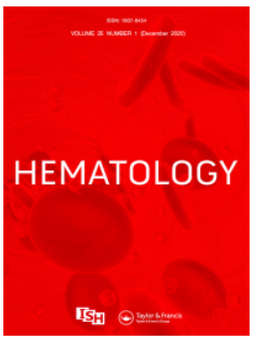

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Does glucose-6-phosphate dehydrogenase deficiency worsen the clinical features of sickle cell disease? A multi-hospital-based cross-sectional study

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ABSTRACT

Background: The impact of glucose-6-phosphate dehydrogenase deficiency(G-6-PD) on the clinical course of sickle cell disease(SCD) is still controversial. The objectives of this study were to determine the prevalence of G-6-PD deficiency in patients with SCD and its effect on their clinical course.

Methods: A cross-sectional study of 122 SCD patients and 211 healthy blood donors was conducted in Kisangani city. Data were collected through clinical examination supplemented by patient medical records, and laboratory tests based on a survey form. G-6-PD activity was measured by spectrophotometry and the screening for SCD by the HemoTypeSC® rapid test. Statistical analysis was done using SPSS ver. 20.0.

Results: The prevalence of G-6-PD deficiency did not differ between SCD and non-SCD subjects, 35.2% vs. 33.6% respectively($p = .767$). When comparing the hemoglobin level between SCD patients with and without G-6-PD deficiency, no significant difference was observed. However, in the 6 months prior to the study, SCD patients with G-6-PD deficiency had on average more transfusions than non-deficient SCD patients, 0.64 ± 0.897 vs. 0.24 ± 0.486($p = .004$). Similarly, considering the clinical events of the last 12 months prior to the study, there were more hospitalizations, major vaso-occlusive crises and anemia requiring blood transfusion among G-6-PD deficient SCD patients compared to no-deficient, respectively 1.42 ± 1.451vs. 0.76 ± 1.112($p = .007$); 1.37 ± 1.092 vs. 0.85 ± 1.014($p = .005$); 0.74 ± 0.902 vs. 0.38 ± 0.739 ($p = .007$).

Conclusion: The prevalence of G-6-PD deficiency in SCD patients was high but did not differ from that observed in controls. In addition, G-6-PD deficiency appeared to worsen the clinical features of SCD. Nevertheless, prospective studies further clarifying this observation are needed.

KEYWORDS
Sickle cell disease; G-6-PD deficiency; prevalence; clinical features; Democratic Republic of the Congo; comorbidity; sub-Saharan Africa; red blood cell disorders

Introduction

Sickle cell disease (SCD) and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency are the most common genetic and hemolytic red blood cell diseases worldwide, particularly in sub-Saharan Africa (SSA). On the one hand, it is estimated that nearly 5% of the world's population carry the hemoglobin S(HbS) allele [1,2], and that every year approximately 300,000 infants are born with SCD of which approximately 75.5% in SSA [3]. On the other hand, G-6-PD deficiency is the most common human enzyme defect affecting nearly 400 million people in the world [4,5]. The G-6-PD enzyme is critical to protect erythrocytes against oxidative stress and subjects with deficiency in this enzyme are at risk of hemolysis under certain conditions.

Sickle cell disease and G-6-PD deficiency are genetically independent, their loci being located on chromosome 11 for SCD and chromosome X for G-6-PD deficiency. Therefore, they are expected to assort independently. Nevertheless, the assumption that G-6-PD deficiency was more common in SCD patients than in normal subjects was raised in the 1960s [6]. But the reports on this subject remain conflicting, indicating the need for more studies especially in areas where these two diseases are prevalent. Gibbs et al in Jamaica [7] and Fasola et al in Nigeria [5] reported that the prevalence of G-6-PD deficiency in SCD patients does not differ significantly from that observed in controls. In contrast, Diop et al in Senegal [8] found a significantly higher G-6-PD deficiency in SCD patients than

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in controls. This comorbidity is of great importance in the management of SCD patients since it has been postulated that G-6-PD deficiency could worsen the clinical features of SCD mainly through exacerbation of hemolysis [9]. Indeed, under oxidative stress conditions resulting from infections, the use of certain medications including anti-malarials and antibiotics, or the consumption of fever, subjects with G-6-PD deficiency may develop hemolysis. However, this hypothesis is still controversial. According to the findings of Karafin et al, G-6-PD deficiency does not appear to worsen the clinical course of SCD [6].

In the Democratic Republic of the Congo (DRC), malaria is endemic and infectious diseases are common. Therefore, the use of anti-malarials and antibiotics including those implicated in hemolysis in G-6-PD deficient subjects such as trimethoprim-sulfamethoxazole [11], sulfadoxine-pyrimethamine [12], ciprofloxacin [13], is also common, especially in SCD patients owing to recurrent infections. Data on G-6-PD deficiency in DRC are scarce. According to the a geostatistical model-based map by Howes et al, the prevalence of G-6-PD deficiency is estimated to range from 4% to 32% in the DRC [14]. However, to our knowledge, the relationship between sickle cell disease and G-6-PD deficiency have not yet been assessed in this country. In the context of the DRC, this knowledge is essential as it may have interesting therapeutic implications in the management of SCD patients. Thus, this study aimed to determine the prevalence of G-6-PD deficiency in SCD patients and its effect on their clinical course.

Methods

Study site/study design/study population

This cross-sectional study was conducted simultaneously in five health facilities in the city of Kisangani (northeastern DRC): The University hospital of Kisangani, Makiso and Kabondo general hospitals of reference, ALABUL and Gracia Fondation health centers. These healthcare facilities were chosen based on their high attendance by SCD patients. The study was carried out from September 28, 2019 to March 04, 2021. The study population consisted of known SCD patients mostly of pediatric age, whose diagnosis had already been clinically and biologically established either by high-performance liquid chromatography coupled to mass spectrometry or by the HemoTypeSC® rapid test, and followed up in the above health facilities for various health issues. Subjects were enrolled by convenience sampling during their follow-up appointment. The requested minimum number (n) for the study was 117 participants obtained by setting 95% confidence level, 80% statistical power, and considering the estimated prevalence of the sickle cell trait of 23.3% in Kisangani [15]. A total of 163 subjects were regularly followed in the above health facilities during the study period. But ultimately, 122 subjects were included in the study as they fulfilled the inclusion criteria. Inclusion criteria consisted of (1) having consented to participate in the study or parental/guardian consent for subjects under 18 years of age, (2) not having received a blood transfusion during the 3 months preceding the survey, and (3) being at the inter-critical stage at the time of the survey. The inter-critical stage was defined by the absence of acute complications of SCD at the time of the survey. Subjects with high reticulocyte counts (greater than 3%) were excluded from the study. The control group consisted of 211 healthy volunteer blood donors recruited from the provincial blood transfusion center of Kisangani through convenience sampling.

Data collection

Data were collected through clinical examination and laboratory tests based on a survey form. The variables of interest were gender, age, number of transfusions received in the last six months, number of hospitalizations for SCD complications (fever, anemia or painful crisis) in the last 12 months, frequency of major painful attacks (i.e. requiring management in a hospital or health center) in the last 12 months, frequency of anemia requiring transfusion in the last 12 months, hemoglobin phenotype, hemoglobin rate and G-6-PD enzyme activity.

Clinical data

Clinical data were obtained through a clinical examination of SCD patients including an anamnesis, and the use of their medical records if required. The data collected were related to the sociodemographic characteristics and the evolutionary history of the disease. For children, the disease history was obtained from their parents or guardians. For the control group, sociodemographic data were collected at the time of the pre-donation examination.

Biological data

Laboratory procedures. For each subject, 4 ml of whole blood were collected by vein puncture in the elbow fold, previously disinfected, into a vacuum tube containing Ethylene Diamine Tetra Acetatic acid. Following vein puncture, samples were stored immediately at 4–8°C in an isothermal box containing cold packs, and then transferred to the laboratory within two hours at most for the determination of hemoglobin level, reticulocyte level, the hemoglobin phenotypes and the G-6-PD enzymatic activity.

The hemoglobin level was determined by an automatic hematology analyzer (Model: DF 50, Shenzhen Dymind Biotechnology Co. Ltd, SN: DM11042037008).

The reticulocyte count was determined manually after staining with brilliant cresyl blue.

The quantitative G-6-PD enzymatic activity was determined by spectrophotometry [16] using a commercial G-6-PD assay kit (G6-PDH Enzymatic UV) from Cypress Diagnostics (Cypress Diagnostics: Nijverheidsstraat 8.2235 Hulshout. Belgium) following the procedure outlined in the manual provided with the kit. UV spectrophotometry measures the formation of NADPH from the enzymatic activity of G-6-PD by measuring the change in absorbance of the sample at 340 nm. This absorbance variation is proportional to the G-6-PD activity. After determining the difference between the absorbances and the average absorbance differences per minute (ΔAbs./min) using a semi-automate (CYANSmart REF.CY009, SN BS61k028E. Cypress Diagnostics: Langdorpsesteenweg 1603201 Langdorp,Belgium), we used the following formula to determine the enzymatic activity:

$$\text{G6-PDH(U/g Hb)} = \frac{\Delta\text{Abs/min} \times 33650}{\text{Total Hb(g/dL)} \times 10};\ \text{Hb} = \text{Hemoglobine}$$

ΔAbs./min = Difference between the absorbances and the average absorbance differences per minute.

The normal reference values were 10.01–14.19U/g Hb (37°C) [16]. The quality control was made using the control sera supplied with the kit.

The hemoglobin phenotypes were determined using the HemoTypeSC® rapid test kit according to the manufacturer's instructions [17].

Operational definition:

The major vaso-occlusive crisis was defined as the one that was not relieved at home and required treatment in a healthcare facility.

Ethical statement and statistical analysis

This study has been cleared by the Ethics Committee of the University of Kisangani (Réf. UNIKIS/CER/007/2018). Furthermore, Freely-given and informed consent to participate in the study was obtained from all participants. For children under 18 years of age, the consent of parents or guardians was required.

Data were reported on specific questionnaires and then transferred to an electronic database. Statistical analysis was done using SPSS ver. 20.0. The normality of the data was checked by Shapiro–Wilk test, and the homogeneity of variances by Levene test. The parametric data were expressed in mean ± SD. We used independent t-test to measure the statistical significance of differences between group means in case of homogeneity of variances of data and Mann Whitney test in case of non-homogeneity of variances. For categorical variables we used Chi-square (χ2) test and Fisher's exact test. The statistical significance threshold used was 0.05 with a 95% confidence interval, and a p-value < .05 was considered significant.

Results

In this study, males were predominant (64.8%) among SCD patients, with a male/female sex ratio of 1.8. Their mean age was 13.79 ± 6.77 years while it was 26.12 ± 8.16 years in control group. The prevalence of sickle cell trait(HbAS) was 17.5% among blood donors. In addition, no SCD patient and no blood donor had ever been screened for G-6-PD deficiency. Finally, no blood donor had ever been screened for SCD Table 1.

The overall prevalence of G-6-PD deficiency was 34.2%. Among SCD patients, G-6-PD deficiency was observed in 35.2% of subjects vs. 33.6% in controls, but without significant difference (p = .767). Glucose-6-phosphate dehydrogenase deficiency was significantly predominant in males (p = .038). Regarding G-6-PD deficiency according to hemoglobin phenotypes, no difference was observed (p = .214) Table 2.

Among SCD patients, hemoglobin levels were on average higher in non-G-6-PD-deficient patients compared to deficient patients (6000 ± 1687 g/dL vs. 5605 ± 2172 g/dL) although the difference was not statistically significant (p = .964). Clinically, in the 6 months prior to the study, G-6-PD-deficient SCD patients had on average more transfusions than non-deficient subjects, 0.64 ± 0.897 vs. 0.24 ± 0.486(p = .004). Similarly, considering the clinical events of the last 12 months prior to the study, there were more hospitalizations, major vaso-occlusive crises and anemia requiring blood transfusion among G-6-PD deficient sickle cell patients, 1.42 ± 1.451 vs. 0.76 ± 1.112(p = .007); 1.37 ± 1.092 vs. 0.85 ± 1.014(p

Table 1. Characteristics of the study participants.

Characteristics	Overall N = 333 *n*(%)	Sickle cell disease patients N = 122 *n*(%)	Non-sickle cell participants N = 211 *n*(%)
Sex			
Female	51(15.3)	43(35,2)	8(3,2)
Male	282(84,7)	79(64,8)	203(96,2)
Age(years)			
≤ 5	9(2.7)	9(7.4)	0(0)
> 5	324(97.3)	113(92.6)	211(100)
Mean age ± SD		13,79 ± 6.77	26,12 ± 8.16
Hemoglobin phenotypes			
AA	174(52.3)	0(0)	174(82.5)
AS	37(11.1)	0(0)	37(17.5)
SS	122(36.6)	122(100)	0(0)
History of G-6-PD screening			
Yes	0(0)	0(0)	0(0)
No	333(100)	122(100)	211(100)
History of SCD screening			
Yes	122(100)	122(100)	0(0)
No	211(100)	0(0)	211(100)

N, total number; n, number; SD, standard deviation; G-6-PD, glucose-6-phosphate dehydrogenase, SCD, Sickle cell disease.

Table 2. Prevalence of G-6-PD deficiency and its distribution according to the characteristics of the study participants.

Variables	Overall *n*(%)	G-6-PD deficiency *n*(%)	Non- G-6-PD deficiency *n*(%)	*p*-value
Overall prevalence	333(100)	114(34.2)	219(65.8)	
SCD status				.767[1]
SCD patients	122(100)	43(35.2)	79(64.8)	
Non-SCD participants	211(100)	71(33.6)	140(66.4)	
Sex				**.038**[1]
Female	51(100)	11(21.6)	40(78.4)	
Male	282(100)	103(36.5)	179(63.5)	
Age				.498[2]
≤ 5	9(100)	4(44.4)	5(55.5)	
> 5	324(100)	110(33.9)	214(66.1)	
Hb phenotypes				.214[1]
AA	174(100)	54(31)	120(69)	
AS	37(100)	17(45.9)	20(54.1)	
SS	122(100)	43(35.2)	79(64.8)	

G-6-PD: Glucose-6-phosphate dehydrogenase, n: Number; SCD: Sickle cell disease.
[1]Chi-squared test.
[2]Fisher's exact test.

= .005); 0.74 ± 0.902 vs. 0.38 ± 0.739 ($p = .007$), respectively Table 3.

Discussion

Herein, we report the observation made on the prevalence and clinical impact of G-6-PD deficiency in subjects with SCD in a malaria endemic region of the Democratic Republic of the Congo. The overall prevalence of G-6-PD deficiency was 34.2%. The prevalence of G-6-PD deficiency observed in SCD patients is high but does not differ significantly from that in no SC subjects, i.e. 35.2% vs. 33.6% respectively ($p = .767$). However, considering the G-6-PD deficiency among SCD patients, the findings indicate that G-6-PD deficiency appears to worsen the clinical features of SCD.

Prevalence of G-6-PD deficiency

In DRC, there is a scarcity of data on the comorbidity of SCD and G-6-PD deficiency. However, the prevalence of G-6-PD deficiency observed in sickle cell and non-SCD subjects in this study, is close to that estimated in DRC by Howes et al (4%–32%) [14]. As the DRC is a malaria endemic country, the high prevalence observed in this study (34.2%) supports the widely accepted hypothesis that G-6-PD deficiency may have arisen, spread or been maintained in frequency by natural selection by malaria [18]. In Ghana [19], G-6-PD deficiency was found in 35.8% of SCD patients, which is similar to the result of the present study (35.2%). Our findings also corroborate those reported elsewhere, notably those of Gibbs et al [7] and Fasola et al [5] who did not find a significant difference in the prevalence of G-6-PD deficiency between SCD patients and non-sickle cell patients. Similarly, in the study by Bouangaa et al in Brazzaville(Congo), the prevalence of G-6-PD deficiency in subjects with SCD did not differ significantly from that found in the control population [20]. In contrast, Diop et al [8] in Senegal observed that G-6-PD deficiency was significantly higher in SCD patients compared to the control group (21.6% vs. 12.3%) ($p = .001$). Our result, while indicating a high prevalence of this genetic disorder among SCD patients in the DRC, also indicates that SCD patients in the DRC have a high likelihood of being transfused with G-6-PD-deficient blood units. This raises the question of the clinical effectiveness of blood transfusions made with such units since in DRC the transfusion is often undertaken in an infectious context, the patients being under medication (antibiotics and antimalarials) likely to cause oxidative stress and to induce hemolysis of G-6-PD deficient red blood cells. In addition, it is not routine practice to screen blood donors for G-6-PD deficiency. In the United States, G-6-PD deficient red blood cell units have been shown to be associated with decreased red blood cell survival after transfusion in children with SCD [21]. Thus, studies evaluating erythrocyte transfusion yield in SCD patients transfused with G-6-PD-deficient blood are required in DRC.

Table 3. Clinical characteristics of sickle cell disease patients according to their G-6-PD status.

Characteristics	G-6-PD deficiency	Number of subjects	Mean ± SD	Mean difference	95% CI of difference	*p*-value[1]
Hemoglobin level, g/dL	yes	43	5.605 ± 2.172	-0.3953	−1.156–0.366	.964
	no	79	6.000 ± 1.687			
Number of blood transfusions received in the last 6 months	yes	43	0.65 ± 0.897	0.411	0.116–0.706	.004
	no	79	0.24 ± 0.486			
Number of hospitalizations in the last 12 months for fever, anemia or painful crisis	yes	43	1.42 ± 1.451	0.659	0.152–1.166	.007
	no	79	0.76 ± 1.112			
Frequency of major vaso-occlusive crises* in the last 12 months	yes	43	1.37 ± 1.092	0.524	0.133–0.915	.005
	no	79	0.85 ± 1.014			
Frequency of anemia requiring blood transfusion in the last 12 months	yes	43	0.74 ± 0.902	0.364	0.044–0.685	.007
	no	79	0.38 ± 0.739			

G-6-PD: Glucose-6-phosphate dehydrogenase; SD: Standard deviation; CI: Confidence interval.
*Vaso-occlusive crisis requiring care in a health facility.
[1]Student t-test.

Effet of G-6-PD deficiency on sickle cell disease

Studies investigating the possible influence of G-6-PD deficiency upon the clinical manifestations of SCD have produced conflicting reports. In this study, although the mean hemoglobin level in G-6-PD deficient and non-G-6-PD deficient SCD patients was not statistically different, the clinical course showed significant differences in the two groups. Indeed, in the 6 months prior to the study, SCD patients with G-6-PD deficiency had on average more transfusions than non-deficient subjects, 0.65 ± 0.897 vs. 0.24 ± 0.486($p = .004$). Similarly, considering the clinical events of the last 12 months prior to the study, there were more hospitalizations, major vaso-occlusive crises as well as anemia requiring blood transfusion among G-6-PD deficient sickle cell patients. In 2013, in a prospective study, Benkerrou et al demonstrated that G-6-PD deficiency in babies with SCD worsens anemia and increases blood transfusion requirements in the first years of life [22]. In Nigeria, it was recently shown in a G6PD-deficient sickle cell patient with frequent hemolytic crises that with glutathione and selenium supplementation and advice to avoid exposure to oxidizing drugs, there was a respite in the frequency of acute episodes of hemolysis requiring blood transfusion [23]. Igwilo et al observed that G-6-PD deficiency significantly contributes to recurrent painful vasoocclusive crisis in SCD patients. Nevertheless, there was no difference in red cell indices [24], supporting our observation since we did not observe a significant difference in the mean hemogobin level according to the G-6-PD enzymatic activity. The results obtained by Antwi-Baffour et al led to the conclusion that, G-6-PD deficiency may increase the severity of anemia in SCD patients [19]. However, opposing observations have also been reported. In the study by Diop et al [8] in Senegal, no difference was found in the two groups concerning number of vaso – occlusivecrisis, number of transfusion, frequency of infectious episodes, number of chronic complications, disturbances on patient's activity and total index severity. According to Karafin et al, overall, G-6-PD deficiency has few, if any, effects on laboratory values and clinical outcomes in patients with SCD, but it may have an impact on the effectiveness of transfusions [10]. In Burkinafaso, Simpore et al argued that G-6-PD deficiency does not seem to increase the severity of SCD [25].

The severity of hemolytic anemia varies among individuals with G-6-PD deficiency. Specific G-6-PD alleles are associated with G-6-PD variants with different enzyme activities and, therefore, result in different levels of disease severity. For example, in Southeast Asia where the most common variant alleles appear to be G-6-PD Kaiping and Canton, which are different from those found in Caucasians or Africans, Ya-Wen Lu and Tsung-Chia Chen reported a case of a patient with G-6-PD deficiency, treated with trimethoprim-sulfamethoxazole without hemolysis [11]. This may partly account for the differences reported in the different studies. Despite these conflicting reports, the findings of this study advocate for routine screening of G-6-PD in patients with SCD in the DRC.

Study limitation

This study has some limitations. Indeed, some of the data were collected retrospectively with risk of recall bias, and women were underrepresented in the control group. In addition, we did not measure markers of hemolysis [bilirubin, haptoglobin, lactate dehydrogenase(LDH)]. Finally, given the context of the limited resources, we were not able to determine whether patients also had β^0 thalassemia or α-thalassemia. Similarly, the fetal hemoglobin level was not determined. These limitations indicate that more studies are needed for further evidence of the impact of G-6-PD deficiency on the clinical course of SCD.

Conclusion

Our findings indicate that the prevalence of the G-6-PD deficiency is high in SCD patients, but does not differ from that observed among non-SCD subjects in the DRC. However, the G-6-PD deficiency appears to worsen the clinical features of SCD. Therefore, a systematic screening for G-6-PD deficiency in all SCD patients in the DRC is essential and should be considered to prevent the occurrence of iatrogenic hemolytic accidents. In addition, there is a need for prospective studies, on the one hand, to further clarify the impact of G-6-PD deficiency on the clinical course of SCD, and on the other hand, for assessing post-transfusion clinical outcomes after transfusion with G-6-PD-deficient blood units.

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Data accessibility statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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