dizygous for X chromosome. As such, the probability of finding the two genes for the G-6-PD mutations on the chromosome X is lower. In this study we found a very slight but significant difference of G-6-PD enzyme activity between male ( $121.2 \pm 13.2$  mU.109/Eryth) and female ( $123.9 \pm 12.1$  mU.109/Eryth)  $p < 0.05$ . This similarity of G-6-PD enzymatic activity between male and female is due to the fact that the phenomenon of lyonization activates only one X

chromosome in each woman's cell. G-6-PD deficiency and SCD are two genetic disorders of red blood cells (RBCs) which predispose to hemolytic anemia. Their presence in patients should lead those providing medical care to avoid using oxidative drugs. In our research we found a significant difference between G-6-PD deficiency in SCD patients (27.03%) and in the control population with HbAA (7.81%)  $p < 0.001$  (Table 3). Similar results were found in Congo Brazzaville (Samuel *et al.*, 1986), in Senegal (Diop *et al.*, 2005), in Kenya (Rattazzi *et al.*, 1971), in Ghana (Lewis, *et al.*, 1973) and in Turkey (Akoglu *et al.*, 1986). But other studies do not confirm this association (El-Hazmi *et al.*, 1987; Steinberg and Dreiling, 1974; Saad *et al.*, 1992). More often than not, at the time of meiosis during the cycle of cell division, the HbS and G-6-PD deficiency genes, which are located on two different chromosomes, independently segregate according to Mendel's Law. But the phenomenon of selection, due to the presence of plasmodia, pushes these pathogenic genes to stay together and thus associated. Comparing the profile of SCD subjects with G-6-PD deficiency and SCD subjects with normal G-6-PD activity, no statistical difference was found between these two groups with regard to annual VOAs ( $p = 0.869$ ), annual hospitalizations ( $p = 0.901$ ), annual transfusion frequency ( $p = 0.805$ ) and annual activity suspension (0.118) (Table 5). Similarly, no statistical difference was found for hematological parameters: RBC counts ( $p = 0.773$ ), reticulocyte counts (0.292), WBC counts ( $p = 0.227$ ), hemoglobin level ( $p = 0.988$ ), hematocrit ( $p = 0.776$ ) and mean corpuscular Hb (MCH) ( $p = 0.065$ ). We identified a statistical difference between the two groups only for MCV values ( $p < 0.001$ ). These results agree with the studies of Bienzle *et al.* (1975), Steinberg and Dreiling (1974), Diop. (2000) and El-Hazmi. (1986), which showed that G6PD deficiency, even in the tropical area, seems to have no effects on the hematological data and clinical evolution of HbSS patients. According to these authors, G6PD deficiency does not offer any advantage or disadvantage to patients with sickle cell disease. However, other authors like Bouanga. (1998) and Znaidi. (1995) offer different results. And some authors argue that G-6-PD deficiency has a protective effect in SCD patients because the absence of enzymatic activity contributes to the elimination of premature RBCs. There is a elevated generation of young erythrocytes in these G-6-PD deficiency persons (Steinberg and Dreiling, 1974). There was a significant difference in malaria attack frequency between the group of SCD patients with G-6-PD deficiency and SCD subjects with normal G-6-PD activity ( $p = 0.048$ ). SCD subjects who have a G-6-PD deficiency suffer fewer crises of malaria. It is known that the

frequency of the G-6-PD deficit increases with age (Table 2), which could indicate a longevity advantage in malaria zones as compared to people with normal enzyme activity. Nonetheless, these results should not lead us to forget that when SCD patients with G-6-PD deficiency have malaria, there is a significant risk of developing hemolytic anemia crises, sepsis, hemoglobinuria and renal failure after taking anti-malarials or eating oxidative foods like fava beans. SCD, which is responsible for a high rate of medical consultations and increased mortality in children, remains a public health problem for tropical countries. It remains vital to screen for G-6-PD deficiency among SCD patients in order to provide appropriate preventive and therapeutic measures.

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