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Factors Predictive of Glomerular Hyperfiltration in Sickle-Cell Anemia Males

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Abstract

Background: Renal manifestations, including glomerular hyperfiltration during sickle cell disease (SCD), are very frequent and constitute the starting point for renal failure. Few data are available on this subject in Togo. The aim of this study was to describe the predictive factors of glomerular hyperfiltration in SCD in our Togolese context. **Methods:** This was a retrospective descriptive and analytical study carried out at the Centre National de Recherche et de Soins aux Drépanocytaires du Togo located in the commune of Lomé. Hyperfiltration was defined for all major sickle cell patients by a glomerular filtration rate (GFR) > 130 ml/min/1.73m^2 and renal failure by a GFR < 60 ml/min/1.73m^2 calculated according to the Modification of Diet in Renal Disease (MDRD) equation. We investigated factors associated with glomerular hyperfiltration using univariate and multivariate logistic regression. The dependent variable was GFR status > 130 coded 1 and 0 if not. **Results:** 82.0% of major sickle cell patients had glomerular hyperfiltration, and 1.7% were in renal failure. The mean age of our patients was 14.1 years, with a female predominance of 53.2%, giving a sex ratio (M/F) of 0.88. Homozygous sickle cell patients represented 55.3% of the population and heterozygous SC 38.5%. In a comparative analysis, there was a statistically significant difference between the proportion of patients with and without glomerular hyperfiltration according to age ($p < 0.001$), gender ($p < 0.001$), economic activity ($p < 0.001$), marital status ($p < 0.001$), educational level ($p = 0.007$), hemoglobin phenotype ($p < 0.001$), proportion of HbS ($p < 0.001$); to certain circumstances of discovery as painful crises ($p = 0.002$), infection ($p < 0.001$), hand-foot syndrome ($p = 0.015$) and asthenia ($p = 0.032$); of certain complications as occurrence of at least one complication ($p = 0.025$), anemia ($p = 0.003$), priapism ($p = 0.048$), renal fail-

ure (p = 0.001), osteonecrosis (p = 0.041) and retinopathy (p = 0.001). Risk factors for hyperfiltration were male gender (p = 0.016), age under 10 years (p = 0.001), age between 10 and 19 years (p < 0.001), hemoglobin S > 70% (p = 0.009) and low azotemia (p = 0.004). **Conclusion:** Glomerular hyperfiltration is very frequent in sickle cell disease syndromes in Togo, with a non-negligible presence of renal failure. Risk factors are dominated by a young age, as in the literature.

Keywords

Sickle Cell Syndrome Major, Glomerular Hyperfiltration, Renal Failure, Risk Factors, Togo

1. Introduction

Sickle cell disease is an autosomal recessive genetic disorder of hemoglobin, causing the synthesis of abnormal hemoglobin, hemoglobin S (HbS), whose major sickle cell syndromes (MSCS) include homozygous SS sickle cell disease and composite heterozygosities associating hemoglobin S with another abnormal hemoglobin (C, D, O-Arab) or with β-thalassemia [1]. The prevalence of the sickle cell gene in Africa varies from 10% to 40%. It is 5% to 20% in West Africa and 9% to 10% in Madagascar [2]. In Togo, the prevalence of the HbS gene is estimated at 16.1%. Major forms of sickle cell disease, essentially SS, S-thalassemia and SC, are estimated to affect 3% to 5% of the population, *i.e.*, over 170,000 people [3] [4].

Sickle cell disease is a systemic disease that affects every system in the body. Recurrent episodes of vaso-occlusion and inflammation result in progressive damage to most organs, including the brain, lungs, bones, cardiovascular system and kidneys that manifest with age [2]. The kidneys are particularly sensitive to the disease. Sickle cell disease alters kidney structure and function, and is the cause of several kidney diseases and syndromes [5]. We now know that sickle cell disease is a growing cause of chronic kidney disease. The spectrum of renal impairment associated with sickle cell disease includes a variety of renal manifestations [6]. Renal, tubular and glomerular abnormalities are frequently encountered in MSCS. Glomerular damage is observed in 40% of young adults, with rapid progression to end-stage renal failure in half of cases, a major risk factor for mortality [7]. Glomerular damage manifests itself early in childhood with glomerular hyperfiltration, followed by microalbuminuria. Glomerular hyperfiltration, corresponding to an above-normal filtration rate, is in fact the earliest glomerular abnormality in MSCS preceding proteinuria or even renal failure [8].

In Togo, there are several studies on major sickle cell syndromes in general [3] [4] [9]-[11], but there is little data on renal impairment associated with MSCS [12] [13]. Moreover, in view of the concern that hyperfiltration may progress to renal failure, we felt it appropriate to carry out this study with the aim of describing the factors predictive of glomerular hyperfiltration in carriers of major sickle cell syndromes.

2. Framework and Method

Setting, method and study period: This was a descriptive and analytical cross-sectional study based on the records of major sickle cell patients followed up in the period from January 1, 2018 to December 31, 2020 at the Centre National de Recherche et de Soins aux Drépanocytaires (CNRSD).

Inclusion and non-inclusion criteria: Records of patients followed up at the CNRSD, diagnosed with major sickle cell syndrome, with a minimum creatinemia workup, and at least 1 year of age were included. Data were collected using a pre-established survey form. The parameters studied were sociodemographic, anamnestic, clinical and paraclinical data.

The following operational definitions have been adopted:

- Glomerular filtration rate (GFR) was calculated using the simplified MDRD formula with their first creatinine achieved. Increased GFR above 130 ml/min/1.73m^2 corresponds to hyperfiltration (HF) [5] [14].
- Baseline hemoglobin < 7 g/dl defined severe anemia, 7 - 10 g/dl moderate anemia and >10 g/dl mild anemia.
- The informal sector encompasses all economic activities carried out on the bangs of criminal, social and fiscal legislation, or outside the scope of national accounting.
- A civil servant is an agent in public administration, *i.e.*, a person who is employed on a permanent basis by the state to carry out a mission, a job, and is remunerated for this work.

Data collection and Statistical analysis: Data were entered and analyzed using Epi Info 7 software. Qualitative variables were presented according to their respective numbers and percentages, and quantitative variables according to their mean and/or extremes. A comparative analysis was performed to look for a difference between variables collected at inclusion according to GFR groups of less than or equal to 130 ml/min/1.73m^2 (hyperfiltration) and greater than 130 ml/min/1.73m^2 (non-hyperfiltration). Chi2 and Fisher tests were used to compare proportions, depending on the situation. For quantitative variables, after checking the normality of the distribution using the graphical method and the Shapiro-Wilk test, non-parametric tests (Kruskall-Wallis, Wilcoxon) were used. The significance threshold was $p < 0.05$.

Univariate and multivariate logistic regression was performed to investigate factors associated with hyperfiltration. The dependent variable was GFR status > 130 coded 1 and 0 if not. The independent variables were selected as sociodemographic, clinical, and paraclinical variables. After univariate analysis, variables that were sufficiently associated ($p < 0.2$) and/or of significant clinical interest were introduced into the initial model. A top-down step-by-step procedure was used to select the final model. This involved including all selected variables in the initial model and then progressively removing the least significant variables. At each step, we checked that there was no major confounding between the removed variable and those remaining in the model, based on changes in their Odds Ratio

(OR) (tolerated variation: 20%) or even radical changes in their degrees of significance. Multivariate analysis was used to estimate the adjusted Odds ratio (ORa) and its 95% confidence interval for each retained variable. Once the final model had been obtained, we looked for interactions between the different variables in the final model by including interaction terms (product of the 2 variables concerned) in the model and checking their non-significance. The adequacy of the model was verified on the basis of the R^2 value. In the context of our study, we have kept the patients' anonymity on the data sheets in order to respect medical confidentiality. We did, however, obtain authorization from the management of the said center before processing the files.

3. Results

3.1. Overall Results

In the course of this study, we identified 782 major sickle cell patients followed at the CNRSD, 723 of whom we included on the basis of a minimum creatinine level. We excluded 22 patients aged < 1 year. Five hundred and seventy-five (575) patients, with a frequency of 82.1%, had glomerular hyperfiltration (GFR > 130 ml/min/1.73m^2). The study sample comprised 373 women (53.2%) and 328 men (46.8%), giving a sex ratio (M/F) of 0.88. According to GFR, there were 12 patients (1.7%) with GFR < 60 ml/min; 23 patients (3.3%) with GFR between [60 - 90 ml/min] and 91 patients (12.9%) with GFR between [90 - 130 ml/min]. The mean hemoglobin level was 9.13 g/dl in the study sample and 8.89 g/dl in the hyperfiltrated population. HIV serology was performed in 4% of the study population, and 0.3% was positive. Hepatitis B virus (HBV) serology was performed in 7.1% of cases, and 0.4% of major sickle cell patients were HBV positive.

3.2. Comparative Analysis

The 1 - 10 age group was the most hyperfiltrated. In the hyperfiltration patient population, there were 283 women (40.4%) and 292 men (41.7%), compared with 90 women (12.8%) and 36 men (5.1%) in the non-hyperfiltration patient population.

There was a statistically significant difference between the proportion of patients with and without glomerular hyperfiltration according to age ($p < 0.001$), gender ($p < 0.001$), economic activity ($p < 0.001$), marital status ($p < 0.001$) and educational level ($p = 0.007$), hemoglobin phenotype ($p < 0.001$) and proportion of HbS ($p < 0.001$) as shown in Table 1.

Table 2 shows the results of the comparative analysis of clinical variables according to the presence or absence of hyperfiltration. The mean age of onset of MSCS in the study sample was 6 years and 5 months, and in the glomerular hyperfiltration group was 4 years and 11 months. 576 (82.2%) major sickle cell patients had fewer than 3 attacks per year, 471 of whom were in the hyperfiltration group. In the study population, 54.01% of major sickle cell patients had presented at least one documented complication. 51.5% of the hyperfiltration population had presented at least one complication. There was a statistically significant asso-

ciation between the proportion of patients with glomerular hyperfiltration and that of patients without hyperfiltration according to certain circumstances of discovery: painful crises (p = 0.002), anemia (0.048), infection (p < 0.001), hand-foot syndrome (p = 0.015), asthenia (p = 0.032), stroke (p = 0.048) and renal failure (p = 0.017); of certain complications: occurrence of at least one complication (p = 0.025), anemia (p = 0.003), priapism (p = 0.048), renal failure (p = 0.001), osteonecrosis (p = 0.041), retinopathy (p = 0.001) and hepatic steatosis (p = 0.032).

Table 3 shows the results of a comparative analysis of paraclinical variables according to the presence or absence of hyperfiltration. Simple urine dipstick proteinuria was positive in 2.6% of cases and negative in 58.2%. Simple proteinuria was not performed in 275 cases (39.2%). There was an association between glomerular hyperfiltration and simple proteinuria (p = 0.046), and several biological parameters including hemoglobin level (p < 0.001), aremia (p < 0.001), Aspartate aminotransferase (p < 0.001), alanine aminotransferase (p = 0.042), Gamma glutamyl transpeptidase (p < 0.001) and total bilirubin (p = 0.040).

3.3. Univariate Analysis

The results of the univariate analysis are summarized in Table 4 and Table 5.

In terms of socio-demographics, male gender (p < 0.001), age under 10 years (p = 0.001), age group 10-19 years (p < 0.001), pre-school (p = 0.005), primary school (p < 0.001) respectively increased the risk of developing hyperfiltration in sickle cell patients by 2.59-fold, 25.51-fold, 2.50-fold, 4.62-fold and 8.01-fold. The same was true for the SS phenotype (OR = 4.17; CI95% [2.73 - 6.37] p < 0.001) and an HbS proportion greater than 70% (OR = 3.59; CI95% [2.23 - 5.78] p < 0.001), which were risk factors for hyperfiltration. In contrast, secondary (OR = 0.51; CI95% [0.30 - 0.88] p = 0.013) and higher levels of education (OR = 0.06; CI95% [0.03 - 0.12] p < 0.001) were protective factors for glomerular hyperfiltration (Table 4).

Clinically, the circumstances of discovery as: anemia (OR = 2.14; CI95% [1.08 - 4.24] p = 0.02), infection (OR = 5.31; CI95% [2.12 - 13.31] p < 0.001), hand-foot syndrome (OR = 3.17; CI95% [1.25 - 8.04] p = 0.010) were risk factors associated with hyperfiltration, whereas discovery of sickle cell disease through vaso-occlusive crises (OR = 0.49; CI95% [0.32 - 0.73] p < 0.001) was a protective factor for glomerular hyperfiltration (Table 5). Anemia (p = 0.013) or having had at least one complication (p = 0.003) increased the risk of developing hyperfiltration by a factor of 2.46 and 1.83 respectively. The same was true for a hemoglobin level of less than 7 g/dl (OR = 2.23; CI95% [1.12 - 4.41] p = 0.0019), between 7 and 10 g/dl (OR = 2.84; CI95% [1.86 - 4.33] p < 0.001), low azotemia (OR = 3.08; CI95% [1.98 - 4.76] p < 0.001), high AST (OR = 2.78; CI95% [1.78 - 4.33] p < 0.001) which were risk factors for hyperfiltration. Protective factors for hyperfiltration were: the existence of complications such as: renal failure (OR = 0.07; CI95% [0.00 - 0.69] p = 0.003), vesicular lithiasis (OR = 0.34; CI95% [0.16 - 0.72] p = 0.003) and retinopathy (OR = 0.15; CI95% [0.07 - 0.31] p < 0.001); elevated uremia (OR = 0.13; CI95% [0.04 - 0.40] p < 0.001) and elevated gamma glutamyl transpeptidase (OR = 0.59; CI95% [0.36 - 0.94] p = 0.028) as shown in Table 6.

Table 1. Comparative analysis of socio-demographic factors and electrophoretic profile.

	Total (N = 701)	Hyperfiltration (GFR > 130 ml/min)		p-value
		NO (n = 126)	YES (n = 575)	
Sociodemographic				
Age (years)	701			<0.001
[1 - 10[	327 (46.7%)	6 (4.8%)	321 (55.8%)	
[10 - 20[	210 (30.0%)	23 (18.2%)	187 (32.5%)	
≥20	164 (23.3%)	97 (77.0%)	67 (11.7%)	
Business activity	485			<0.001
Informal sector	68 (9.7%)	39 (31.0%)	29 (5.0%)	
student	367 (52.6%)	43 (34.1%)	324 (56.3%)	
official	50 (7.3%)	25 (19.8%)	25 (4.3%)	
Marital Status	521			<0.001
Single	46 (6.6%)	16 (12.7%)	30 (5.2%)	
Marie/couple	20 (2.9%)	14 (11.1%)	6 (0.1%)	
Child	454 (64.8%)	19 (15.1%)	435 (75.7%)	
Widowed	2 (0.3%)	1 (0.8%)	1 (0.1%)	
Education level	549			0.007
Out of school	54 (7.7%)	0 (0%)	54 (9.39%)	
preschool	91 (13.0%)	3 (2.4%)	88 (15.3%)	
primary	200 (28.5%)	5 (4.0%)	195 (33.9%)	
secondary	143 (20.4%)	25 (19.8%)	118 (20.5%)	
superior	61 (8.7%)	32 (25.4%)	29 (5.0%)	
Electrophoretic profile				
Phenotype Hb	700			<0.001
S beta thalassemia	42 (6.0%)	8 (6.3%)	34 (5.9%)	
SC	270 (38.5%)	83 (65.9%)	187 (32.5%)	
SS	288 (55.3%)	35 (27.8%)	353 (61.4%)	
Hb S	582			<0.001
<70%	283 (40.4%)	74 (58.7%)	209 (36.3%)	
≥70%	299 (42.6%)	27 (21.4%)	272 (47.3%)	
Hb F	276			0.075
<20%	207 (29.5%)	23 (18.3%)	184 (32.0%)	
≥20%	69 (9.8%)	10 (7.9%)	59 (10.3%)	

Table 2. Comparative analysis of clinical factors.

	Total (N = 701)	Hyperfiltration (GFR > 130 ml/min)		p-value
		NO (n = 126)	YES (n = 575)	
Clinical aspects				
Circumstances of discovery				
Vaso-occlusive seizures	361 (51.5%)	83 (65.9%)	278 (48.3%)	0.002
Anemia	99 (14.1%)	10 (7.9%)	89 (15.5%)	
Infection	109 (15.5%)	5 (4.0%)	104 (18.1%)	
Health check	101 (14.4%)	15 (11.9%)	86 (15.0%)	
Hand-foot syndrome	71 (10.1%)	5 (4.0%)	66 (11.5%)	0.015
Ictere	4 (0.6%)	0 (0%)	4 (0.7%)	>0.9
Asthenia	2 (0.3%)	2 (1.6%)	0 (0%)	0.032
AVC	4 (0.6%)	2 (1.6%)	2 (0.3%)	0.048
Renal failure	1 (0.1%)	1 (0.8%)	0 (0%)	0.017
Osteonecrosis	2 (0.3%)	1 (0.8%)	1 (0.1%)	0.3
Incessant crying	5 (0.7%)	0 (0%)	5 (0.9%)	>0.9
Priapism	2 (0.3%)	1 (0.8%)	1 (0.1%)	0.3
Growth retardation	1 (0.1%)	0 (0%)	1 (0.1%)	>0.9
Splenomegaly	2 (0.3%)	0 (0%)	2 (0.3%)	>0.9
Complications				
Anemia	111 (15.8%)	10 (7.9%)	101 (17.6%)	0.003
Priaprism	3 (0.4%)	1 (0.8%)	2 (0.3%)	0.048
Hematuria	1 (0.1%)	0 (0%)	1 (0.1%)	>0.9
Stroke	5 (0.7%)	0 (0%)	5 (0.9%)	>0.9
Thoracic syndrome	57 (8.1%)	9 (7.1%)	48 (7.8%)	0.2
Painful crisis	140 (20.0%)	23 (18.3%)	117 (20.3%)	0.6
Renal failure	4 (0.6%)	3 (2.4%)	1 (0.1%)	<0.001
Splenectomy	10 (1.4%)	1 (0.8%)	9 (1.6%)	>0.9
Osteonecrosis	49 (6.7%)	13 (10.3%)	36 (6.3%)	0.041
Vesicular lithiasis	32 (4.6%)	12 (9.5%)	20 (3.5%)	0.008
Leg ulcer	3 (0.4%)	0 (0%)	3 (0.5%)	>0.9
Epistaxis	2 (0.3%)	0 (0%)	2 (0.3%)	>0.9
Cardiomegaly	42 (6.0%)	12 (9.5%)	30 (5.2%)	0.2
Infections	81 (11.6%)	8 (6.3%)	73 (12.7%)	0.11
Retinopathy	32 (4.6%)	18 (14.3%)	14 (2.4%)	<0.001
Hepatic steatosis	2 (0.3%)	2 (1.6%)	0 (0%)	0.032

Table 3. Comparative analysis of paraclinical factors.

	Total (N = 701)	Hyperfiltration (GFR > 130 ml/min)		p-value
		NO (n = 126)	YES (n = 575)	
Paraclinical aspects				
Hemoglobin level (g/dl)	696			<0.001
<7	103 (14.7%)	10 (4.4%)	93 (16.2%)	
[7 - 10[	343 (49.0%)	36 (23.1%)	307 (53.4%)	
≥10	250 (35.7%)	78 (71.4%)	172 (30.0%)	
Uremia	646			<0.001
Low	325 (46.4%)	33 (29.7%)	292 (50.8%)	
Normal	310 (44.2%)	75 (59.3%)	235 (40.9%)	
High	11 (1.6%)	8 (2.2%)	3 (0.5%)	
Aspartate aminotransferase	690			<0.001
Normal	409 (28.3%)	96 (82.4%)	313 (54.4%)	
High	281 (40.1%)	26 (15.4%)	255 (44.3%)	
Alanine aminotransferase	688			0.042
Normal	557 (79.5%)	101 (85.7%)	456 (79.3%)	
High	131 (18.7%)	20 (10.2%)	111 (19.3%)	
Gamma glutamyl transpeptidase	662			<0.001
Normal	548 (78.2%)	86 (75.8%)	462 (82.9%)	
High	114 (16.3%)	29 (16.5%)	85 (14.8%)	
Alkaline phosphatase	120			0.5
High	20 (2.9%)	2 (1.1%)	18 (3.1%)	
Normal	100 (14.3%)	22 (14.3%)	78 (13.6%)	
Bilirubin Total	621			0.04
Low	184 (26.2%)	41 (35.2%)	143 (24.9%)	
High	437 (62.3%)	62 (47.3%)	375 (65.2%)	
Direct bilirubin	561			>0.9
Normal	146 (20.8%)	24 (20.9%)	122 (21.2%)	
High	415 (59.2%)	68 (52.7%)	347 (60.3%)	

Table 4. Univariate analysis of socio-demographic parameters and electrophoretic profile.

	N	OR	IC	p-value
Sociodemographic				
Gender	575			
Male		2.59	[1.70 - 3.94]	<0.001
Female				
Age (years)	575			
[1 - 10[		25.51	[11.05 - 58.87]	0.001
[10 - 20[		2.5	[1.47 - 4.25]	<0.001
≥20				
Education level	484			
Preschool		4.62	[1.42 - 15.06]	0.005
Primary		8.01	[3.16 - 23.31]	<0.001
Secondary		0.51	[0.3 - 0.88]	0.013
Superior		0.06	[0.03 - 0.12]	<0.001
Electrophoretic profile				
Hb phenotype	574			
S beta thalassemia				
SC		0.25	[0.17 - 0.37]	<0.001
SS		4.17	[2.73 - 6.37]	<0.001
Hb S	481			
<70%				
≥70%		3.59	[2.23 - 5.78]	<0.001
Hb F	243			
<20%		1.36	[0.61 - 3.02]	0.285
≥20%				
Number of crises per year	525			
<3				
≥3		0.83	[0.55 - 1.24]	0.362

Table 5. Univariate analysis of clinical and paraclinical parameters.

	N	OR	IC	p-value
Clinics				
Circumstances of discovery				
Vaso-occlusive seizures	278	0.49	[0.32 - 0.73]	<0.001
Anemia	89	2.14	[1.08 - 4.24]	0.026
Infection	104	5.31	[2.12 - 13.31]	<0.001
Health check	86	1.29	[0.72 - 2.32]	0.388
Hand-foot syndrome	66	3.17	[1.25 - 8.04]	0.01
Ictere	4	-	-	0.454
Stroke	2	0.21	[0.03 - 1.54]	0.09
Osteonecrosis	1	0.22	[0.01 - 3.49]	0.326
Incessant crying	5	-	-	0.372
Priaprism	1	0.22	[0.01 - 3.49]	0.326
Growth retardation	1	-	-	0.821
Splenomegaly	2	-	-	0.674
Complications				
At least “one”	296	1.83	[1.22 - 2.73]	0.003
Anemia	101	2.46	[1.24 - 4.86]	0.013
Priaprism	2	0.21	[0.03 - 1.54]	0.149
Hematuria	1	-	-	0.821
Stroke	5	-	-	0.372
Thoracic syndrome	48	1.2	[0.57 - 2.52]	0.622
Painful crisis	117	1.14	[0.69 - 1.86]	0.612
Renal failure	1	0.07	[0.00 - 0.69]	0.003
Splenectomy	9	1.98	[0.24 - 15.75]	0.441
Osteonecrosis	36	0.58	[0.30 - 1.12]	0.1.02
Vesicular lithiasis	20	0.34	[0.16 - 0.72]	0.003
Leg ulcer	3	-	-	0.553

Continued

Epistaxis	2	-	-	0.674
Cadiomegalia	30	0.52	[0.26 - 1.05]	0.603
Infections	73	2.13	[1.00 - 4.54]	0.045
Retinopathy	14	0.15	[0.07 - 0.31]	<0.001
Paraclinical aspects				
Hemoglobin level (g/dl)	572			
<7		-	-	
[7 - 10[		2.84	[1.86 - 4.33]	<0.001
≥10		2.23	[1.12 - 4.41]	0.019
Uremia	530			
Normal		-	-	
Low		3.08	[1.98 - 4.76]	<0.001
High		0.13	[0.04 - 0.40]	<0.001
Aspartate aminotransferase	568			
Normale		-	-	
High		2.78	[1.78 - 4.33]	<0.001
Alanin aminotransferase	567			
Normal		-	-	
High		1.26	[0.75 - 2.10]	0.381
Gamma glutamyl transpeptidase	547			
Normal		-	-	
High		0.59	[0.36 - 0.94]	0.028
Bilirubin Total	518			
Low		-	-	
High		1.55	[0.98 - 2.45]	0.059
Direct bilirubin	469			
Normal		-	-	
High		1.1	[0.59 - 2.06]	0.765

Table 6. Multivariate analysis.

	Initial model			Final model		
	OR	IC 95%	p	ORa	ICa 95%	p
Gender						
Male	2.59	[1.70 - 3.94]	<0.001	2.5	[1.19 - 5.26]	0.016
Age (years)						
[1 - 10[	25.51	[11.05 - 58.87]	0.001	16.21	[3.05 - 86.06]	0.001
[10 - 20[	2.5	[1.47 - 4.25]	<0.001	5.72	[2.52 - 12.99]	<0.001
≥20						
Education level	-	-		-	-	
Preschool	4.62	[1.42 - 15.06]	0.005	0.77	[0.29 - 2.07]	0.607
Primary	8.01	[3.6 - 23.31]	<0.001	1.63	[0.16 - 16.75]	0.682
Secondary	0.51	[0.30 - 0.88]	0.013	7.22	[1.16 - 44.99]	0.345
Superior	0.06	[0.03 - 0.12]	<0.001	2.28	[0.80 - 6.49]	0.122
HbS						
<70%	-	-		-	-	
≥70%	3.59	[2.23 - 5.78]	<0.001	2.53	[1.26 - 5.07]	0.009
Uremia	-	-		-	-	
Low	3.08	[1.98 - 4.76]	<0.001	10.74	[1.15 - 99.98]	0.037
Normal	-	-		-	-	
High	0.13	[0.04 - 0.40]	<0.001	0.09	[0.01 - 0.86]	0.004

3.4. Multivariate Analysis

After adjustment for other factors in the original model, being male, less than 10 years old or between 10 and 19 years old, having a hemoglobin S proportion of over 70% and having low azotemia were associated with hyperfiltration with adjusted odds ratios of 2.5-fold, 16.21-fold, 5.72-fold, 2.53-fold and 10.74-fold.

4. Discussion

In the literature, authors agree on the preponderance of renal impairment, notably glomerular hyperfiltration and microalbuminuria, in major sickle cell syndromes, and on the natural evolution of these different impairments towards renal failure in major sickle cell disease [6]. It is therefore important to be able to control the risk factors associated with hyperfiltration in particular, and prevent progression to renal failure. The pathophysiology of hyperfiltration has not yet been fully elucidated, but is thought to be linked to increased renal blood flow [6] [15]. Several

mechanisms could be at the origin of this increase in renal flow, notably increased cardiac output in relation to chronic anemia, the release of vasodilatory substances in relation to chronic hemolysis, medullary vaso-occlusion and alteration of the endothelium. In our series, risk factors included age under 10 years, with a 16.21-fold risk; age between 10 and 19 years, with a 5.72-fold risk, compared with age over 19 years; male sex, with a 2.5-fold risk compared with female sex; a hemoglobin S content of over 70%, with a 2.50-fold increased risk of glomerular hyperfiltration; and low azotemia, with a 10.74-fold increased risk of hyperfiltration.

Hyperfiltration usually begins as early as 9 to 19 months of age, with a progressive increase until the second decade of life [6] [16], then decreases towards normal [8] [17] [18]. In several studies, young age has been associated with glomerular hyperfiltration in major sickle cell disease. Indeed, Ackoundou-N'guessan *et al.* (Cote d'Ivoire) using logistic regression analysis found that an age of less than 30 years was a risk factor for glomerular hyperfiltration [15]. Aloni *et al.* in the Democratic Republic of Congo in 2017 [16] and Haymann *et al.* in 2010 in France [19] found young age to be a factor associated with hyperfiltration, using multivariate analysis. Thus, as our results and the literature show, young age (less than 20 years, particularly less than 10 years in our series) is an important risk factor for glomerular hyperfiltration. The link between age and hyperfiltration is not fully understood. According to Wang *et al.*, the onset of hyperfiltration occurs around 13 months of age, just a few months after the onset of sickle cell disease symptoms, usually chronic hemolysis and vaso-occlusive phenomena. Hemolysis leads to increased blood flow to the glomerulus. This leads to glomerular hyperfiltration, with glomerular hypertrophy and progressive alteration of the filtration membrane. This alteration of the filtration membrane is thought to be responsible for the decline in filtration rate towards normal with age, and even to a fall below normal value. In our study, males were 2.5 times more likely to have glomerular hyperfiltration. Indeed, men would be more affected by chronic hemolysis during sickle cell disease major and therefore more affected by hyperfiltration. According to a study by Raslan *et al.* in 2018 on the comparison of hemolysis in male and female sickle cell patients, testosterone would have a potentiating effect on hemolysis [20]. In addition, there is a hypothesis that there is a loci on the X chromosome responsible for regulating the quantity of hemoglobin F. Women would therefore have a higher quantitative production of hemoglobin F than men. Women would therefore have a higher quantitative production of hemoglobin F and would be less exposed to hemolysis and glomerular hyperfiltration [20]-[22]. And it should be added that G6PD deficiency, which is total in men, is an additional source of hemolysis in the few men who have it, and therefore implicated in glomerular hyperfiltration. However, Ackoundou-N'guessan *et al.* found female gender to be a risk factor [15]. We have found no explanation for this difference.

We found a high proportion of hemoglobin S to be a risk factor for hyperfiltration. Indeed, a higher proportion of hemoglobin S implies greater chronic hemol-

ysis and vaso-occlusion phenomena in the medulla, as well as increased release of vasodilatory substances.

In our study, azotemia was associated with hyperfiltration. Silva Junior *et al.* also found a link between urea and hyperfiltration [23]. Azotemia levels could be affected by hyper- or hypoprotein diet, certain drugs, intestinal bacteria or variations in glomerular filtration rate [24]. The low azotemia associated with glomerular hyperfiltration would be a consequence of increased glomerular filtration. Similarly, a high level of azotemia as a protective factor would be due to a decrease in filtration rate.

5. Conclusions

We conducted a descriptive and analytical cross-sectional study of major sickle cell patients at the Centre National de Recherche et de Soins aux Drépanocytaires (CNRSD) in Lomé, the general aim of which was to describe factors predictive of glomerular hyperfiltration.

In our study, we found that glomerular hyperfiltration is very common in our setting, affecting 82.1% of major sickle cell patients. The risk factors for hyperfiltration were age less than 20 years, male sex, a hemoglobin S proportion of over 70% and low azotemia. Unfortunately, these factors cannot be modified. Hyperfiltration is one of the earliest manifestations of kidney damage, the natural progression of which is towards CKD, a growing source of mortality in MSCS. For this reason, renal function must be carefully monitored so that appropriate therapeutic measures can be taken at an early stage.

Ethics

As the study concerned patient files and not the patients themselves, there was no need to obtain the agreement of the ethics committee; however, we did obtain the agreement of the hospital management and respected patient anonymity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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