

Gallstones in Ghanaian children with sickle cell disease

*R. Darko, O. P. Rodrigues¹, J. O. Oliver-Commey¹ and C. N. Kotei**

¹Department of Surgery, ¹Department of Child Health and Korle Bu Teaching Hospital, Accra, Ghana.

Summary

Objective: This prospective, cross-sectional study was done to define the prevalence and age of onset of gallstones in Ghanaian children with Sickle Cell Disease (SCD) in steady state, using ultrasonography.

Materials and method: The study was conducted at the Paediatric SCD clinic, Korle Bu Teaching Hospital, Accra, Ghana.

Three hundred and fifteen (315) children comprising 162 males and 153 females aged 2 to 13 years with a confirmed diagnosis of SCD of haemoglobin SS, (HbSS), Haemoglobin SC, (HbSC) or Haemoglobin S- β thalassemia (S β Thal) genotype whose parents/guardians gave informed consent, were recruited consecutively. The main outcome measure was the detection of gallstones in the gall bladder or common bile duct by ultrasonography.

Results: Thirteen children, 12 males and 1 female had gallstone, giving an overall prevalence of 4%. The youngest was aged 6. Four children had sludge only. Peak age of prevalence was 12 years. All patients under 12 years with gallstone were males (92.3%). The very high male: female ratio in these sickle cell disease children is at variance with the normal male: female ratio of 1: 4.6.

Although twenty percent of all the patients were genotype SC, only one SC patient had gallstones, giving a prevalence rate of 0.3%, and a prevalence ratio of stone in SS: SC of 12:1.

Twenty patients had no spleen detectable clinically or on ultrasound examination and none of them had gallstones.

Conclusion: Gallstones occur at an early age in children with sickle cell disease in Ghana.

Key-words: Sickle cell disease, Gallstones, Ghanaian children, Ultrasonography.

Résumé

Objectif: Cette étude en prospective et en coupe-transversale était effectuée afin de déterminer la prévalence et l'âge et la première attaque du calcul biliaire chez des enfants ghanais atteints de la drépanocytose dans un état régulier à travers l'utilisation d'échographie.

Matériels et méthode: Cette étude a été effectuée au centre médical pédiatrique de la drépanocytose, centre hospitalier universitaire du Korle Bu, Accra, Ghana.

Trois cents quinze (315) enfants y compris 162 du sexe masculin et 153 du sexe féminin âgés de 2 à 13 ans avec un diagnostic confirmé d'hémoglobine SS, (HbSS) de la drépanocytose, Hémoglobine SC, (HbSC) ou Hémoglobine S - β thalassemie (S β Thal) génotype dont les parents/gardiens ont donné du consentement, ont été recrutés l'un après l'autre. Le résultat principal était la détection du calcul biliaire dans la vésicule ou bien canal biliaire ordinaire à travers l'échographie.

Résultats: Treize enfants, 12 du sexe masculin et 1 du sexe féminin étaient atteints du calcul biliaire ce qui donne une prévalence du rendement globale de 4%. Le plus jeune était âgé de 6 ans. Quatre enfants avaient eu la fange seulement. L'âge maximum de la prévalence était 12 ans. Tous les patients moins de 12 ans avec calcul biliaire était du sexe masculin soit 92,3%. Le taux élevé d'une proportion sexe masculin et sexe féminin chez ces enfants atteints de la drépanocytose est incompatible avec une proportion normale du sexe masculin: féminin 1: 4,6. Bien que vingt pourcent de tous les patients soient du génotype SC, un patient SC seulement avait eu le calcul biliaire, ce qui donne un taux de la prévalence de 0,3% et un rapport de la prévalence de caillou dans SS: SC de 12: 1

Vingt patients n'avaient aucune rate détectée cliniquement ou à travers l'ultrason et aucun d'entre eux n'avait le calcul biliaire.

Conclusion: Calcul biliaire arrive tout jeune chez des enfants atteints de la drépanocytose au Ghana.

Introduction

Sickle cell disease is a major health problem in Ghana with 16% and 10% carrier rates for the haemoglobin S (HbS) gene and the haemoglobin C (HbC) gene respectively. Of every one million children born in Ghana, more than 20,000 of this number will suffer from sickle cell disease.¹

Abdominal pain due to vaso-occlusion in the mesenteric circulation is common among SCD patients² but it may also be due to other causes including gallstone disease.³ Distinguishing between abdominal crisis and other causes of acute abdominal pain of which cholecystitis is one can be difficult. Gall stone disease is more common in sickle cell disease children than in the general population.⁴ The stones arise as a result of haemolysis, which leads to the formation and deposition of breakdown pigments as pigment stones.⁵ In Accra, Ghana, while the incidence of gallstone disease among adults in Accra with sickle cell disease was reported at 14.67% in 1975,⁴ that of sickle cell disease children is largely unknown. Ultrasonographic examination is a safe, effective and non-invasive method of diagnosis of gall bladder diseases.^{6,7}

The aim

The aim of the study was to define the age of first detection and the relative prevalence of gallstones in sickle cell disease children in a steady state attending the Paediatric Sickle Cell Disease clinic at the Korle Bu Teaching Hospital using ultrasonography.

Materials and methods

The Paediatric Department Sickle Cell Disease Clinic at the Korle Bu Teaching Hospital caters for all children, predominantly from southern Ghana, up to age 13 years who

* Correspondence **Deceased

have sickle cell disease. Three thousand patients attend annually of which 400 are new cases. Children with Sickle Cell Disease are otherwise seen in the general out patients' clinic.

Study design

The study was limited to children between 2 and 13 years with confirmed diagnosis of Sickle cell haemoglobinopathy by haemoglobin electrophoresis. This included patients who were SS, SC or SSF and SBTHa.

Table 1 Prevalence of gall stones in sickle cell disease patients

Age (Yrs)	Number	% with stones	Male: Female
2 - 4	41	0%	
5 - 9	149	4%	6:0
10 - 13	125	5.8%	6:1

All patients between 2 years and 13 years who attended the clinic during the three months study period who were in a steady state and whose parents/guardians gave informed consent were recruited for the study. The children were selected consecutively. Those under 2 years were not recruited due to the logistic difficulty of ensuring the overnight fast and doing ultrasonography on them. The children were examined by Dr. Rodrigues and Prof. Oliver-Commey and information recorded on a structured questionnaire included name, age, sex, genotype, height, weight, liver and spleen sizes, and details of previous crises including bone pain, severe anaemia, severe abdominal pain and the number of transfusions received. They were then instructed to return for abdominal ultrasonography one week later and after an overnight fast. A haemoglobin test was done during the week before the ultrasonography.

The abdominal ultrasonography was performed by Dr. Kotei using a Picker echo view model 80-L with a 3.5 MHz transducer. Examinations were performed in the supine and lateral-decubitus positions and involved the spleen, the liver, gall bladder and bile duct system, pancreas, and the kidneys.

Result

In all 315 patients were entered into the study. There were 162 males and 153 females. There were 13 patients with gall stones, 12 (92.3%) of whom were males. In addition, 4 patients had only sludge. Biliary sludge is a mixture of bile and particulate matter, which consists of a variety of precipitates such as cholesterol monohydrate, calcium bilirubinate, and other calcium salts.⁸ It presents as an echogenic material within the gall bladder lumen that layers and changes shape and position on moving the patient. All the patients with gallstones under the age of 12 years were males (92.3%). The only female patient with gallstone was aged 12 years. The prevalence of gallstone disease in the 2 - 13 years age-group was 7.4% in the male and 0.68% in the female (mean 4%). The prevalence by age is as shown in Table 1.

Though we examined children from age of two years the

earliest age of detection of gall stone by ultrasonography, was 6 years. The genotype SC patients formed 20% of all the patients but the prevalence of stones in the SC patient was 0.3% giving the prevalence ratio of stone in the SS: SC to be 12:1. This shows that the incidence of gallstones in the SC patient is much lower than the incidence of gallstones in the SS patient under the age of 14 years.

Associated abnormalities

There was no spleen in 20 patients and none of these had gallstone detected on ultrasonography. None of these patients with or without gallstone was found to have a dilated common bile duct.

There was no significant difference between those who had stones and those who did not have stones in the frequency of bone pain and abdominal crisis.

Eighty three percent of patients with gallstone had one or more blood transfusions as opposed to 47% of those without gallstones.

Discussion

Gall stone disease has been shown to occur with increasing frequency in Ghanaian adults.⁹

It is however uncommon to see gallstones in children who do not have haemolytic disease or who have not had *Salmonella* cholecystitis.¹⁰ Other predisposing factors in children are total parenteral nutrition,¹¹ ileal disease¹² and prolonged fasting.¹³ In Korle Bu Teaching Hospital, in 1990 - 91 out of 98 cholecystectomies performed 8 (8%) were sickle cell disease patients and all were adults.⁹

The natural history of gallstone disease in sickle cell disease patients is not well defined. None of these patients studied so far has had cholecystectomy and we shall be guided by their symptoms and signs as to whether and when they should have cholecystectomy.

The very high male: female ratio (12:1) is at variance with the normal sex ratio in adults which is 1:4.6 in Ghanaians.⁹ In Jamaica the male: female ratio is 2.5:1 in children aged 5 - 7 year and 1.3:1 in the 11 - 13 year old.¹⁴ The higher prevalence in males may be due to a higher frequency of haemolytic crisis in males¹⁵ as Omenge et al showed the association between reticulocyte count (an index of haemolysis producing hyperbilirubinaemia) and gallstone.¹⁶

Prospective studies restricted to children have shown that the prevalence of gall stones is from 6 to 29% and increases with age.⁹

The prevalence of gallstones in this group of sickle cell disease patients in Ghana was 4%. A similar study in Nigeria in 1979 by oral cholecystogram involving 77 patients aged 8 - 31 years showed a prevalence of 9%.¹⁷ Later studies using ultrasonography reported similar findings to ours; 4.4% in children under 17 years¹⁸ and 5% for those under 15 years.¹⁹ In Saudi Arabia, the prevalence was 27.5% in 29HbSS patients under 15 years.²⁰ Sarnaik et al in 1976 - 79 described the rather high incidence of gallstones in sickle cell disease patients in Detroit USA shown by ultrasound.²¹

The reason for the rather high prevalence of gallstones in sickle cell disease patients in the USA is not clear but may

be tied with the general higher incidence of gallstones in their general population.²² Another reason may be the selection of symptomatic patients in the USA study at the time of examination as symptomatic patients are more likely to have stones that had triggered the symptoms. These reasons may also account for the prevalence of 13% in Jamaican patients of 5 - 13 years and in Kuwait (15.6% in 1 - 16 year olds).²³ We decided to study patients who were asymptomatic as we felt this would give a more realistic idea of the prevalence of this condition in a population of children with sickle cell disease. The cholesterol level of stones in sickle cell disease patients is less than 10% as shown by Darko et al.²⁴ Since the cholesterol level is that low, gallstone in sickle cell disease patients are not suitable for dissolution and are best managed by cholecystectomy when indicated.

Sludge in sickle cell disease patients

There were only 4 patients with sludge. There is no consensus in the management of biliary sludge especially in sickle cell disease patients. While some believe that sludge is silent and does not convert to stone with time,²⁵ others believe that sludge is a precursor of stone.²⁶ Walker and Serjeant followed 17 symptoms free patients with sludge for 5 years and 12 out of the 17 developed stones by the following year but remained symptom free.^{27,28}

Stones in the common bile duct in sickle cell disease patients

None of our patients was found to have stones in the common bile duct by clinical, laboratory and ultrasonic examination. However, in Quatif, Saudi Arabia, cholecystectomy was performed in 39 children with sickle cell disease. Out of these, 18 (46%) were found to have associated common bile duct stones.²⁹

Conclusion

Since gallstone disease is not often considered as a cause of acute abdominal pain in children, the diagnosis is often delayed. Gallstone disease occurs rather early in sickle cell disease patients and therefore should be considered in the differential diagnosis of acute abdominal pain in children with sickle cell disease. From our study the sickle cell disease male patient is more likely to form a stone rather than the female patient. None of the patients with asplenia had gallstones. The natural history of gallstone in the sickle cell disease patients needs to be studied.

Acknowledgment

We wish to thank Mr. Nyamekye Addo for his help with data collection.

References

1. Konotey-Ahulu F I D. *The Sickle Cell Disease Patient* Macmillan 1991; pp xv - xix.
2. Jenkins M I et al. Sudden death during sickle cell anaemia crisis in young children. *Pediatr* 1960; 56: 30 - 8.
3. Jordan R A. Cholelithiasis in sickle cell disease. *Gastroenterology* 1957; 33: 953 - 8.

4. Archampong E Q, Konotey-Ahulu F I D. Biliary tract disease and sickle cell anaemia in Korle Bu Teaching Hospital. *Ghana Medical Journal* September 14; 1975; 175 - 180.
5. Buchanan G R and Glader B E. Benign course of extreme hyperbilirubinaemia in Sickle cell anaemia: analysis of six cases. *J Pediatr* 1977; 91: 21 - 4.
6. Lachman B S, Lazerson J, Vaughters F M and Werlin S L. The prevalence of cholelithiasis in sickle cell disease as diagnosed by ultrasound and cholecystography. *Paediatrics* 1979; 64: 601 - 3.
7. Billa R F, Biwole M S, Jumo A G, Bejanga B I and Blackett K. Gallstone disease in African patients with sickle cell anaemia. a preliminary report from Yaounde. *Cameroon Gut* 1991; 32: 539 - 41.
8. Werlin S L, Scott J P. Is biliary sludge a stone in waiting? *The Journal of Paediatrics* 1996; 129: 321 - 2.
9. Darko R, Archampong E Q. The changing pattern of cholelithiasis in Accra. *West African Journal of Medicine* 1994; Vol. 13: 204 - 208.
10. A Wright J, Thomas P, Serjeant G R. Septicaemia caused by Salmonella infection: an overlooked complication of sickle cell disease. *Journal of Paediatrics* March 1997; 39: -9.
11. Manji N, Bistran B R, Mascioli E A et al. Gallstone disease in patients with severe short bowel syndrome dependent on parenteral nutrition. *J Parenter Enteral Nutr* 1989; 13: 461 - 4.
12. Brink M A, Sloss S F, Kenlemons Y C, Mok K S, de Waart D R, Carely M C, Groen M K, Tygat G N. Enterohaptic cycling of bilirubin, a putative mechanism for pigmented gall stone formation in ileal Crohn's disease. *Gastroenterology* 2001; April; 1310 - 1.
13. Rescorla F J, Grosfeld J L. Seminars in Paediatric Surgery. Cholecystitis and cholelithiasis in children 1992 May; 1: 98 - 106.
14. Webb D K H, Darby J S, Dunn D T, Terry S I, Serjeant G R. Gallstones in Jamaican children with homozygous sickle cell disease. *Arch Dis Child* 1989; 64: 693 - 6.
15. McCall W I, Desai P, Serjeant E B, Serjeant R G. Cholelithiasis in Jamaican patients with homozygous sickle cell disease. *American J Hematol* 1997; 3: 15.
16. Omonge E, Ogutu E O, Aluoch J R. *East African Medical Journal* Vol. 75 June 1998; 347 - 350.
17. Akinyanju O, Ladipo F. Cholelithiasis and biliary tract disease in sickle cell disease in Nigerians. *Postgraduate Medical Journal* 1979; 55: 400 - 402.
18. Adekile A D. Experience with cholelithiasis in patients with Sickle Cell disease in Nigerians. *Amer J Pediat Haematol Oncol* 1985; 7: 261.
19. Akamaguma A I, Odita J C, Ugbodaga C I, Okafor L A. Cholelithiasis in sickle cell disease: a cholecystographic and

- ultrasonographic evaluation in Nigerians. *Eur J Radiol* 1985; 5: 271 - 2.
20. Adzaku F K, Annobil S H. Admission pattern of sickle cell disease in children in the Assir region of Saudi Arabia. *Ghana Medical Journal* 1996; 31a: 789 - 795.
21. Sarnaik S, Slovis T L, Corbett D P, Emami A, Whitten C F. Incidence of cholelithiasis in sickle cell anaemia using grey-scale technique. *J. Paediatrics* 1980; 96: 1005 - 8.
22. Adejoke A D, Makanjuola D. Ultrasonography in children with sickle cell anaemia *Journal of Nigerian Pediatrics* 1983; 10: 35 - 38.
23. Haider M Z, Ashebu S, Aduh P, Adekile A D. Influence of alpha thalasaemia on cholelithiasis in SS patients with elevated HbF. *Acta Haematologica* 1998 Dec; 100: 147 - 50.
24. Darko R, Archampong E Q, Qureshie Y, Murphy G M, Dowling R H. How often are Ghanaian gallbladder stones cholesterol-rich? *West African Journal of Medicine* 2000; 19: 64 - 70.
25. Lee S P, Nicholls J F. Nature and composition of biliary sludge. *Gastroenterology* 1986; 90: 677 - 8.
26. Carey M C, Cahalane M J, Whither. Biliary sludge. *Gastroenterology* 1988; 95: 508 - 23.
27. Walker T M, Serjeant G R. Biliary sludge in sickle cell disease. *Journal of Pediatrics* 1996; 129: 443 - 5.
28. Winter S S, Kinney T R, Ware R E. Gallbladder sludge in children with sickle cell disease. *Journal of Pediatrics* 1994 125(5 pt 1): 747 - 9.
29. Al-Salem A Hm Nourallah H. Sequential endoscopic/laparoscopic management of cholelithiasis and choledocholithiasis in children who have sickle cell disease. *Journal of Pediatric Surgery* 1997; 32: 1432 - 5.