Hospital Topics

Admissions to hospital of children with sickle-cell anaemia: a study in south London

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Abstract

Admissions to hospital of 171 children with sickle-cell anaemia, genotype Hb SS, were reviewed over a 20-year period. Altogether 887 admissions occurred in 797 patient-years. The commonest cause of admission was painful vaso-occlusive crisis. Appreciable morbidity also resulted from pulmonary disease, infection, and anaemic episodes. The complications resulting in the most severe illness were acute splenic sequestration, pneumococcal meningitis, and some episodes of erythroid hypoplasia resulting in very low haemoglobin concentrations. Most deaths occurred in children aged under 5. Mortality and morbidity could be reduced by measures including prophylaxis of pneumococcal infections and more active treatment of seemingly minor illness in children with sickle-cell anaemia.

Introduction

In Britain the number of children with sickle-cell anaemia has gradually increased over the past 20 years. This condition is most likely to be encountered here in those of Caribbean or African descent, and in such children we have found a carrier rate of 8·7% and 17·6% respectively. So far there has been no account of the pattern of morbidity of sickle-cell anaemia in children in Britain.

Methods

We reviewed the hospital admission records of children aged 1 month to 17 years who attended the Belgrave Children's and King's College Hospitals between 1 January 1960 and 31 December 1979 to define the most common and the most serious complications. All patients were homozygous for haemoglobin S (Hb S) so far as could be ascertained, complete family studies not always being available to differentiate any case of Hb S β^0-thalassaemia. Applying known frequency rates for a sample of the size studied, 13 cases of Hb S β-thalassaemia would be expected. Nine cases of Hb S β^+-thalassaemia were identified in patients not included in this study.

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Results

During the 20 years reviewed, 171 children (98 boys, 73 girls) with Hb SS were seen, representing 797 patient-years. Eighty per cent of the children were seen in the second decade of the period (fig 1). Follow-up ranged from 1 month to 17·8 years (mean 4·7 years). Eighty-nine patients were of West African and 82 of Caribbean descent. All patients received daily folate supplements and, since 1971, penicillin prophylaxis against pneumococcal infection.

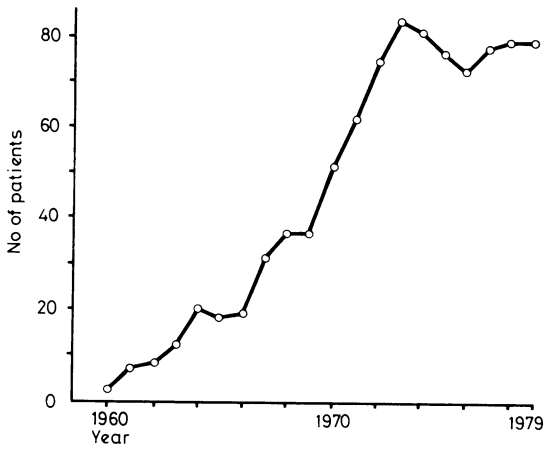

Fig 1—Number of children attending clinic at King's group for any given year 1960-79 with Hb SS genotype.

There were 887 admissions in all (table I). The number of admissions per patient varied widely; 17 patients aged from 1 month to 17 years (median 18 months) had no admissions, while a boy of 14 had 53. In the 113 patients whose complete medical history was known the mean number of admissions per year of age ranged from 0 to 3·79 (median 0·53).

TABLE I—*Causes of admission in children with sickle-cell anaemia*

Diagnosis	No of admissions	% of admissions
Painful vaso-occlusive crisis	313	35·3
Planned transfusion	213	24·0
Pulmonary disease	74	8·3
Infection	68	7·7
Anaemic episodes	52	5·9
Hepatobiliary complications	9	1
Central nervous system complications	7	0·8
Other complications of SCA	47	5·3
Surgery:		
SCA-related	6	0·7
SCA-unrelated	26	2·9
Miscellaneous causes unrelated to SCA	57	6·4
Mistakenly diagnosed as anaemic episode	15	1·7
Total	887	

PAINFUL CRISES

Painful crises caused 313 (35·3%) admissions and occurred at all ages (fig 2), the youngest with skeletal pain being 7 months old. Two patients with abdominal pain developed ileus. Infection, usually a viral upper respiratory infection, preceded or was noted at the time of admission in 31% of painful crises including dactylitis ("hand-foot syndrome"), which occurred on 15 occasions in 11 children aged 4 years or under (table II). Other stated precipitating factors of pain crises were trauma (5), air travel (4) and physical exertion (3).

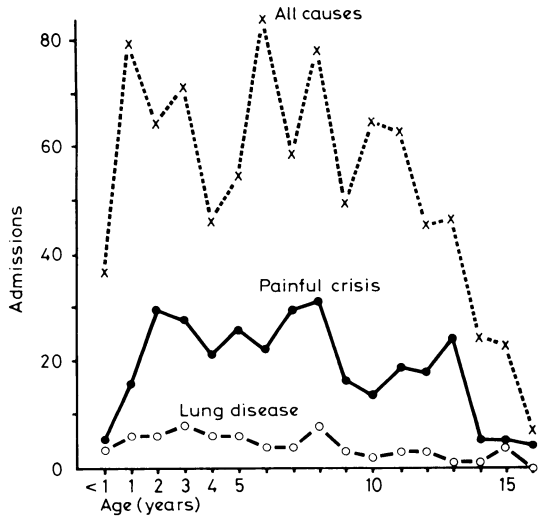

Fig 2—Total admissions and those admissions due to painful crises and pulmonary disease according to age.

TABLE II—*Factors precipitating painful crises*

Site	No of crises	Concurrent infection	Preceding infection	Other precipitating factors
Skeletal	171	39	16	11
Abdominal	83	24	3	1
Skeletal + abdominal	59	11	5	0
	313	74	24	12

PLANNED REGULAR TRANSFUSIONS

Planned regular transfusions (table III) accounted for 213 (24%) admissions, the aim being to keep the haemoglobin concentration above 11 g/dl, thus suppressing marrow production of Hb S-containing cells. Sixty-three transfusions were for medical reasons such as chronic bone disease of the spine or femoral head, hemiparesis, pulmonary tuberculosis, chronic ill-health, and impaired growth; thirty-eight preceded surgery; and 60 were given as prophylaxis against crises during air travel. An additional five children with persistent pronounced splenomegaly associated with severe anaemia received 52 transfusions over several months before splenectomy.

PULMONARY INVOLVEMENT

Pulmonary involvement confirmed by radiography or scan, or both, led to 74 (8·3%) admissions in children aged 9 months to 15 years (fig 2). It is difficult to differentiate between so-called infarction and infection in sickle-cell anaemia.[1]

Pneumococcus was cultured from the throat swab in three cases, and *Haemophilus influenzae* from the sputum in one. Two children had pulmonary tuberculosis. One child had a pulmonary abscess, but no organism was isolated. In the other 67 episodes no pathogen was found, but in five there was coryza and in one an axillary abscess. Other complications of sickle-cell anaemia often accompanied lung disease: skeletal pain was present in 17, epistaxis in two, and in one case with skeletal pain, fat was found in the sputum.

TABLE III—*Planned transfusions*

Indication	No of transfusions	No of children	Ages
Medical	63	11	1-14 yr (median 10 yr)
Presplenectomy	52	5	6-11 yr (median 8 yr)
Before surgery (excluding splenectomy)	38	12	7 m-15 yr (median 9 yr)
Before travel	60	30	6 m-13 yr (median 6 yr)
	213	58	

INFECTION

Infection alone accounted for 68 (7·7%) admissions, 51 of which were judged to be viral on clinical grounds. There were 39 respiratory infections, mainly affecting the upper respiratory tract, without lung consolidation on radiography. The remaining infections were gastroenteritis, herpetic stomatitis, and infectious mononucleosis. Excluding those with lung consolidation, there were 10 proved bacterial infections. Five children aged four months to 10 years had pneumococcal meningitis. Spinal osteomyelitis due to *Salmonella typhimurium* occurred in a 10-year-old girl, and a six-year-old boy had septic arthritis due to *H influenzae*.

Other proved bacterial infections were pertussis (1), *Escherichia coli* urinary infection (1), and streptococcal tonsillitis (1). In five cases of apparent bacterial infection no organism was isolated (meningitis where penicillin had already been given (1), osteomyelitis diagnosed on clinical and radiological grounds (1), and tonsillitis (3)). Two children recently arrived from Nigeria presented with *Plasmodium falciparum* malaria.

ANAEMIC EPISODES

Anaemic episodes, defined as a drop in haemoglobin from the known steady-state concentration, were considered an immediate indication for admission because of the danger of hypoplastic or sequestration crises. Of 67 such admissions, as indicated by manual haemoglobin screening, 15 proved unnecessary on repeat measurement.

Splenic sequestration with a rapid fall of haemoglobin to concentrations of 2·8-4·9 g/dl accompanied by sudden enlargement of the spleen sometimes with hepatomegaly, occurred six times in six children aged 8 months to 8 years. Five of these patients were under 21 months old. Two episodes were accompanied by a viral upper respiratory infection.

Erythroid hypoplasia was the presumed cause of anaemic episodes in 11 children aged 6 to 11 years. Seven had haemoglobin concentrations of 3-5 g/dl (mean 3·7 g/dl), with reticulocyte counts of less than 1%; marrow examination confirmed hypoplasia in one. Four had haemoglobin concentrations of 2·5-5·2 g/dl with uncharacteristically low reticulocyte counts (2·4-5·1% as compared with steady-state concentrations of 14-16%). The moderately raised reticulocyte count in these patients was probably an indication of recovering erythroid hypoplasia. Marrow aspiration was performed in one and showed erythroid hyperplasia, presumably indicating such recovery. Three hypoplastic episodes were associated with infection: viral upper respiratory infection (2) and infectious mononucleosis (1).

There were seven admissions for anaemia due to increased haemolysis as evidenced by an increase in reticulocytosis to double the steady-state concentration or much higher. Two of these episodes occurred with viral upper respiratory infection and one with persistent lung consolidation.

On 28 other occasions there was a drop in haemoglobin to concentrations of 2·9-6·2 g/dl (mean 5·2 g/dl) with no clear evidence of hypoplasia or increased haemolysis. Seven of these episodes occurred with an infection, and three after painful crises. Possibly these episodes represented recovering hypoplasia or mild degrees of increased haemolysis. Reticulocyte counts were not available in seven cases.

HEPATOBILIARY COMPLICATIONS

Hepatobiliary complications caused nine admissions. Three children had right upper quadrant abdominal pain, one during a viral upper respiratory infection and another with a skeletal vaso-occlusive crisis. There were two episodes of biliary colic. Another two children

presented with enlarged tender livers six days and three weeks after transfusion; serology for hepatitis B was performed in one and proved negative. In all these episodes liver enzymes were severely abnormal; abnormal liver enzymes were also found in two children admitted with upper respiratory symptoms.

CENTRAL NERVOUS SYSTEM

Central nervous system complications precipitated seven admissions. Three episodes of hemiparesis occurred in two patients at 5, 6, and 10 years of age, one after an upper respiratory infection and another joint pain. A series of convulsions occurred in an 8 year old after a minor head injury and a 6 year old had an isolated convulsion with fever due to tonsillitis. Another child went into coma for 24 hours after a convulsion and then recovered completely. An 18-month-old child died with cerebral oedema due to intracranial sickling during a febrile illness.

OTHER COMPLICATIONS

There were several admissions for miscellaneous complications such as vague ill-health (7), epistaxis (6), chronic bone disease (6), nephrotic syndrome (1), haematuria (1), and eye pain accompanied by loss of vision lasting 10 minutes (1).

Four children were admitted on five occasions with haemoglobinuria six to 13 days after transfusion with rhesus-positive blood. Anti-E was detected in two of these children, one of whom was subsequently found to have a genotype of R_1R_0 (CDe/cDe); the genotype of the other child was not obtained. The remaining two children had rhesus genotypes R_0r (cDe/cde) and R_2R_2 (cDE/cDE) but were not examined for antibodies.

A fifth child, with no history of recent transfusion, was admitted when found as an outpatient to have haemoglobinuria, but results of repeat investigations were normal.

Nineteen other admissions were for assessment and investigation—for instance, of persistent splenomegaly, convulsions, etc. No leg ulcers were seen in our patients.

SURGERY

Six children underwent surgery necessitated by their sickle-cell anaemia. Splenectomy, in one case along with cholecystectomy for cholelithiasis, was performed in five children because of increasing anaemia associated with persistent and progressive splenic enlargement. The sixth child had a lobectomy at 5 years of age because of bronchiectasis after repeated lung consolidation. An 11 year old had replacement of a mitral valve with mucinous degeneration, a condition not previously reported in sickle-cell anaemia.

Surgical procedures unconnected with sickle-cell anaemia were carried out under general anaesthesia on 25 occasions.

REMAINING ADMISSIONS

Four admissions occurred in three children with raised blood lead concentrations; one child had convulsions, another had Pappenheimer bodies and punctate basophilia on blood film, and the third had abdominal pain with a history of pica. The remaining 53 admissions were for conditions not directly related to sickle-cell anaemia, such as trauma, asthma, and social problems.

DEATHS

Three deaths occurred in our care. Two children aged 18 months and 4 years died within 12 hours of admission with probable infective illness. The third patient was the 11 year old mentioned above with mitral valve disease. Six other children died during the period studied but were not seen by us during their last illness (table IV).

Discussion

As a study of the complications of any disease, a retrospective review of hospital admissions has obvious limitations. It does indicate, however, the overall pattern of common or severe complications. In our population vaso-occlusive crisis was the most common complication (35·3%) as was found in African studies.[2 3] In many hospital-based studies of childhood sickle-cell anaemia in America lung disease was the most common reason for admission,[1 4–6] whereas this complication occurred in only 8·3% of our admissions. Such comparisons do not take into account differing admission policies.

Planned transfusions accounted for the second largest group of admissions (24%), and again this could be due to local attitudes to the role of transfusion when treating some complications of sickle-cell anaemia. In addition to the medical and surgical reasons indicated transfusions were given to 30 children before air travel. We advocate this precaution because we have seen four vaso-occlusive crises after flying.

Infection, mainly viral upper respiratory infection, was an important cause of morbidity, leading to 7·7% of admissions as well as being implicated in 31% of painful crises, many episodes of anaemia, and two of the six splenic sequestration crises.

The most life-threatening illnesses occurred in children with splenic sequestration, pneumococcal meningitis, and some with very low haemoglobin concentrations due to erythroid hypoplasia.

Splenic sequestration, where a rapid fall in haemoglobin occurs with sudden splenic (and sometimes hepatic) enlargement and hypovolaemic shock, is a potent cause of death in young children with sickle-cell anaemia.[7 8] Infection, often pneumococcal, has been implicated in some cases.[8 9] None of our six patients had pneumococcal infection. Erythroid hypoplasia was probably more common than it appeared, as apart from seven definite cases a further 32 were probably recovering from an episode by the time they were seen. A temporary fall in red cell production associated with infection is probably more common than is realised,[10] and its effect would be accentuated in patients with sickle-cell anaemia because of the short life span of their circulating red cells.[11]

TABLE IV—*Sickle-cell anaemia: deaths in children followed up at Belgrave Children's Hospital*

Case No	Age yr	Age m	Sex	Last illness	Place of death	Necropsy findings
1	1	6	M	Fever, diarrhoea, vomiting, convulsions	KG*	Cerebral oedema + coning due to widespread intracranial sickling
2	4	1	F	Fever, abdominal pain, diarrhoea	KG*	"Sickle-cell anaemia" (coroner's necropsy)
3	11		F	Lung consolidation, cardiac failure 12 months after replacement of mitral valve	KG*	Refused
4	3	11	F	Fever, leg pain, diarrhoea, vomiting, Hb 2·2 g/dl, *H influenzae* septicaemia	Other hospital	Not available
5	7		M	"Cerebral haemorrhage"	Other hospital	Not available
6	3	8	F	Vomiting, convulsions	Dead on arrival at hospital	Splenic sequestration
7		8	M	Cot death	At home	"Sickle-cell anaemia" (coroner's necropsy)
8		10	F	Sudden death	At home	Not available
9	2	2	F	Fever, vomiting, respiratory arrest	At child minder's house	Lungs: upper lobes oedematous. Slight pericardial effusion. Pale. "Acute SCA" (coroner's necropsy)

* King's Group of Hospitals.

Functional asplenia[12] and a deficiency in opsonisation[13 14] put children with sickle-cell anaemia at a greatly increased risk of pneumococcal infection, especially meningitis.[15 16] In some series pneumococcal meningitis has been noted to be more severe in children with this disease than in other children, often with a rapid onset, few clinical signs, and only mild changes in cerebrospinal fluid.[16-18]

In the five patients with proved pneumococcal meningitis in our series all had been unwell in some way for three or more days, and were noted to be ill, lethargic, or drowsy on admission, although two had no signs of meningeal irritation. White cell counts in the cerebrospinal fluid ranged from $0{\cdot}056\text{-}5{\cdot}4 \times 10^9/l$, with 60% or more neutrophils; cerebrospinal fluid protein and sugar abnormalities were not always present. Although all were severely ill, and one developed concurrent erythroid hypoplasia, none of these patients died. One remains retarded 10 years later, but the others have no long-term sequelae. It is important that three of these children were aged 15 months or younger (as was the additional patient with meningitis who had received penicillin before lumbar puncture), an age at which there is doubt about the efficacy of pneumococcal vaccine.[19 20] Although all but one of these children were known to have sickle-cell anaemia, for various reasons none was receiving penicillin prophylaxis at the time. We have not seen pneumococcal infection in any child taking regular penicillin prophylaxis.

Haemoglobinuria after transfusion emphasises the importance of genotyping patients with sickle-cell anaemia before transfusion. In our experience about half of these children carry the genotype R_0 (cDe) and if given rhesus (D)-positive blood may develop anti-C or anti-E.

Deaths have been mentioned, though not all occurred during an admission. They illustrate three points: five out of nine were under 5 years of age, most were sudden (four occurring outside hospital), and necropsies, including coroner's necropsies, were not always helpful in determining the exact cause of death.

The reduction of morbidity and mortality in sickle-cell anaemia demands careful follow-up of children in the early years of life and prompt attention in the first 24 hours of admission, even with seemingly minor illness. Prophylaxis against pneumococcal infection by long-term penicillin as well as pneumococcal vaccine is indicated, especially as some deaths from pneumococcal infection occur before the age at which the vaccine is fully effective.[7 8]

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A woman was given stilboestrol to suppress lactation when she was eight weeks pregnant. She probably received about 120 mg in 12 days. The girl who was born is now 12 years old and the mother is worried by reports she has read about an increased risk of cancer in the reproductive tract in girls whose mothers were given stilboestrol during pregnancy. What are the risks?

It has been estimated that between 1940 and 1971 stilboestrol was given to about 7500 British women[1] and over a million American women to treat or "prevent" threatened abortion. A female fetus exposed to stilboestrol between weeks eight and 22 of pregnancy has an 80% chance of being born with benign vaginal epithelial changes[2] —which, however, appear to regress with age and are found in only 34% of the 3000 at-risk women now being followed up in the United States. It is not known if these changes are premalignant but the risk of clear-cell adenocarcinoma of the vagina is about 0·14-1·14 per stilboestrol-exposed girls. In the United States over 200 cases of stilboestrol-associated vaginal cancer have occurred and one case has been reported in Britain.[1] Possibly up to 10 more cases are awaiting discovery here. The symptoms of vaginal cancer are abnormal bleeding or blood-stained discharge and young women with such symptoms should be examined carefully. Cases can be diagnosed early at an asymptomatic stage, and at-risk women should have six-monthly pelvic examination, cervical smear, and colposcopy, with biopsy of suspicious areas. Cytology of vaginal aspirate and iodine staining have also been recommended.[1] The peak incidence of vaginal carcinoma is at age 19, but the duration of follow-up required is not yet known. A recent report[3] also suggests that these patients have a higher risk of premature labour (but not of other pregnancy complications) and so close antenatal supervision is indicated. On a more optimistic note there is evidence that some at least of these risks are dose-related, and since this particular patient had a relatively brief exposure to stilboestrol, she may be at less risk.

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Does vasectomy have any effect on chronic prostatitis?

There is no available evidence that vasectomy undertaken for chronic prostatitis favourably influences the condition itself. Vasectomy may be effective, however, in preventing recurrent epididymo-orchitis in those patients with chronic bacterial prostatitis in whom this has been a problem. There is, however, a report that vasectomy undertaken in the presence of chronic bacterial prostatitis may occasionally cause epididymitis or inflammation and abscess formation at the site of vasectomy.[1] This suggests that there may be infection in the vasa in some cases of bacterial prostatitis and that interruption of the drainage can precipitate acute local infection. This possible occasional complication should not detract from the use of vasectomy in preventing epididymo-orchitis in patients with chronic lower urinary tract infection including prostatitis.

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