Research Article

Journal of Pediatrics & Neonatology

Prevalence and Factors Associated with Pulmonary Arterial Hypertension (PAH) in Sickle Cell Children Residing in Yaoundé, Cameroon

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Received: 02 June 2019; **Accepted:** 30 June 2019

Citation: Chelo David, Fokeng Kessel, Ba Hamadou, et al. Prevalence and Factors Associated with Pulmonary Arterial Hypertension (PAH) in Sickle Cell Children Residing in Yaoundé, Cameroon. J Pediatr Neonatal. 2019; 1(1): 1-7.

ABSTRACT

Introduction: *Sickle cell disease is the most widespread single gene disease in the world. Pulmonary arterial hypertension (PAH), a late complication, is one of its most serious causes of morbidity and mortality. In the absence of data on PAH in paediatric settings in Cameroon, we proposed to conduct a prevalence study and research on its determinants in a group of sickle cell patients.*

General Objective: *Identify the determinants of pulmonary arterial hypertension in a group of children with major sickle cell disease.*

Methods: *We conducted a cross-sectional and analytical study from November 1, 2017 to May 31, 2018 in a group of sickle cell children regularly monitored at the Mother and Child Centre of the Chantal Biya Foundation. For each patient recruited, we collected socio-demographic data, medical history, clinical, biological and echocardiographic data. PAH was defined as mean pulmonary arterial pressure (mPAP)>25mmHg, obtained by measuring the pressure gradient between the pulmonary artery and the right ventricle (Bernoulli equation), to which we added the pressure of the right atrium. The data were analyzed with IBM SPSS 21.0. The association between variables was assessed by the Chi-square or Fisher test for qualitative variables and the Student t-test or Pearson Rho correlation test for quantitative variables.*

Results: *Overall, we enrolled 129 patients, 79 (61.2%) were female. That is to say a sex ratio Male/Female of 0.63. The average age was 11.6 ± 3.2 years. We found PAH (mPAP>25mmHg) in 27 (20.9%) patients. In univariate analysis, the determinants found were high age (p=0.001), presence of dyspnea (p<0.001), high number of blood transfusions (p=0.043), history of pneumonia (p=0.01) dilated LV (DLV) (p=0.031) and dilated aorta (DA) (p=0.05). In multivariate analysis, the independent determinants we found were: age (p=0.041); high number of blood transfusions (p=0.005); history of pneumonia (p<0.001) and dyspnea (p=0.001).*

Conclusion: *PAH is a common complication of sickle cell disease in children and its independent determinants are: age, number of blood transfusions, history of pneumonia, and dyspnea.*

Keyword

Pulmonary arterial hypertension, Major sickle cell syndrome, Determinants, Echocardiography, Child.

Introduction

Sickle cell disease is a genetic disease of hemoglobin that is transmitted in an autosomal recessive mode. It is the most common

single gene disease in the world. Every year, nearly 300,000 children are affected [1]. The disease results from a point mutation of the sixth codon of the synthetic gene of β globin leading to the formation of an abnormal hemoglobin, the S hemoglobin. The polymerization of HbS in the deoxygenated state causes the loss of deformability of the red blood cell, responsible for vaso-occlusive phenomena and chronic hemolytic anemia. Sickle cell disease was recognized as a public health priority by UNESCO and the African Union in 2005, WHO in 2006, and the United Nations in 2008 [2,3]. According to the WHO, more than 120 million people are infected with sickle cell trait on all continents of the world and about 500,000 homozygous SS children are born each year. In Africa, the prevalence of sickle cell trait varies between 1 and 45% depending on the country. In Cameroon, the prevalence of sickle cell trait is 22.3% [4].

The prevalence of SS homozygosity varies from 1.7% to 9% depending on the region. A study conducted at the Essos Hospital in Yaoundé on 5856 newborns detected at birth revealed a prevalence of the heterogeneous form at 13.2% and that of the homozygous SS form at 0.1% [4]. The acute complications of this disease are mainly vaso-occlusive, anemic and infectious. The chronically ill patient is subject to hyperhemolysis-related complications such as leg ulcers, priapism and pulmonary arterial hypertension [5].

Pulmonary arterial hypertension (PAH) has been reported by authors as a frequent complication of sickle cell disease [6-9]. It is a severe and rare disease resulting from the proliferation of medial smooth muscle cells and endothelial cells in small pulmonary arteries. This proliferation is the result of a decrease in the production of vasodilating and antiproliferative substances (nitric oxide or prostacyclin), and an increase in the production of vasoconstrictive and proliferative substances (endothelin). Such biochemical imbalance is observed during sickle cell disease.

Pulmonary arterial hypertension is an increase in mean pulmonary arterial pressure (mPAP) greater than or equal to 25mmHg at rest. In the updated classification of pulmonary arterial hypertension, sickle cell disease appears as a distinct entity in the subgroup of cases of pulmonary arterial hypertension associated with identified diseases [10]. Studies on sickle cell patients have found a prevalence of pulmonary arterial hypertension diagnosed by echocardiography ranging from 6% to 30% [11,12].

Cardiac catheterization is currently the only test to confirm the diagnosis of PAH. It also makes it possible to specify the pre or post capillary mechanism. However, it is an invasive examination that is performed in specialized centers. For this reason, trans-thoracic echocardiography, a less invasive examination, is more commonly used in diagnosis; it allows a good estimation of the level of pulmonary arterial pressures for all etiologies combined [13].

To date, prevalence studies have been conducted in Africa on PAH in adult sickle cell patients. Most of these studies concluded that the prevalence of PAH was significantly high, and recommended systematic and early screening in patients followed for sickle cell disease [14,15]. In addition, the CADRE study (Cœur Artère DREpanocytose) conducted in Cameroon and four other African countries on PAH in adult sickle cell disease found a correlation between vascular complications and hyperhemolysis [5]. On the other hand, epidemiological data on PAH in African sickle cell children are sparse or non-existent, especially with regard to the factors that influence its occurrence. It is with this in mind that we have proposed to conduct this study to determine the prevalence of PAH and to investigate the factors associated with its occurrence in a paediatric population residing in the city of Yaoundé, Cameroon.

Methods

Study type and site

We carried out a cross-sectional and analytic study from the 1st of November, 2017 to the 31st May, 2018 at the Mother –Child center of the Chantal Biya Foundation, situated in Yaoundé the administrative capital of Cameroon. This center is a reference paediatric center for the country and the central African sub region with about 30,000 annual paediatric consultations and also 700 sickle-cell children and adolescents being followed up regularly here.

Participants

We included patients aged between 6 to 18 years, suffering from major sickle-cell syndrome and followed up at the Mother – Child center of the Chantal Biya Foundation. Patients who had been transfused upon or had experienced a vaso-occlusive crisis within the two previous weeks, those who had presented with a febrile episode in the last eight days or with any other PAH-causing pathology (patent ductus arteriosus, pulmonary stenosis, acquired mitral valvulopathies) were not included in our study. We then obtained participants by consecutive and exhaustive sampling throughout our study period.

Data collection procedure

We identified patients from the follow-up records of the sickle cell service of the Mother and Child Centre of the Chantal Biya Foundation. These follow-up registers contain patients' personal information, including telephone contacts. From these telephone numbers, we contacted each parent or patient guardian, whom we invited to participate in our study in strict compliance with the fundamental principles of medical research.

The data were collected using a structured, standardized and pre-tested questionnaire. It was divided into six sections and collected information on the patient's identity (gender and age), medical history related to sickle cell disease, symptoms present at the time of the study. The questionnaire was completed by the investigator during an interview; then a complete physical examination was done. In addition, hemoglobin electrophoresis, blood count (CBC) with reticulocyte levels and serum Lactate dehydrogenase (LDH) levels were performed. In addition, an appointment was made within 48 hours depending on the patient's availability to perform the transthoracic ultrasound.

Performing transthoracic ultrasound

This screening was performed by a Pediatric Cardiologist to any person included in the study to determine the presence of PAH or not, based on a mPAP>25mmHg. This ultrasound was performed using a Vivid 7 pro ultrasound scanner using a 3S cardiac probe. A pulmonary regurgitation signal was obtained in a small axis para sternal section using color Doppler. We measured the maximum rate of pulmonary regurgitation. The maximum pressure difference (calculated by the Bernoulli equation) was then added to the pressure in the right atrium. We assumed a pressure in the right atrium at 10mmHg.

Statistical Analyses

The software IBM-Statistical Package for Social Sciences (IBM-SPSS) 21.0 was used for data analysis. The Kolmogorov-Smirnov normality test was used to verify normally distributed quantitative variables. The chi square and Fischer's exact tests were used to ascertain associations between qualitative variables. For quantitative variables, comparisons between groups were made using the Student's t-test for independent variables or the Mann-Whitney test with respect to normality of distributions. Correlations between variables were evaluated using the Spearman's r correlation.

We used logistic univariate and multivariate analysis to obtain factors associated to occurrence of PAH, with the help of the odds ratio and at a 95% confidence interval (CI). We included in our multivariate analysis other known associated factors of PAH and variables with p values <0.25. We considered p values <0.05 to be statistically significant.

Ethical considerations

Before initiating this study, we obtained an ethical clearance delivered by the Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I. In addition, we have obtained authorization from the Study Site Directorate. The procedures applied were in line with the revised Helsinki Declaration. The parents or guardians/accompanists of the children were fully discussed on all aspects and procedures related to the study and we only included children whose parents or guardians/accompanists had given their voluntary consent, as evidenced by the signature of the informed consent form. The confidentiality of the information collected and the anonymity of the participants were respected.

Results

Sociodemographic data

Our study population was made up of 79 girls (61.2%) and 50 boys (38.8%) giving us a boy to girl sex ratio of 0.63. Our study participants were averagely aged 11.68 years ± 3.26 years with the youngest being 6 years and the oldest 17 years. The most represented age range was 10 to 14 years.

Prevalence of PAH

Overall, 27 patients were diagnosed with PAH and thus a prevalence of 20.9% (95% CI: 13.9-27.9).

Sociodemographic data and PAH

There was no significant gender difference between patients with PAH and patients without PAH. Similarly, there was no significant difference in region of origin between patients with and without PAH. However, the risk of PAH increased with age (p=0.001). We found a positive and significant correlation (r=0.34) between age and mPAP.

Anamnestic/Clinical factors and PAH

The table below (Table 1) summarizes univariate analysis of qualitative anamnestic variables.

Qualitative anamnestic Variables	Modalities	mPAP (mmHg)		p Value
		≤ 25	> 25	
Sex	Female	61 (77.2%)	18 (22.8%)	0.515
	Male	41 (82%)	9 (18%)	
Past history of jaundice	Yes	91 (78.4%)	25 (21.6%)	1
	No	11 (84.6%)	2 (15.4%)	
Number of blood transfusions	≤ 3	102 (80.3%)	25 (19.7%)	0.043
	>3	0	2 (100%)	
Number of Hospitalisations	≤ 3	99 (80.5%)	24 (19.5%)	0.106
	>3	3 (50%)	3 (50%)	
Number of VOC	≤ 3	54 (80.6%)	13 (19.4%)	0.658
	>3	48 (77.4%)	14 (22.6%)	
Past history of Pneumonia	Yes	7 (50%)	7 (50%)	0.010
	No	95 (82.7%)	20 (17.3%)	
Past history of Stroke	Yes	2 (66.7%)	1 (33.3%)	0.509
	No	100 (79.4%)	26 (20.6)	
Lumbago	Yes	19 (82.6%)	4 (17.4%)	0.782
	No	83 (78.3%)	23 (21.7%)	
Abdominal Pain	Yes	21 (75%)	7 (25%)	0.550
	No	81 (80.2%)	20 (19.8%)	

Table 1: Analysis of qualitative anamnestic variables.

We found a significant (p=0.043) difference in the proportions of patients with PAH and without PAH with respect to blood transfusions within the previous 12 months. Similarly, a past history of pneumonia was strongly found to be associated to PAH (p=0.01). We didn't find any associations between the other anamnestic variables and PAH.

Qualitative clinical variables	Modalities	mPAP (mmHg)		p Value
		≤ 25	> 25	
Dyspnoea	Yes	0	7 (100%)	< 0.001
	No	102 (83.6%)	20 (16.4%)	
Stress hepatic pain	Yes	12 (66.7%)	6 (33.3%)	0.209
	No	90 (81.1%)	21 (18.9%)	
Jaundice	Yes	27 (81.8%)	6 (18.2%)	0.653
	No	75 (78.1%)	21 (21.9%)	
Lower limb oedema	Yes	1 (50%)	1 (50%)	0.376
	No	101 (79.5%)	26 (20.5%)	

Loud S2	Yes	19 (76%)	6 (24%)	0.674
	No	83 (79.8%)	21 (20.2%)	
Regular heart rythm	Oui	99 (80.5%)	24 (19.5%)	0.106
	No	3 (50%)	3 (50%)	

Table 2: Analyses of qualitative clinical variables.

The presence of dyspneawas significantly associated to PAH (p<0.001). We did not find any significant associations between the other qualitative clinical variables and PAH.

Quantitative clinical variables	mPAP	N	Mean	Standard deviation	P value
Age (years)	≤ 25 mmHg	102	11.196	3.2152	0.001
	> 25 mmHg	27	13.519	2.7924	
Height/age Percentiles	≤ 25 mmHg	102	34.3521	25.93749	0.912
	> 25 mmHg	27	35.5604	30.81805	
BMI Percentiles	≤ 25 mmHg	102	30.5964	23.8108	0.917
	> 25 mmHg	27	31.0985	25.64443	
Respiratory Rate	≤ 25 mmHg	102	23.66	2.361	0.837
	> 25 mmHg	27	23.78	2.136	
Heart Rate	≤ 25 mmHg	102	95.06	10.955	0.935
	> 25 mmHg	27	94.44	14.319	
O_2Sat	≤ 25 mmHg	102	93.89	4.907	0.322
	> 25 mmHg	27	93.15	4.663	
Systemic BP Percentiles	≤ 25 mmHg	102	63.12	19.21	0.867
	> 25 mmHg	27	63.81	19.684	

Table 3: Analysis of quantitative clinical variables.

We found a significant association between age and pulmonary arterial pressure, this was not the case for the other quantitative clinical variables.

Biological factors and PAH

Biological Variables	mPAP	N	Mean	Standard deviation	P value
HbF (%)	≤ 25 mmHg	88	10.603	7.2352	0.078
	> 25 mmHg	20	7.96	6.09	
HbS (%)	≤ 25 mmHg	88	85.142	7.9503	0.146
	> 25 mmHg	20	87.49	6.7639	
HbA2 (%)	≤ 25 mmHg	88	3.951	5.129	0.812
	> 25 mmHg	20	3.175	0.7239	
LDH (UI/L)	≤ 25 mmHg	62	1792.79	855.822	0.383
	> 25 mmHg	16	1619.63	848.703	
Hb (g/dl)	≤ 25 mmHg	88	7.825	1.2008	0.672
	> 25 mmHg	20	7.57	1.2144	

Table 4: Analysis of Biological variables.
Hb: Hemoglobin; LDH: Lactate dehydrogenase.

There were no significant differences in the distribution of participants with or without PAH with respect to the biological parameters (Hb electrophoresis, LDH level, Hb values, haematocrit and reticulocyte count).

Echocardiography Parameters and PAH

The table below summarizes univariate analysis of echocardiography (Table 5).

Echocardiograph Variables	mPAP	N	Mean	Standard deviation	p value
IVSd thickness Z-Score	≤ 25 mmHg	102	1.9516	0.86432	0.075
	> 25 mmHg	27	1.6289	0.85021	
LVDd Z-Score	≤ 25 mmHg	102	0.4683	0.97092	0.108
	> 25 mmHg	27	0.8626	1.02415	
PWd thickness Z-Score	≤ 25 mmHg	102	1.7625	0.87494	0.774
	> 25 mmHg	27	1.7833	0.9259	
IVSs thickness Z-Score	≤ 25 mmHg	102	1.7525	0.98648	0.051
	> 25 mmHg	27	1.3152	0.97984	
LVDs Z-Score	≤ 25 mmHg	102	0.2676	1.66068	0.031
	> 25 mmHg	27	0.9278	1.18638	
PWs thickness Z-Score	≤ 25 mmHg	102	1.313	1.06882	0.876
	> 25 mmHg	27	1.2811	0.94391	
LVEF	≤ 25 mmHg	102	67.5148	7.72466	0.064
	> 25 mmHg	27	65.2759	6.17889	
LVSF	≤ 25 mmHg	102	38.2283	6.24349	0.084
	> 25 mmHg	27	36.0111	4.7585	
LVM Z-Score	≤ 25 mmHg	102	2.1135	1.16686	0.637
	> 25 mmHg	27	2.0678	1.35103	
ARD Z-Score	≤ 25 mmHg	102	2.0505	1.2733	0.05
	> 25 mmHg	27	1.4741	1.22798	
RAD Z-Score	≤ 25 mmHg	102	2.2484	0.90528	0.69
	> 25 mmHg	27	2.2241	0.88217	
PAD Z-Score	≤ 25 mmHg	102	0.8717	0.72453	0.376
	> 25 mmHg	27	1.043	0.92372	
Mitral E wave speed	≤ 25 mmHg	102	1.453	0.24721	0.836
	> 25 mmHg	27	1.4789	0.24981	
Mitral A wave speed	≤ 25 mmHg	102	0.8418	0.63155	0.359
	> 25 mmHg	27	0.7493	0.11619	
RVD Z-Score	≤ 25 mmHg	102	2.4548	0.53883	0.768
	> 25 mmHg	27	2.4763	0.83527	
TAPSE Z-Score	≤ 25 mmHg	102	3.5552	2.83482	0.524
	> 25 mmHg	27	3.293	3.01823	

Table 5: Analysis of echocardiograph variables.

IVSd: Inter-ventricular septum in diastole; IVSs: Inter-ventricular septum in systole; LVDd: Left ventricle diameter in diastole; LVDs: Left ventricle diameter in systole; PPs: Posterior wall in systole; PWd: Posterior wall in diastole; RVM: Right ventricle mass; ARD: Aortic root diameter; LAD: Left atrium diameter; PAD: Pulmonary artery diameter; RVD: Right ventricle diameter; TAPSE: Tricuspid annular plane systolic excursion; EF: Ejection fraction; LVEF: Left ventricle ejection fraction; LVSF: Left ventricle shortening fraction.

As concerns echocardiographic parameters, the left ventricular diameter in systole was significantly larger in patients with PAH (p=0.031). The aortic root diameter was also found to be significantly larger in patients with PAH (p=0.05). There was no

significant difference observe for the other parameters.

Multivariate analysis

We entered our data in a logistic regression model. Table 6 below summarises multivariate analysis for our quantitative variables.

Variable	mPAP	N	Mean	Standard deviation	P value
Age	≤ 25 mmHg	102	11.196	3.2152	0.041
	> 25 mmHg	27	13.519	2.7924	
HbF	≤ 25 mmHg	88	10.603	7.2352	0.205
	> 25 mmHg	20	7.96	6.09	
HbS	≤ 25 mmHg	88	85.142	7.9503	0.199
	> 25 mmHg	20	87.49	6.7639	
LDH	≤ 25 mmHg	62	1792.79	855.822	0.466
	> 25 mmHg	16	1619.63	848.703	
IVSd thickness Z-Score	≤ 25 mmHg	102	1.9516	0.86432	0.699
	> 25 mmHg	27	1.6289	0.85021	
LVDd Z-Score	≤ 25 mmHg	102	0.4683	0.97092	0.381
	> 25 mmHg	27	0.8626	1.02415	
IVSs thicness Z-Score	≤ 25 mmHg	102	1.7525	0.98648	0.312
	> 25 mmHg	27	1.3152	0.97984	
LVDs Z Score	≤ 25 mmHg	102	0.2676	1.66068	0.198
	> 25 mmHg	27	0.9278	1.18638	
LVEF	≤ 25 mmHg	102	67.5148	7.72466	0.317
	> 25 mmHg	27	65.2759	6.17889	
LVSF	≤ 25 mmHg	102	38.2283	6.24349	0.121
	> 25 mmHg	27	36.0111	4.7585	
Z-Score PAD	≤ 25 mmHg	102	0.8717	0.72453	0.11
	> 25 mmHg	27	1.043	0.92372	

Table 6: Multivariate analysis for quantitative variables.

Age was the only quantitative variable of our study that was independently associated to PAH.

Variable	Modalities	mPAP (mmHg)		P Value
		≤ 25	> 25	
Number of blood transfusions	≤ 3	102 (80.3%)	25 (19.7%)	0.005
	>3	0	2 (100%)	
Number of hospitalisations	≤ 3	99 (80.5%)	24 (19.5%)	0.134
	>3	3 (50%)	3 (50%)	
Past history of pneumonia	Yes	7 (50%)	7 (50%)	< 0.001
	No	95 (82.7%)	20 (17.3%)	
Dyspnea	Yes	0	7	0.001
	No	102 (83.6%)	20 (16.4%)	
Stress hepatic pain	Yes	12 (66.7%)	6 (33.3%)	0.079
	No	90 (81.1%)	21 (18.9%)	

Table 7: Logistic regression aalysis for qualitative variables.

We found a high number of blood transfusions, a past history of pneumonia and dyspneato be independentl qualitative determinants.

Discussion

The overall objective of our study was to identify the determinants of pulmonary arterial hypertension (PAH) in children with major sickle cell syndrome. To achieve this objective, we have chosen to carry out a descriptive and analytical cross-sectional study because this framework allows us to highlight the frequency of PAH, to describe its distribution and to search for its determinants. All our patients were at least 6 years old and strictly under 18 years old. According to the French High Authority for Health (haute autorité de santé), the age at which echocardiographic screening is beneficial for sickle cell patients is 6 years [16]. The 18-year limit was in order to remain exclusively in paediatrics. We excluded patients who had been transfused or had a CVO episode within two weeks and patients who had had a febrile episode within the previous 8 days. These exclusions were intended to keep patients in as stable a state as possible. PAH was defined as an increase in mean pulmonary arterial pressure (mPAP) above 25mmHg. This method of estimating pulmonary pressures by mPAP (calculated from the maximum pulmonary regurgitation flow) is certainly not the standard method that remains catheterization. However, it remains a reliable, fair and appropriate method in pediatrics that estimates of systolic pulmonary arterial pressure (sPAP) (based on maximum tricuspid regurgitation flow) that tends to overestimate pulmonary pressure [12,17].

We found a PAH prevalence of 20.9% (27/129) in our study. Farzana et al. [18] observed a prevalence of 30%, equal to that of adults. It should be noted that the population of Farzana was closer to an adult population than ours. On the other hand, his diagnostic method was using an estimate of sPAP from the tricuspid regurgitation velocity (TRV). However, this method tends to overestimate the values of the sPAP [12]. Qureshi et al. [19] who compared echocardiograms of sickle cell disease patients with those of healthy control subjects reported a prevalence of 16% of PAH in sickle cell disease patients. However, this study was retrospective, and only a subset of patients was included.

Like Ambrusko et al. [20] we did not find any significant association between sex and PAH in our study. The age distribution was significantly different between our PAH patients and those who were free of PAH (p=0.41). We have indeed observed a positive and significant correlation between age and PAPm in our series. Qureshi et al. and Farzana et al. found similar results. This correlation is explained by the pathophysiological mechanism underlying the occurrence of PAH in sickle cell patients: the older the subject, the longer he/she has been vascularly exposed to the effects of hemolysis [5].

A number of blood transfusions in the past 12 months greater than 3 were significantly associated with PAH (p=0.043). A high number of blood transfusions indicates a high hemolysis index, which explains the strong association between the number of transfusions and PAH [5]. This result was similar to that of the study by Suell et al. [21] in which a significant association between a number of blood transfusions greater than 10 since birth and high TRV was demonstrated. A history of pneumonia has also

been found to be significantly associated with PAH (p=0.010). This association between pneumonia and PAH is explained by the observed alteration of the pulmonary parenchyma, leading to an increase in pulmonary resistance [22]. It should be noted, however, that in our study, history collection failed to distinguish lung infections from acute chest syndromes. It is not excluded that some cases considered as lung infections are actually acute thoracic syndromes.

There was no significant difference in the number of hospitalizations over the past 12 months. The high morbidity potential of sickle cell disease justifies the plethora of reasons for hospitalization that are not always related to vascular complications. Similarly, we did not find any significant difference in the number of vaso-occlusive seizures. This finding was also made by Ambrusko et al.

Although Hydroxyurea prophylaxis has a protective effect against chronic hemolysis [23], we have not found a significant association between this treatment and PAH. However, it should be noted that the duration of hydroxyurea intake at the time of data collection is not clear. However, the beneficial effects of this preventive measure are related to its duration of use [24].

Dyspnea in our study was one of the symptoms found. It was significantly associated with PAH. All our dyspnoeic patients were at NYHA stage 2. This result is similar to that of Parent et al. [12] who, in their study on the hemodynamic aspects of PAH in adult sickle cell patients, found dyspnea at stages 3 and 4 in 45% of his patients. This finding was significantly associated with PAH diagnosed by cardiac catheterization although the severity of dyspnea was not correlated with that of PAH.

With regard to oxygen saturation, nearly half of our patients had oxygen desaturation. However, we did not find a significant link between oxygen saturation and PAH. This result was different from Farzana et al. who found a significant association between PAH and hypoxemia. The mechanism of hypoxemia in sickle cell disease may result from the degree of anemia, intrinsic lung disease or upper airway obstruction secondary to obstructive sleep apnea [18]. The findings of our study eventually lead us to an intrinsic lung disease.

With regard to biological parameters, we did not find a significant association between HbF and mPAP. There was also no significant difference in LDH levels in our study. This result is different from that of Gladwin et al. [25] who were the first to show an association between LDH and TRV in a study they conducted on African-American sickle cell adults. Ranque et al. [5] in the CADRE study found a significant association between LDH level and the biological marker NT-proBNP (N-terminal pro Brain Natriuretic Peptide) of PAH. However, they did not find an association with an ultrasound marker. The hemoglobin level in our series was not significantly associated with PAH. This result is similar to that of Farzana et al, who, despite the negative correlation found, had not had any statistical significance. Ambrusko et al. obtained a different result (significant association) by comparing the mean hemoglobin of sickle cell patients included with a TRV<2.5 m/s to that of other patients in a retrospective study.

On the echocardiographic level, we found a significant association between the diameter of the left ventricle and the PAPm (p=0.031). We also found an association between the diameter of the aorta root and the PAPm (p=0.05). These echocardiographic findings are different from those described in the literature. The echocardiographic determinants of PAH according to Hansmann et al. [17] are: the diameter of the right ventricle; the right atrium; and the TAPSE. It should be noted that the work of Hansmann et al. focused on pulmonary arterial hypertension in children, adolescents and young adults free of major sickle cell disease in Germany. The cardiovascular specificities of the African black sickle cell patient may explain this difference.

In logistic regression, we found a significant association between the following variables and PAH: age (p=0.041), number of blood transfusions (p=0.005), history of pneumonia (p<0.001), dyspnea (p=0.001).

Conclusion

At the end of our study we found that although PAH is a serious complication in adults with sickle cell disease, it is a complication that has its origins in childhood. Indeed, in our series conducted in pediatrics, the prevalence found was 20.9% and the youngest patient with the disease was 8 years old. We looked for the determinants of this complication in our context and in univariate analysis, the determinants found were age, presence of dyspnea, high number of blood transfusions, history of pneumonia, dilation of the left ventricle, and dilation of the aorta. In multivariate analysis, the independent determinants we found were: age; high number of blood transfusions; history of pneumonia; dyspnea.

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