Prevalence of Cholelithiasis in Sickle Cell Hemoglobinopathy, Central Indian Scenario

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Abstract- Cholelithiasis is a well-known complication of sustained heme catabolism as in Sickle cell anemia, which has frequency distribution between 22.5 – 44.4 % in central India.

This study was carried at Regional Hemoglobinopathy Detection And Management center, Indira Gandhi Government Medical College Nagpur. This study includes 120 patients with sickle cell disease and 30 cases with sickle cell trait. The prevalence of cholelithiasis in 120 sickle cell disease cases was found to be 28.33% as compared to 10% in each of the sickle cell trait and normal population. The cases were clinically evaluated for frequency of Vasoocclusive crisis (VOC), abdominal pain, jaundice, and biliary colic along with Cholecystosonography, hemoglobin Estimation, reticulocyte counts, peripheral smear, AST, ALT and AlkalinePhosphatase

Age of the youngest patient with gallstone, in the present series was 5 years and that of the oldest patient was 70 years. The reduced hemoglobin percentage, increased reticulocyte count, increased bilirubin concentration (indirect, direct and total) and raised AST were found to be significant factors related with cholelithiasis in homozygous sickle cell disease.

Sickle cell disease cases with repeated abdominal pain, voc coupled with low mean hemoglobin, high reticulocyte count, and bilirubin should be subjected to ultra-sonographic screening as early as at 2 yrs.

Index Terms – Sickle cell anemia, cholelithiasis, Central India

Abbreviations

1. VOC – Vasoocclusive crisis
2. AST – aspartate aminotranferase
3. ALT – alanine aminotranferase

I. Introduction

Cholelithiasis is a well-known complication of chronic hemolysis. Sickle cell anemia, a hereditary hemolytic anemia with sustained heme catabolism, leads to very high frequency of pigment gallstones. The prevalence of gallstones varies from 6.8% to 58.4%[1-8]. This variability can be accounted to the variability in geographic location, dietary habits, environmental factors, genetic factors and the technique employed for detection. Ultrasonography has been considered as fairly sensitive technique for the radio opaque as well as radiolucent stones. In patients with sickle cell anemia, the presence of gallstones poses a medical and surgical dilemma, due to similarities of clinical and laboratory features between acute cholecystitis and acute abdominal crisis. The gallstones can be radiolucent or radio opaque and can be picked up by ultrasonography. Even though 10 to 15% of the patients have symptoms that can be attributed to the biliary tract[9,10] elective cholecystectomy may lead to dramatic decrease in the frequency of abdominal crisis[9,11]. Sickle cell disease especially the Asian – Indian haplotype has relatively benign course (have mild course) and hence the patients tend to live longer[12]. The incidence of cholelithiasis increases with age[13,14] and hence screening for gallstones is necessary to reduce gallstone related morbidity and mortality. The present study was carried out to find out prevalence of cholelithiasis in patients of sickle cell anemia from central India.

II. IDENTIFY, RESEARCH AND COLLECT IDEA

Material & Methods

This study was carried out for two years.150 patients that were positive by solubility test along with 30 control cases (solubility negative) were included. These cases were classified into homozygous (SS) and heterozygous (AS) and normal homozygous (AA), using hemoglobin electrophoresis at alkaline PH with agar gel as support media. The cases were clinically evaluated for frequency of Vasoocclusive crisis (VOC), abdominal pain, jaundice, and biliary colic. The cases were subjected for laboratory investigations like Hemoglobin Estimation, Reticulocyte counts, Peripheral smear, AlkalinePhosphatase AST and ALT and Cholecystosonography. Cholecytosonography was carried out using machine GE Logic 3 PRO with a curvilinear probe of frequency 3.5 MHz. The sonographic images and records were obtained. Examination of gallbladder was performed after a minimum of 4 hours of fasting, because ingestion of food, particularly of a fatty nature stimulates the gallbladder to contract. The contracted gallbladder may appear thick walled and may obscure luminal or wall abnormalities. Evaluation of the gallbladder was performed with routine agital and transverse sonograms. Small stones less than 5 mm did not cast shadow but were echogenic. Mobility was the key feature of stone, allowing differentiation from polyps or other entities. Scanning with the patient in the right or left lateral decubitus or upright standing positions allowed stone to roll within the gallbladder.

Observations

The 150 solubility positive cases on Hb electrophoresis, showed 'SS' pattern (sickle cell disease) in 120 cases and 'AS 'pattern in 30 cases. The prevalence of cholelithiasis in 120 sickle cell disease cases was found to be 28.33% as compared to 10% in each of the sickle cell trait and normal cases group (Fig1). In gender wise distribution of cholelithiasis, males outnumbered females and the prevalence of cholelithiasis was also more in males as compared to females (Table I). The prevalence of gall stones in age group of 2 to 5 years was 6.25%, in age group of 6 to 10 years it was 10%, in age group of 11 to 13 years it was 14.29% and in age group of 14 to 18 years it was 31.58% (Table II) The 34 cases of cholelithiasis include the youngest patient of 5 years who presented with right upper quadrant pain, nausea, fever, leukocytosis & hepatomegaly. As against that oldest patient was 70 years, who was admitted with severe right upper quadrant pain, nausea, jaundice, leukocytosis and negative Australia antigen test. It was also observed that the prevalence of cholelithiasis increased with increase in age (Table II)

120 patients of homozygous sickle cell anemia were classified in two groups as

1) Group A: Patients with cholelithiasis
2) Group B: Patients without cholelithiasis

Both the groups were clinically evaluated for VOC and abdominal pain. Number of vaso-occlusive episodes was more in SS cases with cholelithiasis as compared to those without cholelithiasis (Table III). So also, SS cases with cholelithiasis had increased abdominal crises episodes as compared to those without cholelithiasis (Table IV). All the pointers of chronic hemolysis i.e. reduced hemoglobin percentage with increased reticulocyte count & increased bilirubin concentration (indirect > direct), were found to be statistically significant factors, related to cholelithiasis in homozygous sickle cell disease as compared to those without cholelithiasis (Table V). The mean ALT, ASTand alkaline phosphatase levels were high in SS cases with gallstones as compared to those without stones (Table V). These differences between the two groups were statistically significant (Table V).

Discussion

Sickle Cell Anemia has frequency distribution between 22.5 – 44.4 % in central India[12]. Regional Hemoglobinopathy Detection And Management center was established in 2000 at Indira Gandhi Government Medical College Nagpur. Nagpur happens to be geographic center of India. This study was carried out to find out prevalence of cholelithiasis in this part of India. The present study comprised of total 150 patients of sickle cell syndromes and 30 normal AA patients. Cholecystosonography was performed in all the cases. Small stones less than 5 mm did not cast shadow but were echogenic. Sonography is currently the most practical and accurate method of diagnosis of acute Cholecystitis. The sensitivity and specificity of sonography when adjusted for verification bias is approximately 88% and 80% respectively[15].

Overall prevalence of cholelithiasis in homozygous sickle cell disease was found to be 28.33% in age group 2 to 70 years. The prevalence in children was 16.13% (below 18 years). AL-Salem reported 19.71% cholelithiasis in 305 children below 18 years on sonography[16] while Karayalcin G et al reported 17% prevalence in 47 children[11].On the other hand Lachman BS et al [17] reported 29%prevalence in 31 cases using sonography Cholecystosonography and abdominal radiography. The youngest child in their series was 4 years old. Age of the youngest homozygous sickle cell patient with gallstone, in the present series was 5 years and that of the oldest homozygous SS patient was 70 years. Parez N et al[18], Akmaguna AL[19] et al also reported youngest patient of 5 years Diagne I[5] in 7 years and Nzeh DA[20] in 10 years child. Incidence as quoted by Sarnaik et al [13] is 12%. All these studies recommend use of, noninvasive technique of ultrasonography to be implemented in screening of all homozygous children from the age of 2 years and onwards. 10% of sickle cell trait patients (AS) showed presence of gallstones, which was comparable with prevalence of gallstone in normal control AA patients. Thus, prevalence of cholelithiasis was higher in homozygous sickle cell disease than sickle cell trait and general population. Various authors have reported prevalence of cholelithiasis that ranged from 6.18 % to 58% [1-8] (Table VI). This wide range can be attributed to the features like sample size, age group, technique used, geographic location, dietary habits etc. Mohanty J et al[8] reported prevalence of 22% in Western Orrisa-India, in their study on 50 cases of homozygous sickle cell disease.

When studied in different age groups, it was observed that there was a steady rise (Table II) in the Prevalence of cholelithiasis in homozygous sickle cell disease patients as the age advances. Repeated Vasoocclusive crisis (55.8%) was commonly associated with cases of cholelithiasis than those without cholelithiasis (15.1%) (Table III). Abdominal crisis was more common in patients with cholelithiasis (14.7%) than in the case without cholelithiasis (1.16%) (Table IV). The mean hemoglobin concentration in patients with cholelithiasis was lower than those without cholelithiasis (p value was highly significant). The mean reticulocyte count was higher in cholelithiasis patients than those without cholelithiasis (p value was highly significant). Total, direct and indirect bilirubin levels and AST was higher in patients with cholelithiasis than those without cholelithiasis. Thus, reduced hemoglobin percentage, increased reticulocyte count, increased bilirubin concentration (indirect, direct and total) and raised AST were found to be significant factors related with cholelithiasis in homozygous sickle cell disease. Sarnaik S et al in their study on 226 patients reported high mean bilirubin only, 3.8mg/dl in cases with cholelithiasis as compared to 2.6in those without cholelithiasis[13]. The authors also reported that mean hemoglobin and reticulocyte counts were not significantly different. Christopher G et al also did not found significant difference in total bilirubin, in their study on 100 homozygous cases of sickle cell anemia[21].

Double heterozygous states with Hb S have variable effect on cholelithiasis. Co existent states like Hb C, β Thalassaemia increases the risk while co existent α Thalassaemia decreases the risk of cholelithiasis[22]. Hb C has not been reported in India so far

and Hb S-β can be diagnosed by quantitation of variant hemoglobins where Hb A2 will be raised beyond normal range. It is very difficult to diagnose co existent state of α thalassaemia with Hb S however such cases tend to have smaller, lighter cells with higher hemoglobin level and fewer reticulocyte[22]. Homozygous sickle cell disease cases without gall stones needs to be evaluated for coexistent α thalassaemia in them. Sickle cell disease has variable clinical manifestations and fortunately is much milder in severity in India as compared to Africa[12]. Analysis of clinical data in sickle cell research center (ICMR) at Burla in India, shows patient of all ages even beyond age of 40 years. Nearly 11% of cases in the present were above the age of 30years and the eldest case had the age of 70 years. With increase awareness regarding disease and better health care facilities, the patients are expected to live/survive longer. As the risk of cholelithiasis and related complications increases with increase in age, cholecystosonography coupled with laproscopic cholecystectomy of all homozygous sickle cell cases is essential to reduce gall stone-related morbidity and mortality in these cases.

Cholecystosonography is fairly sensitive and specific method with added advantage as a noninvasive technique. Laproscopic cholecystectomy is well tolerated by younger cases[23].

Homozygous (SS) cases without gallstones need to be evaluated for co-existent α thalassaemia. Cases with repeated abdominal pain, voc and laboratory features like low mean hemoglobin with high reticulocyte count and bilirubin should be subjected to ultra-sonographic screening and it should be undertaken as early as 2 yrs.

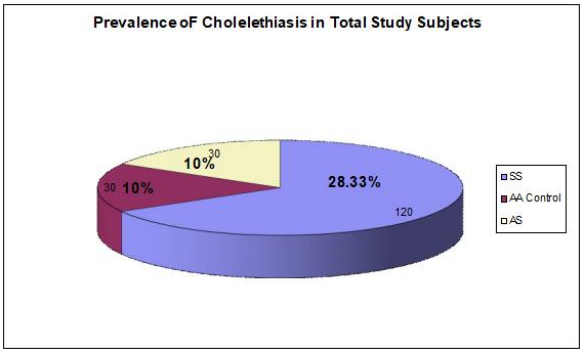

Fig 1 Showing prevalence of cholelithiasis in study population.

Table-I showing SS male patients with gall stones outnumbered females

Sex	No. of cases	Percentage	With Gallstones	Frequency Percentage
Males	67	55.83	22	32.84
Females	53	44.17	12	22.64
Total Cases	120	100.00	34	

Table-II showing increase frequency of gall stones with increase in ageing SS cases.

Age groups in Years	No. of Patients	No. of Patients with Gallstones	Frequency %
2-5 Years	16	1	6.25
6-10 Years	20	2	10.00
11-13 Year	7	1	14.29
14-18 Years	19	6	31.58
19-25 Years	32	11	34.38
26-30 Years	12	5	41.67
31-35 Years	6	3	50.00
36-45 Years	5	3	60.00
> 45 Years	3	2	66.67
Total Cases	120	34	

Table III Vasoocclusive crisis in Group A and Group B

Vasoocclusive crisis	Group A (n=34)		Group B (n=86)	
	No. of Cases	%	No. of Cases	%
≤ 2 per year	15	44.12	73	84.88
3-5 per year	19	55.88	13	15.12
Total cases	34		86	

Group A: SS Patients with Cholelithiasis, Group B: SS Patients without Cholelithiasis

Table No. IV Abdominal crisis in Group A and Group B

Abdominal crisis	Group A (n=34)		Group B (n=86)	
	No. Of Cases	%	No. Of Cases	%
≤ 2 per year	23	67.65%	78	90.70%
3 to 4 per year	6	17.65%	7	8.14%
> 4 per years	5	14.71%	1	1.16%
Total cases	34		86	

Group A: SS Patients with Cholelithiasis, Group B: SS Patients without Cholelithiasis

Table No. V - Laboratory Investigations in Patients In Group 'A' & Group 'B

Variables	Group A (n=34)		Group B (n=86)		P Value
	Mean	SD	Mean	SD	
Hemoglobin	7.05	1.25	8.07	1.35	p < 0.001
Reticulocyte count	7.28	2.02	5.05	1.89	p < 0.001
Direct Bilirubin	0.81	0.88	0.42	0.64	p < 0.05
Indirect Bilirubin	2.84	0.68	1.90	0.82	p < 0.001
Total Bilirubin	3.65	1.12	2.33	1.27	p < 0.001
SG OT	191.09	61.36	97.60	62.79	p < 0.001
SG PT	130.53	99.39	61.28	70.92	p < 0.001
ALK PO4	313.35	169.17	190.55	120.09	p < 0.001

Group A: SS Patients with Cholelithiasis, Group B: SS Patients without Cholelithiasis

Table VI – Prevalence of Cholelithiasis in Homozygous Sickle Cell Disease by various authors.

Sr. No.	Author	No. of Patients	Age Range (yrs.)	Prevalence in %
1	Bond LR (1987)[1]	95	10 to 65	58
2	Akamaguna AI (1985)[2]	48	2 to 35	25
3	Durosinmi MA (1989)[3]	133	9 to 60	22.6
4	Billa RE et al (1991)[4]	90	< 20 and > 30	28.9
5	Diagne I (1999)[5]	106	11 to 22	9.4
6	Olatunji A A (2002)[6]	97	Children & Adult	6.18
7	Longo M (2004)[7]	190	3 to 24	58.4
8	J Mohanty et al (2004)[8]	50	3 to 48	22
9	Present Study (2005)	120	2 to 70	28.33

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