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Cholelithiasis in Children with Sickle Cell Disease in Ouagadougou Pediatric Hospital

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Abstract

Introduction: Sickle cell disease (SCD) causes chronic hemolysis which is a risk factor for cholelithiasis. Its development may lead to severe and life-threatening complications. Objective: Determine the prevalence of cholelithiasis, the conditions of diagnosis and related factors. Materials and Method: We retrospectively reviewed records of 110 patients with sickle cell disease followed up in Charles de Gaulle University Pediatric Hospital from January 2003 to December 2013, including 103 patients who had abdominal ultrasonography. Results: Cholelithiasis prevalence was 24.3%. The mean age of patients was 10.8 years, (range 3 to 15 years). Sex ratio was 2.1. In 88% cases, cholelithiasis was diagnosed based on the characteristic symptoms of right hypocondrial pain, fever and icterus. Most factors associated with cholelithiasis were as follows: age above 10 years (OR = 4), occurrence of at least three (03) vaso-occlusive crises per year (OR = 7.6), history of blood transfusion (OR = 8), right hypochondrial pain (OR = 4.5) and icterus (OR = 15). Only 20% of patients suffering from a symptomatic cholelithiasis underwent laparoscopic cholecystectomy and results were conclusive. Conclusion: Patients with sickle cell disease, especially those aged above 10, should be routinely tested for cholelithiasis using abdominal ultrasonography at least once a year. Because of the difficulties in managing evolutive complications in case of an emergency in our context, we advocate laparoscopic cholecystectomy of any cholelithiasisas soon as it is diagnosed in children with sickle cell disease.

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Keywords

Cholelithiasis, Sickle Cell Disease, Children

1. Introduction

Cholelithiasis is a frequent complication of chronic hemolysis due to sickle cell disease (SCD) [1]. It is sometimes revealed by digestive symptoms difficult to distinguish from painful abdominal vaso-occlusive crises (recurrent abdominal pain sometimes similar to biliary colic, nausea, vomiting). However, cholelithiasis is often asymptomatic and can lead to serious complications (cholecystitis, cholangitis, pancreatitis, septicemia starting in the bile) which can jeopardize patients' lives [2] [3]. If excessive bilirubin excretion related to chronic hemolysis is a major risk factor for gallstones formation, other conducive factors which have not been identified yet could intervene [1] [4]. Many studies show that the prevalence of cholelithiasis in patients with sickle cell disease increases with age and affects 6% of patients before 15 years of age and more than 50% of young adults [1] [5] [6]. Gallstones treatment is equivocal but most of studies recommend cholecystectomy in the symptomatic cases and regular ultrasonography in the other cases [3] [7]. In Charles de Gaulle University Pediatric Hospital of Ouagadougou, children with SCD have been followed up since 2002 but patients have to bear the fees [8]. Ultrasonography is not always accessible due to its cost. The diagnosis of cholelithiasis is often based on clinical signs and the risk of developing complications is high. It is in this context that we found it appropriate to carry out this study to determine the prevalence of cholelithiasis, the conditions of diagnosis, the factors associated with its occurrence and the treatment adapted to our context of limited resources.

2. Patients and Methods

We carried out a retrospective study to describe and review the records of all patients with SCD followed up in Charles de Gaulle University Pediatric Hospital (CHUP-CDG) between January 1st, 2003 and December 31st, 2013. During the period of study, 110 patients with SCD were followed up every 3 months and had at least one biological checkup every 6 months based on full blood count far away from any complication. Annual abdominal ultrasonography was routinely proposed to all patients. It was also performed in case of abdominal pain or in the occurrence of clinical signs of symptomatic cholelithiasis. Thus, one hundred and three (103) patients had had abdominal ultrasonography during the period of study, either routinely or with the occurrence of warning signs and these were all included in the study. For each patient, we collected data on clinical monitoring and/or hospitalization records and on epidemiological aspects (age, sex, parents' socioeconomic status), clinical data (pathological history, motives for consultation, physical examination data), paraclinical data (hemoglobin electrophoresis, full blood count, abdominal ultrasonography, biochemical checkup: serum transaminase, bilirubinemia), data on medical and surgical treatment and on the course of the disease. Parents' socioeconomic status was arbitrarily classified according to the father's occupation and divided into two (02) categories: average socioeconomic level (civil servants, liberal professions, traders, the military and paramilitary); low socioeconomic level (farmers, breeders, informal sector, the unemployed, pupils, students).

To identify epidemiological, clinical and biological factors likely to be associated with the occurrence of cholelithiasis, we compared patients suffering from cholelithiasis (Group I) with the other patients whose abdominal ultrasonography was normal (Group II). Data were collected and analyzed on microcomputer with Epi-Info software, Version 3.5.1. Group I (cases) and group II (witnesses) were compared using the Chi-squared test at a significance level of 5% and calculation of Odds ratio with their confidence intervals (IC) at 95%. Factors in which the confidence interval did not include the value 1 were deemed to be high risk factors for cholelithiasis occurrence.

3. Results

3.1. Epidemiological Data

3.1.1. Prevalence of Cholelithiasis

Out of 103 patients with SCD who had had an abdominal ultrasonography, 25 suffered from cholelithiasis,

hence a prevalence of 24.3%. Hemoglobin electrophoresis revealed 14 SC patients (56%) and 11 SS patients (44%) among patients suffering from cholelithiasis.

3.1.2. Distribution of Cholelithiasis Cases by Age and Sex

Patients' mean age during cholelithiasis diagnosis was 10.8 years (range—3 to 15 years). The age group from 10 to 15 years was the most affected with 16 cases (64%) (see **Table 1**). We registered 17 boys (68%) and 8 girls (32%). Sex-ratio was 2.1.

3.1.3. Socioeconomic Level

The socioeconomic level was deemed average in 17 parents (68%) and low in 8 parents (32%).

3.2. Clinical Data

3.2.1. Frequency of Vaso-Occlusive Crises

Out of 25 patients, 23 had a history of vaso-occlusive crises including 20 who experienced more than 3 vaso-occlusive crises per year, representing 80% of cases.

3.2.2. History of Transfusion

Ten (10) patients had already had at least one blood transfusion, representing 40%.

3.2.3. Conditions of Diagnosis

Right hypocondrial pain (68%), fever (60%) and icterus (56%) were the main conditions for diagnosing cholelithiasis, as shown in **Table 2**. Only 3 cases of cholelithiasis were routinely detected.

3.2.4. Physical Signs

On examination, some general signs were observed: a mucocutaneous paleness in 12 patients (48%) and icterus in the other14 patients (56%). Physically, 14 patients (56%) felt a pain at deep palpation of right hypocondrium and 03 patients (12%) presented with persistent pain in the same hypocondrium. Hepatomegaly and splenomegaly were observed in 6 (24%) and 2 cases (8%), respectively. For 8 patients (32%), physical examination was normal.

3.3. Paraclinical Data

3.3.1. Results of Abdominal Ultrasonography

Abdominal ultrasonography objectived a gall bladder containing gallstones in 24 cases and "Sludge" in 01 case. In 05 cases, gallstones size ranged from 10 to 27 mm in diameter with a mean size of 14.60 mm. In 19 patients, we observed "multi-microlithiases" with gallstones measuring less than 5 mm in diameter and in 1 case, a "small lithiasis" measuring between 5 and 10 mm. Moreover, all patients had normal sonographic patterns of liver and common bile duct. Ultrasonography revealed complications such an acute cholecystitis in 07 patients, representing 28% of cases.

3.3.2. Results of Biological Examinations

Full blood count revealed hemoglobin level below 6 g/dl in 6 patients (24%) and ranging from 06 to 10 g/dl in the other 19 patients (76%). A hyperleucocytosis above 15,000 white blood cells/mm^3 was observed in 16 cases

Table 1. Distribution of the 25 cholelithiasis patients by age and sex.

Range of age (years)	Sex		Total n (%)
	Female n (%)	Male n (%)	
<5	1 (4)	3 (12)	4 (16)
6 - 10	1 (4)	4 (16)	5 (20)
11 - 15	6 (24)	10 (40)	16 (64)
Total	8 (32)	17 (68)	25 (100)

Table 2. Conditions of diagnosis of the 25 cases of cholelithiasis.

Conditionof diagnosis	Number	(%)
Right hypocondrial pain	17	68
Fever	15	60
Icterus/subicterus	14	56
Diffuse abdominal pain	04	16
Nausea/vomiting	03	12
Dark urines	02	8
Routine diagnosis	03	12

(64%) with predominant neutrophils.

Other lab tests revealed high serum transaminase in 46% of patients and high total bilirubin in 60% of cases. Moreover, creatinemia and blood sugar turned normal in all our patients.

3.4. Therapeutic Aspects

Out of 25 cases of cholelithiasis, 19 were hospitalized and the other 6 were followed up as outpatients. Patients were initially admitted in pediatric care unit, then, 9 patients were transferred to surgical care unit in the same hospital. Medical treatment often consisted in healing clinical and biological disorders observed and it was associated with a symptomatic treatment made up of analgesic, anti-inflammatory and antispasmodic medicines. In surgical care unit, 5 patients underwent a cold laparoscopic cholecystectomy within a mean time of 17.4 days after cholelithiasis was diagnosed through abdominal ultrasonography (range—04 to 34 days).No major surgery aftermath was reported in all cases. The mean hospital stay was 7.4 days (range—01 to 19 days) with on average 9 days in pediatric care unit and 5 days in pediatric surgery.

After hospital stay, patients were proposed a monthly, 3 months and then half-yearly follow-up as well as abdominal ultrasonography. Most of patients failed to have abdominal ultrasonography. After one year's follow-up, 14 patients who were not operated became asymptomatic under medical treatment and 4 patients were lost to follow up.

3.5. Factors Associated with Cholelithiasis

Table 3 shows epidemiological and clinical factors likely to be associated with the occurrence of cholelithiasis in our patients. Age above 10 years (OR = 4), occurrence of at least 3 vaso-occlusive crises per year (OR = 7.6), history of blood transfusion (OR = 8), right hypocondrial pain (OR = 4.5) and icterus (OR = 15) were mainly associated with cholelithiasis.

4. Discussion

Sickle cell disease is a genetic disease that causes anemia as well as acute and chronic tissue injuries in many organs [1]. Providing better care in our unit has increased the life expectancy of children with SCD [8]. Yet, its development can lead to chronic complications such as cholelithiasis which should be known and managed. Despite the retrospective nature of our study, which could introduce bias in the estimation of the prevalence of gallstones and especially symptomatic forms, we have achieved significant results and conducted the following discussion.

4.1. Prevalence of Cholelithiais

Prevalence of cholelithiasis in children with SCD varies according to studies. We observed a prevalence of 24.3% in our series. Our results are similar to those of Athanassiou-Metaxa and al in Greece [9] who reported a frequency of 27.1%. Other authors as Silva in Greece and Itoua in Nigeria [10] [11] reported a prevalence greatly superior to ours, 40.9% and 31.30% respectively. However, many other African studies reported lower prevalence: 9.3% in Côte d'Ivoire, 9.4% in Senegal and 11.5% in Sudan [1] [2] [12]. Differences observed

Table 3. Factors associated with cholelithiasis.

Factors	Group I (n = 25)	Group II (n = 78)	OR (IC95%)	p
Type of hemoglobin				
SC	14	41	1 (0.4 - 3)	0.7
SS	11	37	1.0	
Age				
>10 years	16	20	5 (1.8 - 15.2)	0.0004
≤10 years	9	58	1.0	
Sex				
male	17	45	1.6 (0.7 - 4.5)	0.3
female	8	33	1.0	
Socioeconomic level				
low	8	36	0.6 (0.2 - 1.6)	0.2
average	17	42	1.0	
Vaso-occlusive crises ≥ 3/an				
yes	20	27	7.6 (2.3 - 26.1)	0.00007
no	5	51	1.0	
History of blood transfusion				
Yes	10	06	8 (2.2 - 29.9)	0.001
no	15	72	1.0	
Right hypocondrial pain				
Yes	17	30	4.5 (1.6 - 13.3)	0.001
no	8	48	1.0	
Icterus				
yes	14	06	15 (4.3 - 57.4)	$<10^{-6}$
no	11	72	1.0	

between prevalences could be related to patients' age in the series, their mode of selection or clinical signs. In our study, the relatively high prevalence of cholelithiasis can be explained inter alia by better care provision to patients with SCD and increased access to ultrasonography, which is an essential tool in the diagnosis of this pathology. Diagne and al in Senegal [2] reported that cholethiais on the whole occurred less frequently in patients of West Africa than in those of Central Africa. This would be related to the fact that in case of SCD, the Bantu haplotype which is more frequent in Central Africa experiences more severe symptoms with chronic and more important hemolysis whereas the Senegal and Benin haplotype which is the majority in West Africa presents with less severe symptoms. The intermingling of populations could progressively reduce the scope of this observation.

4.2. Conditions of Diagnosis

Conditions under which cholelithiasis is diagnosed in children with SCD vary according to series. In our study as in Sarnaik and al [13] and Bond and al [14], cholelithiasis was, from the onset, diagnosed in case of symptoms evocative of bile ducts disorders (right hypocondrial pain, icterus and fever) in 88%, 60% and 56% of cases, respectively. On the other hand, in the work of Attala [1] and Parez [3], cholelithiasis was initially detected through a routine ultrasonography. The diagnosis of cholelithiasis with clinical signs is a late diagnosis. This

situation is prejudicial to patients due to high risk of death if complications occur [2]. Recurrent high temperature (60%) and cholecystitis in 28% of cases reveal in our series major complications in children with SCD. Annual abdominal ultrasonography required for the follow-up of our patients should therefore be done routinely and free of charge for parents who are unable to bear fees.

4.3. Factors Associated with the Occurrence of Cholelithiasis

Factors that lead to gallstones formation in case of chronic hemolysis such as sickle cell disease have not been fully understood [15]. In our study, age above 10 years, occurrence of at least 3 vaso-occlusives crises per year, history of blood transfusion, right hypocondrial pain and icterus were reported. These observations are similar to those of literature in which the prevalence of cholelithiasis in patients with SCD always increases with age and seriousness of disease [1] [2] [3] [7]. However, if an increased bilirubin excretion related to chronic or recurrent hemolysis remains a significant factor for cholelithiaisis occurrence, all patients who experience an important hemolysis do not develop cholelithiasis. Other contributory factors play therefore a complementary role. According to Everson *et al*. [4], some defects of biliary function and the metabolism of bile acids may contribute. Moreover, some authors reported the role of food factors (fatty food and diet low in fiber) in patients living in Europe and USA [16] [17]. Factors leading to cholelithiasis are numerous, equivocal and depend on age. It is therefore possible that early care while reducing the exposure to factors aggravating chronic hemolysis, reduces the risk of cholelithiasis.

4.4. Therapeutic Aspects

In our series, only 20% of patients with symptomatic cholelithiasis underwent laparoscopic cholecystectomy. Despite the equivocal treatment attitude towards cholelithiasis, most of studies agree on cholecystectomy in symptomatic forms [1]-[3]. In asymptomatic forms, two attitudes are opposed. Some authors advocate abstention and follow-up [7] [18] whereas other authors recommend cold cholecystectomy before the onset of any complication [19] [20]. In our context, the second attitude seems more reasonable because of fear of complications in case of emergency. But this attitude is faced with financial difficulties and sometimes the reluctance of parents who fear the aftermath of surgery which was simple in all our operated patients.

Laparoscopic cholecystectomy is the treatment of choice of cholelithiasis in children with SCD, because of its effectiveness and harmlessness in comparison with laparotomy which is a classical surgery [21]. This technique is used recently though uncommon in our health center. Considering challenges for obtaining regular ultrasonography during follow-up of patients and difficulties in the management of complications in case of emergency, we recommend as Parez and al in Paris and Diagne and al in Dakar [2] [3], the routine laparoscopic cholecystectomy in any patient with SCD showing or not a symptomatic cholelithiasis.

5. Conclusion

Cholelithiasis is frequent in children with SCD in Burkina Faso. It should be routinely screened using ultrasonography in any patient with SCD, especially those above 10 years of age. Because of the difficulties in managing evolutive complications in case of an emergency in our context, we advocate laparoscopic cholecystectomy way of all gallstones since its discovery in sickle cell children. The implementation of a national programme of sickle cell disease, the introduction of a routine neonatal screening and a regular follow-up could contribute to reduce morbidity and mortality in children with SCD in our country.

Conflict of Interest

No.

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