

Impact of G6pd Deficiency on Sickle Cell Disease in Children in Kinshasa Hospitals: a Case-Control Study

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Abstract

Background and aim: Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency and sickle cell disease are two genetic diseases of the red blood cell that both cause hemolytic anemia. The objective of this study is to determine the clinico-biological impact of G6PD deficiency on sickle cell disease in children in Kinshasa.

Materials and method: This is a case-control analytical study of 103 G6PD-deficient sickle cell patients and 309 non-G6PD-deficient sickle cell patients. Analysis of G6PD activity was performed by ELISA, and hemoglobin electrophoresis by capillary to confirm sickle cell disease. For all children, sociodemographic, clinical and biological variables were analyzed.

Results: The mean age of sickle cell deficient and non-deficient patients was 9.82±4.5 years and 9.48±3.8 years respectively. There were slightly more female sickle cell deficient patients (55.2%) while in the non-deficient group, there was a male predominance (51.8%) but no statistically significant difference (p>0.05). All morbid events occurring in sickle cell patients were greater in the G6PD deficiency group (p<0.05). Evaluated antecedent complications occurring in sickle cell patients were associated with G6PD deficiency (p<0.05), except for stroke. No statistically significant difference was noted in physical signs between sickle cell deficient and non-deficient groups (p>0.05). The hemogram showed no difference between the two groups in steady state and the hemolysis markers evaluated also showed no significant differences in steady state (p>0.05) between the two groups.

Conclusion: G6PD deficiency aggravates the acute clinical manifestations and complications of sickle cell disease without affecting the occurrence of stroke. And has no impact on the hematological parameters of sickle cell disease children in stationary phase.

Key words: osteomyelitis; pediatric; methicillin-susceptible *Staphylococcus aureus*; case report; myositis; cellulitis

Introduction

Sickle cell disease and Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency are two genetic diseases of the red blood cell mainly described in Sub-Saharan Africa and in particular in DRC. These two abnormalities are responsible for hemolytic anemia [1]. The genes involved are located on different chromosomes and therefore these two diseases are transmitted independently although they may be associated. Some authors believe that

G6PD deficiency has little or no impact on sickle cell disease while others believe that it worsens the clinical and biological profiles of sickle cell disease [2].

This comorbidity has been the subject of several scientific publications without showing an increase in the number of hemolytic crises, infectious episodes, and transfusions and chronic complications, or a lack of influence on the severity of the disease in such a combination [3-5]. Some authors

believe that G6PD deficiency would have a protective effect since the deficiency of enzymatic activity could contribute to the premature disappearance of red blood cells, which would result in the release of a new generation of young circulating cells. Piomelli et al. in Kenya in 1972 found that these two anomalies seemed to attenuate each other: sickle cell disease made the enzyme deficiency less apparent to the point that the deficient genotype seemed to be masked [6].

Several authors have found that G6PD deficiency does not worsen the clinical and biological status of sickle cell patients; these include Firempong et al. in Ghana in 2016 and Diop et al. in Senegal in 2005 [3,7]. Others on the other hand have found that G6PD deficiency worsens the disease state of sickle cell patients: including: Bernaudin et al, in France in 2018, Benkerou et al , in France in 2013, Lohit et al , in India in 2019, Mounkaila et al , in Niger in 2015 and Bouanga et al , in Congo in 1998 [2, 8-11].

These different studies sufficiently demonstrate the high prevalence of the comorbidity of G6PD deficiency and sickle cell disease mainly in Africa. In the DRC, no study has been conducted on this comorbidity, yet it is one of the countries most affected by G6PD deficiency. Moreover, it is a country located in the sickle cell belt of Central Africa wheresickle cell disease and malaria endemically [12, 13]. In addition, there is a high frequency of self-medication, particularly with antimalarial drugs, which are oxidizing molecules, exposing to acute hemolytic crises in case of G6PD deficiency (Quinine, Chloroquine, Mefloquine, Halophantrine) [14-19].

Thus, given the high prevalence of sickle cell disease - G6PD deficiency comorbidity and the high frequency of self-medication, we found it appropriate to undertake the present study, the objective of which is to determine the clinico-biological impact of G6PD deficiency on sickle cell disease among children in Kinshasa.

Materials and Methods

Nature, setting and period of study

This is a case-control study, which consisted of determining the clinico-biological impact of G6PD deficiency on sickle cell disease in children recruited as an active thread in medical facilities in Kinshasa. It covered the period from June 2017 to June 2019, a duration of 2 years.

Population and sampling

Study hospitals were selected by convenience sampling. The consecutive selection method, in active file, was used to identify the children to be submitted to the inclusion criteria. The first group consisted of homozygous G6PD- deficient sickle cell children confirmed by hemoglobin

electrophoresis or molecular testing, aged 6 months to ≤ 18 years of age recruited in the active file, and followed up as an outpatient in the selected hospitals, and the second group consisted of age- and sex-matched nondeficient sickle cell children recruited in the same setting as the first group, i.e., one case for every three controls [20].

Variables of interest

The variables evaluated based on the clinical and biological manifestations of sickle cell disease were sociodemographic data (age, gender, origin), clinical variables (the notion of coca cola urine emission, the number of previous transfusions, the number of previous vaso-occlusive crises, the number of infectious episodes, the history of complications: priapism, aseptic necrosis of the femoral head, notion of stroke, notion of malleolar ulcer, physical signs) and biological data (determination of G6PD enzyme activity, complete blood count, total bilirubin) [12, 13,14].

The samples were analyzed at the laboratory of the training and health support center (CEFA) and the Monkole hospital Center.

Conduct of the study

All children included in the study were identified using medical records and contacted to participate in the study. Children who met the inclusion criteria were first given a clinical examination that included a history and physical examination. The elements collected during the clinical examination made it possible to set up an ad hoc questionnaire. Acute sickle cell crises were assessed by the average annual number requiring emergency admission over the past 2 years (14). A physical examination, including weight measurement using a scale while undressed; height measurement using a horizontal scale in a supine or standing position according to age, with feet together.

Then, we took blood samples from each child. A 5 ml sample of venous blood was taken in two tubes; one dry for biochemical analysis, and the other with anticoagulant (EDTA) to carry out the haemogram, the determination of G6PD enzymatic activity by the ELISA method as well as haemoglobin electrophoresis; These tubes were stored at 4°C until the analysis was performed and a blood sample was taken on Whatman filter paper with conventional FTATM cards for G6PD. The samples collected were coded and immediately sent to the CEFA and Monkole Hospital laboratories.

Data processing and analysis

All data were collected and entered on Epi info 7, transported to Excel 2010 spreadsheet, analyzed with SPSS for Windows version 22.0, and presented in tables and graphs.

Variables	Whole group n=416(%)	G6PD deficient n=104(%)	Not G6PD deficient n=312(%)	P
Ages (years):	9,5±4	9,82±4,5	9,48±3,8	0,122
X±ET Sex				
Male	207	46 (44,2)	161 (51,6)	0,060
Female	209	58 (55,2)	151(48,2)	
Origin				0,045
HS Kingasani	124	39(37,1)	85(27,3)	
CMMS Mabanga	112	32(30,4)	80(25,7)	
CH Monkole	102	22(20,9)	80(25,7)	
HG Kinsenso	78	11(10,6)	67(21,5)	
Socioeconomic level				0,201
Low	153	54(51,4)	99(31,8)	
Medium	141	33(31,4)	108(34,7)	
Not specified	122	17(16,3)	105(33,7)	
Father's level of education				0,100
None	9	6(5,7)	3(0,9)	
Primary	10	5(4,7)	5(1,6)	
Secondary	141	29(27,6)	112(36)	
University	136	47(44,8)	89(28,6)	
Not specified	120	17(16,3)	103(33)	0,110
Mother's level of education				
None	7	2(1,9)	5(1,6)	
Primary	31	13(12,4)	18(5,8)	
Secondary	188	41(39)	147(47,3)	
University	71	29(27,6)	42(13,5)	
University	119	19(18,3)	100(32,1)	

Table 1: Description of the study population

Variables	Whole group n=416	G6PD deficiency n=104(%)	Non G6PD deficient n=312(%)	P
Clinical manifestations				
No. of transfusions				0,032
Absent	148	35(33,7)	113(36,2)	
1 to 3 times/year	114	29(27,6)	85(27,3)	
>3 times/year	154	40(38,1)	114(36,7)	
Emission of coca urine				0,012
Absent	325	18(17,3)	307(98,4)	
1 to 3 times/year	14	11(10,5)	3(0,9)	
>3 times/year	77	75(71,4)	2(0,6)	
No. of infectious episodes				0,003
Absent	163	40(38,5)	123(39,4)	
1 to 3 times/year	136	28(26,7)	108(34,7)	
>3 times/year	117	36(34,3)	81(26)	
No. of CVOs				0,024
Absent	156	42(40,4)	114(36,5)	
1 to 3 times/year	128	26(24,8)	102(32,8)	
>3 times/year	132	36(34,3)	96(30,8)	
Complications atcd				
STROKE				0,745
No	409	102(98,1)	307(98,3)	
Yes	7	2(1,9)	5(1,6)	
Necrosis of the femoral head				0,030
No	406	95(91,3)	311(99,7)	
Yes	10	9(8,6)	1(0,3)	
Priapism				0,001
Absent	411	100(96,2)	311(99,7)	
Yes	5	4(3,8)	1(0,3)	
Osteomyelitis				<0,000
No	413	101(97,1)	312(100)	
Yes	3	3(2,8)	0	
Malleolar ulcer				0,002
No	405	97(93,3)	308(98,7)	
Yes	11	7(6,7)	4(1,3)	

Table 2: Clinical information of G6PD-deficient and non-deficient children with sickle cell disease.

Variables	Whole group n=416	G6PD deficiency n=104 (%)	Non G6PD deficient n=312 (%)	
Hepatomegaly				0,823
Yes	55	13(12,4)	42(13,5)	
No	361	89(84,8)	260(83,6)	0,867
Size 1 to 3				
>3	15	6(5,7)	9(2,9)	
Splenomegaly	40	10(9,5)	30(9,6)	
Yes				0,630
No	53	15(14,3)	38(12,2)	
Dimension	363	91(86,7)	264(84,9)	0,274
1 à 3				
>3	16	4(3,8)	12(3,9)	
	37	9(8,5)	28(9)	

Table 3: Physical signs of G6PD-deficient and non-deficient children with sickle cell disease.

Variables	Whole group n=416	G6PD deficiency n=104(%)	Non G6PD deficient n=312(%)	P
Blood count				
Hb (g%)	7,36±1,55	7,27±1,60	7,39±1,54	0,494
Hct (%)	22,1±4,8	21,78±4,66	22,19±4,81	0,448
VGM (%)	82,5±11,1	82,82±10,23	82,46±11,34	0,770
TCMH (fl)	27,5±3,9	27,63±3,60	27,49±4	0,744
CCMH (%)	34,8±30,4	33,54±2,53	35,17±35,19	0,637
GB (elts/mm ³)	2677050,49±671317,4	12841,52±6195,37	12227,03±5551,66	0,342
GR (elts/10 ⁶)	51,1±26,77	2,68±0,7	2,67±0,65	0,948
Retic (%)	10,4±8,5	10,6±5,2	9,7±6,3	0,346
PLT (elts/10 ³)	356,5±221,9	346,45±151,7	359,8±241,2	0,691
Hemolysis				
LDH	1121,9±895,41	1171,02±1150,43	1104,23±785,52	0,581
BILT	2,31±0,92	2,59±1,46	2,23±0,70	0,219
BILD	0,71±0,35	0,68±0,23	0,72±0,37	0,793

Table 4: Biological data of sickle cell patients according to their G6PD deficiency status or not

Continuous quantitative variables with a normal distribution were presented as means ± standard deviation; those with an anomalous distribution, as median (interquartile range). Categorical variables were described as absolute and relative frequency (%).

The comparison of the means or medians of the two groups was made, as appropriate, using the Student's T test or the Mann Whitney U test; the Pearson Chi-square test, the Fisher's exact test or the trend test were used to compare the proportions. The factors associated with G-6-PD deficiency were sought using the logistic regression test. The odds ratio and the 95% confidence intervals were represented and allowed to measure this association. For all the tests used, the threshold of statistical significance was $p < 0.05$.

Ethical considerations

The protocol of this work was submitted to the Ethics Committee of the School of Public Health and obtained approval under the number ESP/CE/028/2019. This work was conducted in strict compliance with the fundamental principles of ethics. Informed consent was obtained from the parents or guardians of the children by means of a written form after explanation of the purpose and implications of the study, the observations to be made, and the benefits and risks for the child.

Results

Sociodemographic characteristics of the study population Clinical information of the study population Clinical profile of G6PD deficient and non-G6PD deficient children with sickle cell disease biological information Factors associated with G6PD deficiency

Discussion

The association between sickle cell disease and G6PD deficiency is very high in regions of high malaria endemicity, particularly in sub-Saharan Africa. The Democratic Republic of Congo (DRC) is no exception.

Clinically, our study showed that all morbid manifestations (the number of transfusion episode, coca-cola urine emission, infectious episode and vaso-occlusive crises) occurring in sickle cell patients were greater in the group with G6PD deficiency ($p < 0.05$). Previous complications (osteomyelitis, malleolar ulcer, and priapism) evaluated occurring in sickle cell patients were associated with G6PD deficiency ($p < 0.05$), with the exception of stroke. No statistically significant difference had been noted for physical signs between sickle cell deficient and nondeficient groups ($p > 0.05$).

Our results agree with those of Mathula et al, in 2012 in the USA, Benkerou et al, (2013) as well as Bernaudin et al, in France in 2018, Lohit et al, in India in 2019, Mounkaila et al, in 2015 in Niger, and Bouanga et al, in 1998 in Congo, who reported that there were more transfusions in the G6PD-deficient sickle cell group, but found no significant difference in vasoocclusive crises and infectious episodes [2, 8-11, 21].

In contrast, Foluke et al. in 2019 in Nigeria, Diop et al. in 2005 in Senegal, Simpore et al. in Burkina Faso in 2007, Gbadoe et al. in Togo in 2001, and Firempong et al. in 2016 in Ghana found no significant difference in clinical parameters between G6PD-deficient and non-G6PD-deficient sickle cell disease [3-5,7,22].

We can justify these discrepancies by the fact that the sickle cell haplotype found in the DRC, which is the Bantu haplotype, is the most severe form, in contrast to the Senegal, Benin, Cameroon and Arab-Indian haplotypes; and the variant of G6PD deficiency found in Africans associated with sickle cell disease is type A which is a genetic form of less severity contrary to variants B (Mediterranean), Mahidol, Canton, Guadalajara, Beverly Hills, and

Nashville which are more found in America, Europe and Asia and which are more severe forms [23, 24].

Indeed, the disorders related to G6PD deficiency and sickle cell disease are due to the oxidative effect, which is an imbalance between the production of free radicals and the body's ability to detoxify their harmful effect due to the neutralization through antioxidants. Free radicals are usually formed during normal metabolic reactions, but the body manages to detoxify them and decrease their level in the cell through the antioxidant effect. Sickle cell patients produce a fair amount of free radicals responsible for clinical manifestations and complications causing several organ damages including vaso-occlusive disorders [9, 25]. These free radicals also cause damage to membrane proteins and lipids leading to destruction of RBCs resulting in hyperhemolysis attacks and other morbid manifestations in sickle cell children [26].

There is still much controversy to this day about the impact of G6PD deficiency on sickle cell disease. This is the case of Piomelli et al, (1972), who argue that these two abnormalities seem to be mutually attenuating: sickle cell disease making the deficiency enzyme to the extent that the deficient genotype appears to be masked [6].

The discrepancies and similarities found in the literature can also be explained by various phenomena that influence the course of sickle cell disease. We mention the hereditary persistence of fetal hemoglobin, the association with alpha thalassemia and the haplotype membership; all these elements were not sought in our study [27, 28].

Referring to the biological data of the studied children, the blood count as well as the hemolysis markers showed no difference between the two groups taken in steady state ($p > 0.05$).

These observations meet those of Diop et al. in Senegal, Firempong et al. in Ghana in 2016 [3, 7]. However, Mehdi et al, in the USA in 2010, Bernaudin et al, (2018), and Benkerou et al, (2013) in France, as well as Lohit et al, in India in 2019, Foluke et al, in Nigeria in 2019, found that G6PD-deficient sickle cell patients had lower hemoglobin levels and elevated reticulocytes [2,4,10,29].

This is justified by the fact that in our study, as in the other African studies that found similar results to ours, the biological parameters were evaluated in a steady state, our patients had been in a stable state for about three months before our visit.

It is described that in case of hemolysis, there is a decrease in the number of RBCs, which also results in a decrease in the hemoglobin level, leading to marrow activation with an increase in the number of reticulocytes, which are immature RBCs; this would justify the increased episodes of hemolysis and anemia in G6PD- deficient sickle cell patients.

Our results should not obscure the fact that the association of sickle cell disease and G6PD deficiency carries obvious potential risks. Indeed, most of the drugs used by sickle cell patients are oxidizing and therefore likely to cause hemolysis in deficient patients. It is therefore useful to screen sickle cell patients for G6PD deficiency in order to derive preventive and therapeutic measures.

Study limitations and strengths Study limitation

The single measurement of biological parameters may have led to the under or overestimation of the values obtained.

Strength of the study

Beyond its limitations, the present study has, nevertheless, some strengths. It is the very first large study, which evaluates, through 4 health districts of the city and province of Kinshasa, the frequency and the clinico-biological impact of G6PD deficiency in children with sickle cell disease in DRC. This will certainly contribute to raising awareness in the management of these patients.

Conclusion

The present study aimed to determine the impact of G6PD deficiency on sickle cell disease in children in Kinshasa. Thus, the study showed that G6PD deficiency is associated with acute clinical manifestations as well as complications of sickle cell patients, including: the occurrence of vaso-occlusive crises, malleolar ulcer, osteomyelitis, aseptic necrosis of the femoral head, and priapism without influencing the occurrence of stroke. And it has no impact on the hematological parameters of sickle cell children in stationary phase. Hence the need to systematically search for G6PD deficiency in sickle cell patients in order to take adequate preventive measures in relation to the possible use of oxidizing drugs.

Conflict of interest: No conflicts of interest have been declared by the authors.

Authors' contributions: Ariane KETO and René NGIYULU conceived, collected, interpreted, wrote and corrected the manuscript. Gibency Mfulani and Eric Mafuta analyzed the data, read and corrected the article. Joseph BODI, Léon TSHILOLO, Loukia Aketi and Aléine BUDIONGO supervised, interpreted and corrected the article. Balthazar PHOBA and Yves MUZINGA analyzed the samples in the laboratory of the Monkole Hospital Center. All authors read and approved the final version of the article.

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