

Gall stones in Jamaican children with homozygous sickle cell disease

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SUMMARY Gall stones were detected by ultrasonography in 30 of 226 (13%) children with homozygous sickle cell disease aged 5–13 years participating in a cohort study from birth. Children with gall stones had significantly lower total haemoglobin and fetal haemoglobin and higher bilirubin concentrations, but further analysis showed that the apparent effects of haemoglobin and fetal haemoglobin concentration were secondary to their relationship with bilirubin concentrations. Abdominal pain crises were significantly associated with gall stones but both factors appeared to reflect an increased clinical severity and were probably not causally related. No patients had symptoms specific of gall stones and an association with abdominal pain crisis should not, of itself, be considered an indication for surgery.

Pigment gall stones are well recognised as a complication of sickle cell disease but previous data on their prevalence and pathologic significance have been collected from symptomatically ascertained patient populations. The present study reports the prevalence in a representative sample of patients with homozygous sickle cell disease followed up in a cohort study from birth. This has also allowed an assessment of risk factors for gall stone formation and an analysis of associated symptomatology.

Subjects and methods

The children participated in a cohort study of sickle cell disease, which has been previously described.^{1,2} During the screening of 100 000 consecutive deliveries,³ 314 children with homozygous sickle cell disease were detected of whom six were lost to follow up immediately; 308 were admitted to the cohort study and followed up prospectively. Of these, 53 died, nine emigrated, and 246 (aged 5–13 years) continued to be observed at the time of the study.

From January to May 1987 all available children were examined by an experienced radiologist (JSD) using an ATL Ultramark IV with 3.0 MHz sector transducer. All studies were conducted in both transverse and longitudinal planes, with patients in a fasting state. Gall stones were diagnosed on the basis of echodense images within the gall bladder with either acoustic shadowing or gravitational change in position.

The haematological risk factors for gall stone formation were examined by comparing the means of steady state haematological indices in children with and without gall stones by Student's *t* test and by logistic regression analysis. These analyses were confined to steady state values over the age of 4 years because of rapid age related changes before this age.² All variables except total haemoglobin and direct bilirubin were transformed ($\log_{10}(\text{variable}+1)$) to produce approximately normal distributions before analysis. These observations were also used to predict gall stone frequency according to age and total bilirubin concentration.

Clinical features were also compared in patients with and without gall stones. Pain crises were defined as pain severe enough to limit activity and to require narcotic analgesia and were divided into those affecting primarily the bones or joints (bone pain crisis) or the abdomen (abdominal pain crisis). Dactylitis was defined as painful, tender swelling over the small bones of the hand, foot, or digits with no evidence of local infection. Acute chest syndrome was characterised by fever, tachypnoea, and signs of pulmonary consolidation. Septicaemia referred to a clinically ill child with fever, positive blood culture, and no other focus of infection. The growth of children with and without gall stones was assessed by comparing mean heights and weights at the 5th and 9th birthdays.

The frequency of clinical events was assessed by deriving age specific incidence rates for pain crises, acute chest syndrome, and dactylitis in children with

and without gall stones. As a few children with multiple events may distort these rates, a scoring system of 1-5 was used for bone pain crises and acute chest syndrome (representing 0, 1, 2-4, 5-9, 10 or more events) and of 1-4 for abdominal pain crises (representing 0, 1, 2, 3 or more events). These age specific incidence rates, derived for one year age bands, were compared between groups by analysis of variance. The relation of abdominal pain crisis with gall stones was reanalysed after controlling for bone pain crisis by examining this relation in groups matched for bone crisis frequency. This approach gives similar results to the stratified test for trend suggested by Mantel.⁴

Results

Technically satisfactory ultrasound examinations were obtained in 226 of 246 (92%) of all available patients. Gall stones occurred in 30 (19 boys, 11 girls), increased with age, and reached a prevalence of 20% in those aged 11-13 years (table 1). Among those affected, the male:female ratio was 2.5:1 in the 5-7 year age group and 1.3:1 in children aged 11-13, but the overall sex difference was not significant ($\chi^2=0.62$, $p=0.42$).

Comparison of haematological indices showed that children with gall stones had significantly lower total haemoglobin and fetal haemoglobin and higher

bilirubin concentrations (table 2). As these results may be influenced by mutual correlations between indices and the effects of age and sex, logistic regression analysis was used to assess the effect of each independently. Fitting all variables to two different models utilising either total bilirubin (model 1) or direct and indirect bilirubin (model 2), only total bilirubin ($p=0.02$) and indirect bilirubin ($p=0.04$) were significant indicating that after allowance for these factors, there was no additional effect of either haemoglobin or fetal haemoglobin. Results from the second model are shown in table 3. The predicted frequency of gall stones derived for different ages and bilirubin concentrations is shown in fig 1.

The scores for bone and abdominal pain crises (figs 2 and 3), and for acute chest syndrome, were consistently higher in children with gall stones, although only the difference for abdominal pain crisis reached significance ($F_{1,28}=4.02$, $p=0.05$). This observation could either imply a causal association between gall stones and abdominal pain crisis or that both factors reflect increased clinical severity. Analysis, repeated after controlling for bone pain crisis, showed that the relation of gall stones and abdominal pain crisis was no longer significant implying that their coincidence most likely reflected

Table 1 Prevalence of gall stones according to age and sex

Age group (years)	Boys		Girls		Total	
	No	No (%) gall stones	No	No (%) gall stones	No	No (%) gall stones
5-7	42	5 (12)	37	2 (5)	79	7 (9)
8-10	44	6 (14)	32	3 (9)	76	9 (12)
11-13	35	8 (23)	36	6 (17)	71	14 (20)
Total	121	19 (16)	105	11 (11)	226	30 (13)

Table 2 Haematology investigations in children with and without gall stones

Variable	Gall stones present (n=30)		Gall stones absent (n=196)		t	p Value
	Mean	SD	Mean	SD		
Fetal haemoglobin*	0.72 (4.3)	0.23	0.84 (5.9)	0.28	2.15	0.03
Haemoglobin (g/l)	74	8.5	79	9.6	2.64	0.009
Reticulocytes*	1.09 (11)	0.09	1.06 (10)	0.11	-1.30	0.19
Direct bilirubin ($\mu\text{mol/l}$)	17	3.4	15	4.0	-2.16	0.03
Indirect bilirubin*	1.42 (25)	0.24	1.26 (17)	0.25	-3.19	0.002
Total bilirubin*	1.64 (43)	0.17	1.53 (33)	0.17	-3.46	0.001

*Indices expressed as values transformed by $\log_{10}(\text{variable}+1)$.

Figures in parentheses indicate means re-expressed in original units.

Table 3 Logistic regression analysis of some haematological and clinical features in patients with gall stones

Variable	Slope* (logistic scale)	Significance
Age	0.09	0.32
Sex (female)	-0.19	0.67
Haemoglobin	-0.32	0.25
Fetal haemoglobin†	-0.34	0.37
Reticulocytes†	0.05	0.96
Direct bilirubin	0.06	0.27
Indirect bilirubin†	0.79	0.04

*After allowance for all other variables.

†Transformed variables.

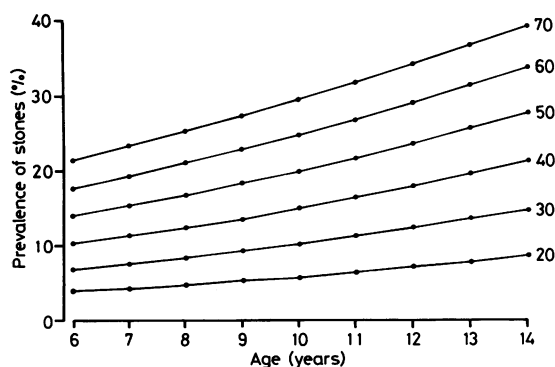


Fig 1 Expected frequency of gall stones at different ages for different total bilirubin concentrations ($\mu\text{mol/l}$) derived from the observations.

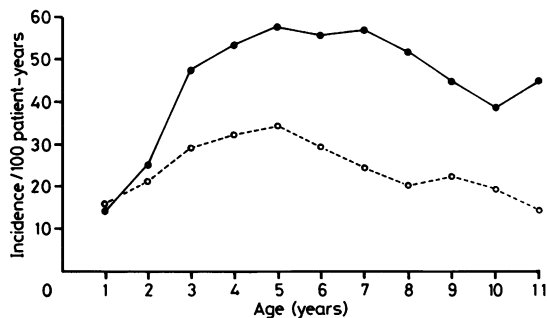


Fig 2 Incidence of bone pain crises (derived as scores) in children with (●—●) and without (○—○) gall stones.

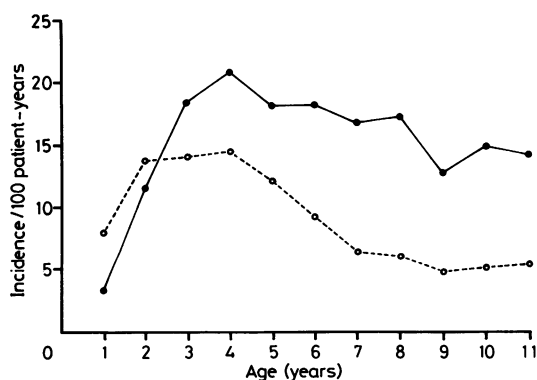


Fig 3 Incidence of abdominal pain crises (derived as scores) in children with (●—●) and without (○—○) gall stones.

an increased disease severity. No child had specific symptoms attributable to gall stones, and pain in the abdominal painful crisis was not localised to the right upper quadrant or epigastrium.

There were no differences in the incidence of septicaemia or dactylitis or in growth between the groups.

Discussion

The prevalence of gall stones in this representative group of Jamaican children with homozygous sickle cell disease was 13%, considerably lower than the figures of 28–33% reported in age comparable groups in the United States.^{5–8} In view of the genetic similarity of the two populations, it is likely that this difference represents the greater symptomatic selection in American series.

Information from other geographic areas is difficult to interpret. In Nigeria a low prevalence of cholelithiasis of 6% in patients under 15 years in one study⁹ might have been attributed to the less sensitive diagnostic method of oral cholecystography, but later studies using ultrasonography reported similar low prevalences of 4.4% under 17 years¹⁰ and 5% under 15 years.¹¹ It therefore seems likely that gall stones are truly infrequent in young Nigerian patients with homozygous sickle cell disease consistent with the infrequency of all gall stones in that population.¹² Since bilirubin concentrations in Nigerian patients with homozygous sickle cell disease are similar to those in Jamaica it must be concluded that pigment cholelithiasis is also influenced by other, possibly environmental, factors. In a Saudi Arabian study using oral cholecystography,¹³ cholelithiasis was observed in only 8% of a population aged 10–64 years and did not occur in 26 patients under 17 years; this is consistent with the low bilirubin and mild haematological change characterising that population.

Apparent risk factors for gall stone formation in homozygous sickle cell disease in other studies have included low fetal haemoglobin concentration and high reticulocyte count¹⁴ and high total⁶ and indirect¹⁴ bilirubin concentration. In the present study gall stones were associated with low total haemoglobin, low fetal haemoglobin, and high bilirubin concentrations. As both haemoglobin and fetal haemoglobin concentrations are inversely related to total bilirubin and as their contribution was lost on regression analysis it seems likely that their apparent effect was secondary to that of bilirubin concentrations.

The clinical significance of gall stones in homozygous sickle cell disease remains unclear. There is no doubt that complications such as acute cholecystitis

or obstruction of the cystic or common bile duct may occur and may require surgical correction. The major question is the frequency of these complications and whether prophylactic cholecystectomy is justified. Gall stones affected 20% of a representative sample of Jamaican children with homozygous sickle cell disease aged 11–13 years, none of whom had symptoms clearly attributable to gall stones, although the significant association of gall stones with abdominal pain crisis might be inappropriately interpreted as an indication for cholecystectomy. Further analysis showed that such children were also more prone to bone pain crisis, and the disappearance of an association with abdominal pain crisis after correcting for bone pain frequency makes it likely that both gall stones and abdominal pain crises reflect clinical severity and are not causally related. Abdominal pain crisis in children with gall stones, therefore, should not be considered an indication for surgery unless there are features clearly referable to the right upper quadrant of the abdomen.

The arguments for prophylactic cholecystectomy of asymptomatic gall stones are based upon the assumption that these stones will become symptomatic.^{5 15–20} This assumption was strengthened by a recent report from the United Kingdom indicating that pain typical of biliary colic occurred in 68% of adults with gall stones and that 21% developed acute cholecystitis.²⁰ It is difficult to reconcile these data with the Jamaican observations in which gall stones, although common, are relatively infrequently associated with typical symptoms. No symptoms have occurred in 30 cohort study children with gall stones—the oldest of whom are now approaching 15 years—and follow up of 32 adults known to have gall stones for 15 years showed only one patient developing specific symptoms during this period (DKH Webb and GR Serjeant, unpublished observations) and a current study of 31 patients with homozygous sickle cell disease over the age of 40 years has shown gall stones in 17 (55%) yet only two (6%) have had cholecystectomy for symptoms. A possible contributing factor to the apparent difference between the populations of the United Kingdom and Jamaica could be a greater symptomatic selection occurring in the group from the United Kingdom, and this is supported by the observation that 18 of 70 (26%) patients aged 16 years and above had already had cholecystectomies before the study in the United Kingdom.

The role of cholecystectomy for symptomatic gall stones is unquestioned but the Jamaican data do not support a policy of prophylactic cholecystectomy.

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