Acute splenic sequestration and hypersplenism in the first five years in homozygous sickle cell disease

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SUMMARY A cord blood screening programme initiated in June 1973 had screened 68 000 normal deliveries by February 1979 with the detection of 216 cases of homozygous sickle cell disease. Regular review of these children in the Medical Research Council paediatric clinic has identified acute splenic sequestration as a major cause of morbidity and mortality in the first 5 years of life. In addition to classical episodes characterised by peripheral circulatory failure, minor episodes of increasing anaemia associated with an enlarging spleen and an active marrow were also common. These minor episodes appeared to have predictive value in children who later developed severe life-threatening episodes of acute splenic sequestration. Sustained hypersplenism was also appreciably more common in children developing minor or major episodes of acute splenic sequestration compared with those without such a history. It is proposed that the classification of acute splenic sequestration be expanded to include these minor episodes, and that consideration be given to prevention of recurrences by splenectomy particularly in patients who also develop sustained hypersplenism.

A prospective cohort study of 216 children with homozygous sickle cell (SS) disease followed since birth has identified acute splenic sequestration (ASS) as a major cause of morbidity and mortality in the first 5 years of life.¹ In addition to these 'classical' life-threatening attacks, minor episodes associated with less striking haematological and clinical changes have often been recognised. These minor episodes form a continuous spectrum with the 'classical' attacks and may precede and possibly be of predictive value for later more severe episodes of ASS. They may also presage the development of hypersplenism. In view of this it is proposed that the concept of ASS be expanded to include these minor episodes.

A minimal definition is required for these minor episodes and in this study we have investigated them using an arbitrary minimal definition of a fall in haemoglobin concentration of at least 2 g/dl, associated with evidence of marrow activity and an acutely enlarging spleen. The incidence, clinical and haematological features, natural history, and outcome of such episodes are presented.

Materials and methods

A cord blood screening programme with haemoglobin electrophoresis to detect cases of sickle cell disease was started at the government maternity hospital (Victoria Jubilee Hospital) in Kingston in

1973. By February 1979, 68 000 normal deliveries had been screened with the detection of 216 cases of homozygous SS disease. The criteria for diagnosis have been described elsewhere.² Haemoglobin F was assessed by a micromodification of the alkali denaturation test.³ Routine haematological procedures were used for the other studies.

After diagnosis, patients attended monthly for the first 6 months, on alternate months from 6 months to 1 year, and every 3 months thereafter. They were encouraged to attend without appointment when sick. The diagnosis of ASS was based on a fall in haemoglobin concentration of at least 2 g/dl, an enlarging spleen, and evidence of marrow activity. A reticulocyte count equal to, or above, steady state values was regarded as evidence of marrow activity and served to differentiate these episodes from aplasia. When the reticulocyte count was less than 10%, normoblasts were counted to confirm an early marrow response.

Results

A total of 71 episodes of ASS occurred in 52 of the 216 children with SS disease. There were 25 boys and 27 girls. The incidence (Fig. 1) indicated that this complication was most common in the second 6 months of life and was fairly unusual after age 2 years. Fatal episodes followed a similar

Fig. 1 Incidence of acute splenic sequestration between 0 and 66 months.

distribution, the median age in 10 fatal episodes being 17½ months (range 8–54) compared with a median age of 12 months (range 3–61) in 61 non-fatal episodes. Of the 71 episodes 21 were detected during routine visits without severe symptoms, and 50 caused an emergency visit of which 35 resulted in hospital admission. A single blood transfusion was administered in 18 episodes and none of the fatal cases reached hospital in time to receive a transfusion.

Clinical features. Symptoms were generally non-specific and included fever ($n=33$), cough ($n=20$), diarrhoea and vomiting ($n=16$), pallor ($n=12$), drowsiness ($n=10$), anorexia ($n=8$), and bone pain ($n=8$). No symptoms were reported in 8 episodes, one of which was fatal. The pattern of symptoms did not vary with the degree of fall in haemoglobin concentration, but not surprisingly the mortality was higher in those with haemoglobin falls greater than 4 g/dl (4 out of 12) than in those with haemoglobin falls of between 2 and 3.9 g/dl (nil out of 52). The degree of fall in haemoglobin concentration was not documented in 7 episodes. The duration of symptoms was much shorter in the fatal group (mean 19 hours, range 0–36 hours) than in the non-fatal group (mean 42 hours, range 3–14 days). The duration of symptoms in the fatal group (shorter than 24 hours in 9 of 10) was reflected in the outcome, with one child dying at home, 5 dying on the way to hospital, 2 dying in the Casualty Department, and 2 dying after admission to hospital but before transfusion could be given.

Mean spleen size during attacks was 4 cm (range 1–9) below the left costal margin, and was smaller on subsequent examination in 62%. The spleen had been previously palpable in 33 (63%) of the 52 patients but in 19 (37%) the episode of ASS represented the first documented appearance of

splenomegaly. Palpable splenomegaly in the first year of life was more common in the ASS group (88%) than in those not developing ASS (51%) but the difference may simply reflect the presence of splenomegaly associated with ASS.

Haematology. The mean haemoglobin concentration during all episodes of ASS was 4.8 g/dl (range 0.8–7.3), the fall from previous values averaging 3.2 g/dl. The mean haemoglobin concentration in the fatal episodes was 2.6 g/dl (range 0.8–4.8) in the 4 of 10 children on whom measurements were performed. Mean reticulocyte counts increased during episodes of ASS from 9 to 19% (range 4–43%). In 8 episodes the reticulocyte count was below 10% but in 6 of these the total nucleated blood count doubled and 5 had high normoblast counts (mean 46/100 WBC; range 15–98/100). Two patients failed to show an increased normoblast count but in both microcytic red cell indices and low serum iron levels suggested that iron deficiency might be limiting the marrow response. The diagnosis of ASS in these two episodes was based on an acutely enlarged spleen which diminished in size in association with a rising haemoglobin level during the next few days. Platelet counts during 13 episodes of ASS gave a mean value of $232 \times 10^9/l$, about half the expected mean count in SS children. A search was made for a prognostic haematological index in patients developing ASS between 6 and 12 months, by examining the distribution of indices at 6 months of age. It failed to show differences in total haemoglobin, reticulocytes, mean cell volume, or total nucleated cell count. Haemoglobin F levels however, were significantly lower ($P<0.05$) at 6 months in patients subsequently developing ASS compared with those who did not.

Bacteriology. Bacteriological investigation during episodes of ASS failed to incriminate a specific infective aetiological agent. Blood cultures in 23 episodes showed pathogens in only 2, 1 *Klebsiella* sp. and 1 *Enterobacter* sp. (probably a contaminant). Stool culture grew a pathogenic *Escherichia coli* in 1 and *Salmonella* sp. in 3. Radiological evidence of pneumonia occurred in 9 episodes and there was clinical evidence with normal radiology in 2. A pseudomonas otitis media occurred in the child with a *Klebsiella* sp. in the blood culture, and pus from a superficial abscess in another child grew *Staphylococcus pyogenes*. Post-mortem bacteriological and gross pathological findings in the 10 fatal cases are shown in the Table. Post-mortem blood cultures in 4 patients showed two or three organisms in each, and in a fifth patient, who had been receiving monthly

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Table Bacteriological and other necropsy findings in 10 fatal episodes of acute splenic sequestration

Case	Age (months)	Sex	Findings at necropsy in addition to ASS	Spleen weight (g)	Hb (g/dl)	Reticulocytes (%)	Necropsy bacteriology	
							Blood	Other sites
1	8	M	Nil	115 (20)	0.8	—	No growth	Throat and ear swabs. No growth
2	8	F	Broncho-pneumonia	122 (20)	—	—	—	Pneumococcus in lung
3	9	F	Nil	92 (20)	—	—	—	Staphylococcus sp. and Pneumococcus sp. in middle ear
4	11	F	Nil	60 (25)	—	—	—	E. coli and Staphylococcus sp. in lung
5	17	F	Pleural effusion	172 (30)	—	—	—	No growth lung and middle ear
6	18	F	Pneumonia	140 (30)	4.8	18	Culture before death. No growth	—
7	20	F	Nil	160 (30)	—	—	Klebsiella sp. and E. coli	Lung Klebsiella sp. and Enterobacter sp.
8	22	M	Gastroenteritis	61 (33)	2.4	16	Pneumococcus and Pseudomonas sp.	Pneumococcus in middle ear and right lung
9	33	F	Gastroenteritis	140 (37)	—	—	Klebsiella sp. and Citrobacter sp.	Lung, S. pyogenes. Brain, E. coli
10	54	M	Nil	445 (47)	2.5	38	S. pyogenes, α -haemolytic streptococcus. Clostridium welchii	No growth

Figures in brackets show mean normal spleen weight for age.¹⁰

injections of benzathine penicillin, blood cultures were sterile. The blood cultures grew *Klebsiella* sp. and *E. coli* in one patient, pneumococcus and *Pseudomonas* sp. in another, *Klebsiella* sp. and *Citrobacter* sp. in the third, and in the fourth patient *S. pyogenes*, an α -haemolytic streptococcus, and *Clostridium welchii*.

Hypersplenism. There was a close relationship between episodes of ASS and the subsequent development of hypersplenism which we have defined as a persistent reduction in the steady state haemoglobin by at least 2 g/dl, reduced platelet counts with raised reticulocyte counts, in association with chronic splenic enlargement. It occurred in 17 (33%) of 52 patients with a history of ASS compared with 7 (4%) of 164 patients without such a history ($P < 0.001$). Hypersplenism was immediately preceded by an episode of ASS in 10 patients and was apparent between 3 and 24 months after an episode of ASS in the other 7 patients. Of the 17 patients with hypersplenism, spontaneous resolution occurred in three at ages 11, 30, and 36 months, splenectomy was performed in seven at 20, 21, 29, 35, 54, 56, and 57 months, and hypersplenism persists in four patients at ages 30, 36, 71, 79 months. Three children with hypersplenism died, two with further episodes of ASS, and one with pneumococcal septicaemia. As might be expected, episodes of ASS superimposed on hypersplenism carried a poor prognosis, death occurring in both episodes documented in the present study (Cases 9 and 10).

Outcome. The outcome of episodes of ASS indicated

a 12% mortality in the first episode. Recurrent episodes were common, 14 patients experiencing two episodes and 5 patients three episodes with mortality rates of 21% and 20% respectively (Fig. 2). Of the 4 children surviving three episodes of ASS, 3 have had palpable spleens for at least one year at ages 55, 62, and 66 months, and 1 child of 21 months has been a persistent defaulter. Mean interval between episodes was 6 months (range 2–17) and no difference in interval was apparent in the 4 recurrent cases with a fatal outcome. The possible prognostic value of mild episodes of ASS was illustrated by the case of a 4½-year-old child, admitted to hospital with a 6-hour history of severe back pain, who was found to be in shock with a greatly enlarged spleen palpable to the right iliac fossa. The Hb was 2.5 g/dl and reticulocytes 38%, and he died before transfusion

Fig. 2 Flow chart showing outcome in cases of acute splenic sequestration.

Fig. 3 Haematological and clinical events in a child who died at 54 months in his third episode of acute splenic sequestration. Arrows show episodes of acute splenic sequestration.

could be instituted. This child had been regularly followed since birth and subsequent review of his haematological and clinical data showed two previous episodes of ASS (Fig. 3). The haemoglobin level had fallen by 4.7 g/dl in the first and by 3.9 g/dl in the second, yet during the first episode he had been totally asymptomatic and during the second he had had a simple upper respiratory tract infection.

Discussion

Acute splenic sequestration in SS disease has not been clearly defined but clinical reports have generally included signs of peripheral circulatory failure in addition to acute splenic enlargement and evidence of red cell trapping within the spleen. The present report suggests that this definition be expanded to include episodes without evidence of peripheral circulatory failure, since such episodes may have prodromal significance in both 'classical' attacks of ASS and in the development of hypersplenism. Having arbitrarily defined minor episodes by a haemoglobin fall of at least 2 g/dl, it would have been instructive to differentiate minor episodes from 'classical' attacks, and compare the prevalence of both entities. However it has not been possible to differentiate with clarity the 'classical' from minor episodes, except in terms of peripheral circulatory shock. The clinical effects of the episode did not correlate well with the degree of fall in haemoglobin concentration, but was more closely related to the speed of fall and the percentage fall from steady state levels.

It might be argued that expanding the definition to include all episodes associated with haemoglobin

falls of at least 2 g/dl will have included many mild and clinically insignificant events and will have detracted from the clinical usefulness of the definition. However, the high incidence of recurrence and the frequent development of hypersplenism suggest that the minor episodes are an indication for close supervision of these children.

Classical attacks of acute splenic sequestration constitute one of the most common causes of death among young children with SS disease in Jamaica.¹ Of 25 deaths in the cohort study so far, the major cause has been acute splenic sequestration in 10 (40%) and 6 of these deaths have been reported in an earlier paper.¹ This fatal complication is probably more common elsewhere than is recognised since death may precede diagnosis of the underlying haemoglobinopathy, as illustrated by a report in which 4 out of 10 patients dying from 'anaemic crises' had not been known to be sicklers before their fatal illness.⁴ In a review of 19 childhood deaths from SS disease in Chicago, one-third died from cerebral or cardiovascular complications whereas only 20% died from ASS.⁵ Such observations are difficult to evaluate in samples ascertained by clinical presentation and biased by early mortality. Valid comparisons of the prevalence and mortality from ASS can only be obtained in prospective studies of children diagnosed at birth. Using our definition of ASS, 52 out of our 216 SS children have experienced an episode of splenic sequestration. Fourteen (30%) of the 46 survivors of the first episode experienced at least one recurrence and a fatal outcome occurred in 14% of attacks and in 19% of the patients (Fig. 2). Recognition of minor episodes may allow more prompt treatment as well as serve to identify some patients at risk from 'classical' attacks. Minor episodes may also contribute to the understanding of hypersplenism in SS disease. One-third of the children with episodes of ASS developed hypersplenism and in more than half of them hypersplenism was immediately preceded by an episode of ASS. Furthermore the possibility that all cases of hypersplenism were preceded by an episode of ASS cannot be excluded since events occurring between clinic visits would not be observed.

Until factors precipitating episodes of ASS can be identified and avoided, the treatment of ASS is limited to the early detection and management of the acute episode and to prophylaxis against further attacks in patients surviving the first episode. Such prophylaxis is currently based on chronic transfusion or splenectomy. Since episodes of ASS become progressively rarer after age 5 years, chronic transfusion therapy has been advocated to protect susceptible children from ASS until the age at which

splenic atrophy normally occurs. However, the effect of chronic transfusion on splenic pathology has not been documented, and since atrophy is less likely with the reduction in circulating sickled cells achieved by transfusion, it is possible that episodes of ASS would simply occur at a later age after stopping transfusion therapy.

Chronic transfusion has also been suggested as a means of retaining any persisting splenic immune function. In this context, the concept of functional asplenia evolved by Pearson and colleagues implies that few children with SS disease in this age group retain normal splenic function as assessed by colloid spleen scans.^{6,7} Pitted red cell counts appear to correlate with evidence of splenic function on colloid scans,⁸ and serial observations of pitted red cell counts indicate that these rise to asplenic levels after an episode of ASS and rarely, if ever, return to low values compatible with normal splenic pitting function.⁹ It seems likely therefore that the spleen makes little contribution to overall immunological function once an episode of ASS has occurred.

Provision of a regular supply of compatible blood, increasing difficulty in adequate matching, transfusion reactions from white cell and platelet antibodies, and risk of hepatitis are problems with chronic transfusion. There is also uncertainty about the most appropriate level of haemoglobin A to maintain and the duration of the overall programme. In addition, the development of iron overload may be a complication of chronic transfusions.

Surgical removal of the spleen undoubtedly abolishes the risk of further episodes of ASS but reluctance to perform splenectomy has been based on the avoidance of an 'unnecessary' operation in a condition likely to proceed to spontaneous splenic atrophy, the desire to retain any residual splenic immune function, and on an assessment of surgical and anaesthetic risks. Elective splenectomy however with modern anaesthetic and surgical techniques appears to be a safe and fairly minor procedure and it would appear therefore that the arguments against splenectomy in these children are less convincing.

The role of bacterial infection in the pathogenesis of ASS is difficult to define on the evidence presented here. The low yield from the 23 blood cultures suggests that bacterial infection is not an important precipitant of ASS, although viral infection, for which we have as yet no evidence, may be more significant. The post-mortem blood culture is difficult to interpret, since in 3 of these the cardiac clot culture was taken several hours after death and may

therefore reflect post-mortem bacterial colonisation of the blood. In Cases 1 and 8 however, the blood cultures were taken within minutes of death. In any event children with ASS who have symptoms and signs of infection, however trivial, would normally receive treatment with antibiotics.

Chronic transfusion therapy and splenectomy are applicable only to patients surviving the first episode of ASS. To avoid the mortality in the first episode, attention must be directed to a search for prognostic haematological or clinical factors which determine the first episode. In the meantime we would suggest that any child with a history of one classical episode of ASS, or a minor episode followed by the development of sustained hypersplenism, should undergo splenectomy. In addition all children who have had one episode of ASS, according to our definition, should be very closely observed until splenic involution occurs.

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Received 8 July 1980