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Cholelithiasis in Children with Sickle Cell Anaemia in Rural and Tribal Central India

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Summary

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Background: Sickle cell anaemia (SCA) is prevalent in central India. Gall stones are known to be present in SCA but its prevalence in the paediatric population is variably reported.

Objective: To study the prevalence of gall stones in children with sickle cell anaemia and its correlation with various crises and serum bilirubin levels.

Setting: Department of Pediatrics, Shri VN.Government Medical College, Yavatmal, Maharashtra, India.

Design: Prospective hospital-based study.

Methods: All patients with SCA aged 12 years and below, admitted to the pediatric ward of the hospital between June 2006 and May 2007 formed the study material. Detailed history of blood transfusion, jaundice, cholelithiasis, haemolytic crises, and vaso-occlusive crises (VOC) was obtained in respect of each patient. Investigations, including serum bilirubin (total and direct) and cholecystosonogram, were carried out in all cases.

Results: The incidence of SCA was 5.2 percent among the 103 patients studied. Gallstones were detected in eight patients, a prevalence of 7.7 percent; the M: F ratio of the eight was 1:1.66. Significant correlation was found between gallstones and recurrent abdominal VOC, frequency of blood transfusion, as well as total bilirubin and indirect bilirubin levels. However, there was no significant correlation with haemoglobin level, direct bilirubin level and age at first transfusion.

Conclusion: SCA is prevalent in central India. Cholecystosonogram is a non-invasive tool that can be used to diagnose gall stones in these children; hence, all SCA patients aged above five years with total serum bilirubin of more than 3mg/dl and recurrent blood transfusions should be screened for gall stones.

Introduction

SINCE the discovery of sickle cell disease (SCD) in 1910[1] and its first description in children by Sydenstricker,[2] its various clinical presentations have been reported.[3] Patients with SCD are at high risk of developing pigment gall stones due to chronic haemolysis and thus may present as acute abdomen which may be difficult to differentiate from hepatic crisis, cholecystitis or cholelithiasis.[4] In the normal population, gall stones are uncommon in the first decade of life. The prevalence of gallstones in children with SCD varies from 8–58 percent,[5-13] is symptomatic in young age group,[11] and is associated with higher morbidity and mortality. Cholelithiasis is therefore an indication for elective cholecystectomy.[12] Cholecystosonography is a very sensitive and preferred non-invasive technique for detecting cholelithiasis with diagnostic accuracy of 90 - 95 percent.[10] Elective cholecystectomy is preferred over emergency cholecystectomy which has intraoperative complications.[13] There is no reported study on gall stones in children with SCD from Central India, although the prevalence of SCD ranges from 0-30 percent,[14] hence this study was

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planned with the aim of determining the prevalence of gall stones (GS) in children with sickle cell anaemia (SCA) and its correlation with vaso-occlusive crisis (VOC), recurrent abdominal pain, blood transfusions, and bilirubin levels.

Patients and Methods

This was a prospective hospital based study, carried out in the department of pediatrics at Shri. Vasantrao Naik Government Medical College, Yavatmal, India from June 2006 to May 2007. This is a tertiary hospital situated in the hilly and tribal area of central India. All cases of SCD aged 12 years and below who were admitted to the paediatric ward during the study period formed the study material. SCD was diagnosed on haemoglobin electrophoresis. A detailed history with regard to jaundice, cholelithiasis, haemolytic crisis, VOC and blood transfusions was taken. The subjects were examined and then subjected to investigations such as serum bilirubin (total and direct) levels. To visualize gall stones, all the children underwent cholecystosonogram of the abdomen, which was done using an ultrasound scanner Toshiba core vision pro 3 MH2 convex or linear probes after 6 to 8 hours of fasting in order to permit distension of the gall bladder by bile.

Statistical analysis was carried out using the chi square test where applicable; $p<0.05$ was regarded as being statistically significant.

Results

There were 4666 admissions to the paediatric ward during the study period. Of these, 126 were children with SCD. They were admitted 243 times and hence the incidence of admissions for SCD was 5.2 percent. Among the 126 SCD patients, 23 had HbAS and no gall stone was detected sonologically in them; they were therefore excluded from further consideration. Among the remaining 103 SCA patients (HbSS), gall stones were present in eight. Thus the prevalence of gall stones was 7.7 percent. All the patients had more than one gall stone; each gall stone was >2mm in size in 87.5 percent. Females were more often affected than males, with an M: F ratio of 1:1.66.

These 103 HbSS cases were divided into an "A group" consisting of the eight patients who had gall stones and a "B group" consisting of the 95 without gall stones. On detailed analysis of recurrent episodes of abdominal VOC, the patients were also classified according to the number of VOC episodes per year (Table I). Among group B patients, 48.4 percent had 1-2 episodes per year, and only one (1.1 percent) of the 95 had more than five episodes. By contrast, four of the eight (50 percent) patients in group A had more than five episodes of abdominal VOC per year. The difference was highly significant ($X^2 = 28.27$, $df=1$, $P<0.001$), suggesting that the higher the number of abdominal VOCs the higher are the chances of detecting gall stones.

The relationship between the occurrence of gall stones and the number of blood transfusions is presented in Table II. SCA patients were divided based on the number of transfusions which they had received up till and during the study period. Fifty percent (4/8) in group A had received >15 blood transfusions as compared to 8.4 percent (8/95) in group B ($P<0.003$), suggesting a significant association between the frequency of blood transfusion and formation of gall stones. However, on comparing the age at first blood transfusion and the presence of gall stones (Table III), there was no significant correlation ($P>0.05$).

Table IV shows the results of haematological and biochemical investigations in both groups. Patients in group A had a significantly higher mean total bilirubin and indirect bilirubin concentrations than those in group B ($P = 0.0001$), whereas haemoglobin concentration and direct bilirubin were not statistically correlated with the presence of gall stones ($P>0.05$).

All the SCA patients who had gall stones were advised to undergo elective cholecystectomy but none of the caregivers gave their consent.

Table I

Abdominal VOC and Cholelithiasis in 103 SCA Patients

Frequency of Crises/Year	*No with Gall stones (%) Group A (N=8)*	*No without Gall stones (%) Group B (N = 95)*
None	0 (0)	4 (4.2)
1-2	0 (0)	46 (48.4)
3-5	4 (50)	44 (46.3)
>5	4 (50)	1 (1.1)

Table II

Relationship between the Number of Blood Transfusions and Occurrence of Gall Stones

No of Transfusions	*No with Gall stones (%) Group A [n= 8]*	*No without Gall stones (%) Group B [n= 95]*
None	0 (0)	7 (7.4)
< 5	0 (0)	36 (37. 9)
5-9	2 (25)	33 (34.7)
10-15	2 (25)	11 (11.6)
>15	4 (50)	8 (8.4)

Table III

Age at First Blood Transfusion in Patients with SCA

Age (Yrs)	*No with Gall stones (%) Group A (N=8)*	*No without Gall stones (%) Group B (N = 95)*
0-1	0 (0)	10 (10.5)
1-<3	1 (12.5)	21 (22.1)
3-<6	6 (75)	41 (43.2)
6-<12	1 (12.5)	23 (24.2)

Table IV

Haematological and Biochemical Investigations in Patients with SCA

Variable	*No with Gall stones (%) Group A (N=8)*		*No without Gall stones (%) Group B (N = 95)*			
	Mean	*SD*	*Mean*	*SD*	*t*	*P value*
Haemoglobin (%)	6.050	1.759	5.935	1.148	0.261	>0.05
Serum bilirubin						
Total	5.013	1.55	2.456	1.637	4.257	<0.0001
Indirect	3.913	1.238	1.835	1.147	4.899	<0.0001
Direct	1.100	0.512	0.625	0.925	1.434	>0.05

Discussion

Sickle cell anaemia is a genetically determined disease whose prevalence in central India ranges from 4.1 percent to 5.7 percent in hospitalized paediatric populations,[15-17] hence the prevalence of SCA obtained in the present study is comparable. The prevalence of gallstones in SCA during the study period was 7.7 percent. The prevalence was 8.5 percent in those below nine years of age, and 11.9 percent in those between nine and 12 years. Various African,[6,7] Western,[8,9] Indian[10] and Saudi Arabian[11] workers have found gallstones in the range of 8-58 percent in their series. The prevalence in our series was lower than those cited above probably because we studied only children aged 12 years and below, whereas these workers took an upper limit of 18 years.

Sickle cell anaemia in India and Saudi Arabia share common "S" mutation haplotype and in general, have a common course.[11] While the prevalence of 7.7 percent reported in the present series is nearly equal to that of the Saudi Arabian study which had 8.8 percent prevalence of gall stones below 10 years, an Indian study[10] reported no gall stones in SCA patients below 10 years and were of the opinion that at least, 12-13 years of haemolysis is required for gall stone formation. The youngest patient in this study was six years old, similar to the findings in Ghanaian patients with SCA,[18] although the youngest age at which gallstones have been reported in SCA was three years.[7]

Cholelithiasis is usually a disease of females in the general population, similar to the M:F ratio of 1:1.66 in the present study. A higher ratio of 1:2 has been reported by Rennels *et al*,[8] while an Indian study[10] reported a reverse sex ratio of 2:1, probably because the female population in their series was low. Gall stones in SCA are usually multiple with each stone measuring >2 mm in size; we also had multiple gall stones in all our eight cases, while Tripathy *et al* reported multiple gall stones in 64.5 percent of their cases.[10]

It is sometimes difficult to differentiate abdominal VOC from acute cholecystitis, acute hepatitis, cholelithiasis, and hepatic crisis which is associated with a more severe clinical picture. In this study, there was significant correlation between abdominal VOC and cholelithiasis, suggesting that as the number of abdominal VOC increases, the occurrence of gall stones also increases. Similarly, Webb *et al*[19] in their series, had shown similar correlation, but although Karayalcin *et al*[20] had the same number of patients presenting with recurrent abdominal pain, they did not apply any statistical test in their series. SCA is a disease of chronic haemolysis precipitated by recurrent VOC, infection and requires frequent blood transfusions which further adds to the bilirubin load, which in turn, leads to the formation of gallstones which are pigmentary in nature.[21] Apart from external source of bilirubin like blood transfusion at earlier age, other factors like recurrent VOC, hepatitis, biliary sludge might also be responsible for the formation of gall stones. In the present series, comparison of "Group A" with "Group B" in relation to gall stones and frequency of blood transfusion showed significant correlation ($P < 0.003$). On extensive review of the literature, we could not find any series that has studied the above correlation. However, gallstones were not statistically correlated ($P > 0.05$) with age at first blood transfusion in the present series.

Chronic haemolysis causes superabundance of unconjugated bilirubin in bile leading to increased solubility of bile which, in the presence of calcium, precipitates as calcium bilirubinate which binds with mucin from the mucosa of the gall bladder to form gall stone.[22] The increased total bilirubin in "Group A" patients compared with "Group B" ones in our series, had significant correlation ($P < 0.001$), a finding that has been reported by others[10,11,22] but in contrast, a study from the United Kingdom reported no correlation with the total bilirubin level.[9] The mean indirect bilirubin level also had highly significant correlation ($P < 0.0001$) in our series whereas an Indian study revealed no such correlation.[10]

In conclusion, SCA is prevalent in central India and accounts for 5-6 percent of admissions in paediatric hospital practice. In patients with SCA, gall stones occur at an earlier age with a prevalence of 7.7 percent. Cholecystosonography provides a good non-invasive tool to diagnose gallstones in SCD and hence, all patients with SCA older than five years who have received more than 15 blood transfusions with a total bilirubin >3mg/dl and indirect bilirubin >1mg/dl should undergo cholecystosonogram for gall stones as elective cholecystectomy will decrease mortality and morbidity in these patients.

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