Significance of fever in Jamaican patients with homozygous sickle cell disease

K J J Wierenga, I R Hambleton, R M Wilson, H Alexander, B E Serjeant, G R Serjeant

Abstract

Objective—To investigate the cause and outcome of high fever in Jamaican children with homozygous sickle cell disease.
Design—Retrospective review of febrile episodes in a three year period (1 September 1993 to 31 August 1996).
Setting—Sickle cell clinic, an outpatient clinic in Kingston run by the Medical Research Council Laboratories (Jamaica).
Patients—Patients with homozygous sickle cell disease under 17 years of age presenting with an axillary temperature ⩾ 39.0°C (102.4°F).
Main outcome measures—Diagnosis, death.
Results—There were 165 events in 144 patients (66 (45.8%) boys) with a median age of 6.1 years. Bacteraemia was found in 10 (6.1%) events (three *Streptococcus pneumoniae*, two *Haemophilus influenzae* type b, two *Salmonella* sp, one *Escherichia coli*, one *Enterobacter* sp, and one *Acinetobacter* sp), and urinary tract infections in four (2.4%). All cultures of cerebrospinal fluid were sterile. Acute chest syndrome occurred in 36 (21.8%) events. A painful crisis was associated with 45 (27.3%) events and was the only pathology identified in 20 events (12.1%). Hospital admission was necessary in 66 cases including all those with bacteraemia and 31 with acute chest syndrome. There were two deaths: a 5 year old boy with septic shock associated with *H influenzae* septicaemia, and a 3 year old boy with the acute chest syndrome.
Conclusions—Painful crisis and acute chest syndrome were the most common complications associated with high fever, but other important associated features included bacteraemia and urinary tract infection. Enteric Gram negative organisms accounted for 50% of positive blood cultures.
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High fever is a cause of concern in children with homozygous sickle cell disease. The well known susceptibility to blood borne infections results in a high awareness of septicaemia although its frequency as a cause of high fever is unknown. This study seeks to explore the clinical features and outcomes associated with high fever (axillary temperature ⩾ 39.0°C or 102.4°F) in a three year retrospective study of Jamaican children attending the sickle cell clinic.

Patients and methods

PATIENTS

The patients attended the Sickle Cell Clinic of the University Hospital of the West Indies, Kingston, Jamaica, run by the Medical Research Council Laboratories (Jamaica). The study was restricted to patients with homozygous sickle cell disease aged under 17 years presenting with axillary temperature ⩾ 39.0°C in the three year period 1 September 1993 to 31 August 1996. Almost all cases were symptomatically referred to the clinic. The diagnosis of homozygous sickle cell disease was based on standard criteria.[1]

METHODS

The investigations, outcome, and probable diagnoses were obtained by retrospective review of notes from the Sickle Cell Clinic or hospitals providing inpatient care (University Hospital of the West Indies and Bustamante Hospital for Children). The Sickle Cell Clinic provides a free service, is open from 8 30 am until 4 30 pm on weekdays, and is responsible for most of the referred admissions. Patients are encouraged to attend at any time when sick, and the clinic is the preferred health care provider for almost all patients, so the clinic notes are likely to document most serious clinical events. Standard care includes monthly injections of intramuscular benzathine penicillin from 4 months (or age at diagnosis if later) until 4 years when the last penicillin injection is given with the first and only dose of pneumococcal vaccine. Immunisation against *Haemophilus influenza* type b was not routinely practised during the study period.

DEFINITIONS

Febrile presentations were arbitrarily considered the same event when separated by < 10 days. Events without definite diagnosis (culture negative fever without focus, non-specific viral illness) were arbitrarily considered to be caused by viruses or atypical organisms. Acute chest syndrome was defined as a febrile episode with radiological evidence of new pulmonary infiltrate. Bone pain crisis was defined as bone pain (not affecting ribs and sternum) of sufficient severity to require clinic attendance and analgesia (severe requiring narcotic analgesia, mild requiring non-narcotic analgesia), and as chest pain confined to the sternum and/or ribs. Avascular necrosis was defined if pain was associated with swelling of the affected areas.

Sickle Cell Unit, formerly MRC Laboratories (Jamaica), University of the West Indies, Mona, Kingston, Jamaica, West Indies
K J J Wierenga
I R Hambleton
R M Wilson
H Alexander
B E Serjeant
G R Serjeant

Correspondence to:
Dr Wierenga, Sickle Cell Trust, 14 Milverton Crescent, Kingston 6, Jamaica, West Indies
kjwier@uwimona.edu.jm

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Table 1 Distribution of clinical diagnoses

Clinical group	Diagnosis	Number	Total
Systemic bacterial	Bacteraemia	10	
	Osteomyelitis	1	11
Local bacterial	Acute tonsillitis	28	
	Acute otitis media	9	
	Urinary tract infection	4	
	Cervical lymphadenitis	3	
	Abscess	1	
	Acute bacterial conjunctivitis	1	
	Proven bacterial enteritis	1	47
Presumed viral/atypical	Culture negative fever without focus	33	
	Upper respiratory tract infection	27	
	Human parvovirus B19 infection	3	
	Presumed viral enteritis	3	
	Asthmatic attack	2	
	Dengue haemorrhagic fever	1	
	Varicella zoster infection	1	
	Mumps infection	1	
	Viral meningitis	1	72
Acute chest syndrome		36	36
Painful crisis	Mild bony pain	15	
	Severe bony pain	16	
	Rib/sternal pain	9	
	Avascular necrosis	3	
	Abdominal pain	4	47
Total diagnoses			213

Abdominal pain crisis was defined as abdominal pain usually associated with distension and reduction/absence of bowel sounds, resolving spontaneously, and without the features of an acute surgical abdomen. More than one diagnosis was allowed and the final diagnoses were classified into five groups (table 1).

HAEMATOLOGY

Haematological indices were measured electronically (Coulter S plus 4; MaxM, Coulter Electronics, Miami, Florida, USA). Haematological values during the acute event were compared with steady state levels, defined as the average values during well patient visits in patients aged over 5 years, or, if unavailable, a routine blood test closest in date to the acute illness. White blood cell counts on presentation with fever were corrected for the presence of nucleated red cells by examination of peripheral blood films.

STATISTICAL METHODS

Multiple diagnoses for the same event and multiple events for the same patient define two levels of clustering. There were 213 diagnoses from 165 events, among 144 patients. Standard statistical methodology assumes complete independence and underestimates variance in these situations.[2] The effect of clustering is adjusted for in all modelling by only assuming independence between clusters.

Sex composition was examined using a binomial exact test. Age of patient and body temperature on presentation were positively skewed and were summarised as median, median absolute deviation (MAD), and range.[3] Among 165 events, the dependence of hospital admission (yes/no) on age, sex, and temperature was assessed using logistic regression. Among patients admitted to hospital, the length of stay (in days) was positively skewed and was log transformed toward Normality. The dependence of this transformed variable on the same risk factors was assessed using Normal regression. Haematological differences between an acute event and steady state were examined using paired *t* tests. Scheffé's correction for multiple comparisons requires a nominal p value of 0.013 for significance at the 5% level. Analyses were performed using Stata 6 statistical software.[4]

Results

PATIENTS

There were 144 patients (45.8% boys), with no significant sex difference (p = 0.36).

EVENTS

There were 165 febrile events (48.5% boys). Age at presentation was marginally younger among boys (median 5.2, MAD 3.1, range 0.6–16.8 years) than girls (median 7.1, MAD 3.3, range 0.9–17.0 years) (p = 0.05). Single events occurred in 125 (86.8%) patients, who accounted for 75.8% of all events, two events occurred in 17 (11.8%) patients (20.6% events), and three events in two (1.4%) patients (3.6% events).

DIAGNOSES

There were 213 diagnoses (table 1) with a single diagnosis in 124 (75.2%) events, two diagnoses in 34 (20.6%) events, and three diagnoses in seven (4.2%) events.

FEVER

Median axillary temperature on presentation was 39.3°C (MAD 0.3, range 39.0–40.8) and did not vary with sex (*t* = 0.5, p = 0.60) or age (*t* = −1.0, p = 0.30).

INFECTIONS

Blood culture, performed in 144 events, yielded bacteria in 10 events (6%) in nine patients (table 2). Of the three events with *Streptococcus pneumoniae*, a 4.7 year old girl presented to the clinic for the first time with acute septicaemia having not received any prophylaxis, but the other two, aged 5.2 and 14.7 years, had received the pneumococcal vaccine at age 4 years. The pneumococcal serotype in these cases was not available. Two events in children aged 2.7 and 4.4 years were caused by *H influenzae* type b infection, and neither had received Hib vaccine. The remaining five positive blood cultures yielded enteric Gram negative bacteria.

Cultures of cerebrospinal fluid in 17 events were sterile, although one patient with cerebrospinal fluid neutrophilia may have had viral meningitis or partially treated bacterial meningitis. Urine cultures in 27 were positive in four events (*Escherichia coli*, two; *Enterobacter* sp, one; *Klebsiella pneumoniae*, one).

ACUTE CHEST SYNDROME

Chest radiographs, performed in 58 (35.2%) events, were abnormal in 36 (21.8%).

PAINFUL CRISES

Painful crisis was associated with 45 (27.3%) events and was the only pathology in 20

Table 2 Events associated with positive blood cultures

Event	Age/sex (years)	Temp. (°C)	Status	Hb (g/dl)	WBC (× 10⁹/l)	Organism	Other diagnoses
1	2.7M	40.1	Alive	7.9	9.5	*Haemophilus influenzae*	—
2	2.9M	40.3	Alive	10.1	15.0	*Enterobacter* spp	Urinary tract infection (*E coli*)
3	3.3M	40.0	Alive	7.0	22.0	*Acinetobacter* spp.	—
4	5.2M	39.3	Alive	6.7	62.1	*Streptococcus pneumoniae*	Acute chest syndrome
5	4.4M	39.1	Died	6.3	8.7	*Haemophilus influenzae*	—
6	4.7F	39.4	Alive	10.6	32.0	*Streptococcus pneumoniae*	Acute chest syndrome
7	9.5M	39.2	Alive	7.3	17.8	*Salmonella* spp.	*Salmonella* enteritis
8	9.6M	39.5	Alive	8.1	25.7	*Salmonella* spp.	*Salmonella* osteomyelitis Urinary tract infection (*Enterobacter*)
9	14.7F	39.5	Alive	7.5	19.2	*Streptococcus pneumoniae*	—
10	17.0F	40.0	Alive	6.1	24.5	*Escherichia coli*	Urinary tract infection (*E coli*)

NB. Events 3 and 4 occurred in the same child.
WBC, White blood count; Hb, haemoglobin.

(12.1%) events (severe bone pain in 10, mild bone pain in six, abdominal painful crisis in one, avascular necrosis in three). In the other 25 events, pain was associated with other clinical features, which included acute chest syndrome in 13 (six events with chest pain) and bacteraemia in three.

HAEMATOLOGY

At febrile presentation, total haemoglobin and reticulocyte percentage did not differ from steady state values (haemoglobin 7.2 *v* 7.4 g/dl ($t = 2.2$, p = 0.03); percentage reticulocytes 14.0 *v* 14.2 ($t = 0.2$, p = 0.82)). White cell counts were significantly higher (23 900 *v* 17 000/mm³; $t = 5.8$, p<0.001) and platelet counts significantly lower (414 000 *v* 485 000/mm³; $t = -4.1$, p<0.001) than steady state values in the same children.

OUTCOME

Hospital admission was necessary in 66 (40%) events, on the day of presentation in 58 events, and one to five days later in eight. The probability of admission was similar across sex ($t = 0.2$, p = 0.88) and age ($t = -1.6$, p = 0.11), but increased with temperature ($t = 3.8$, p<0.001). Admission occurred in all 10 events with invasive bacterial disease, in 31 (86%) events with acute chest syndrome, in 26% of local bacterial infections, and in 28% of those with presumed/proven viral/atypical infections. The median stay was eight days (MAD = three days, range 3–45 days). Length of hospital stay was not influenced by sex ($t = 1.4$, p = 0.16), age ($t = 1.3$, p = 0.18), or temperature on admission ($t = 0.9$, p = 0.38). Two patients died, a 5 year old boy with septic shock following *H influenzae* type b bacteraemia, and a 3 year old boy with asystole during ventilation for respiratory failure secondary to acute chest syndrome.

Discussion

Most patients with homozygous sickle cell disease presenting with fever ⩾ 39.0°C had no evidence of bacterial infection, and the fever was assumed to be attributable to viral or atypical organisms. However, these events remain clinically important because more serious pathology such as acute chest syndrome and bacteraemia cannot usually initially be excluded. Comparison of our experience with other studies on the cause of fever in children

with sickle cell disease are complicated by the inclusion of other genotypes,[5–9] failure to define the age cut off for children,[8 9] and variable definitions of fever.[5 7 9]

The most common specific pathology was the painful crisis, which occurred in 27.3% of events and was the only significant clinical finding in 20 (12.1%) events. The underlying pathological process in bone pain crisis is generally believed to be avascular necrosis of bone marrow,[10] and it is possible that the ensuing inflammatory response is associated with increased body temperature. Fever was common in a prospective study of the painful crisis,[11] but possible infectious illness was not routinely excluded. Until such data are available, it will remain unclear whether painful crises per se are a cause of high fever.

The acute chest syndrome was the second most common association, occurring in 21.8% of cases, consistent with the observations of Kravis *et al*,[6] and accounted for 47% of admissions and contributed to one death. Acute chest syndrome was associated with bone pain in 36% of these events, four with rib or sternal pain, seven with bone pain elsewhere, and affecting both sites in two patients. The prognostic significance of rib or sternal pain in the development of acute chest syndrome has been reported[12] and believed to result from splinting with secondary hypoventilation and pulmonary collapse due to pleuritic pain. Only two cases of acute chest syndrome had positive blood cultures, which is consistent with the low incidence of bacterial isolations in this complication, even in children.[13] Recent observations that acute chest syndrome may be grossly underdiagnosed by doctors[14] imply that it is likely to be more common than our data suggest and that chest radiography should be performed routinely in the management of the febrile child with sickle cell disease.

Bacteraemia was identified in 10 (6.1%) events. Of the three isolations of *S pneumoniae*, two patients, aged 6.7 and 10.6 years, were beyond the age for penicillin prophylaxis but had received the pneumococcal vaccine, and the third, aged 4.7 years, presented with sickle cell disease for the first time with pneumococcal bacteraemia. *Salmonella* species accounted for two events, and the increasing importance, severe clinical course, and high fever characteristic of salmonella blood infections in Jamaica has recently been reported.[15] *H influenzae* type

b accounted for two events in children aged 2.7 and 4.4 years, neither of whom had received vaccine. All 10 cases with invasive bacterial infection were admitted to hospital, and one patient with *H influenzae* type b died from septic shock.

The cause of high fever was often unclear and presumed to be viral or atypical organisms, although confirmatory evidence was rare. Positive viral confirmation was obtained in three cases of human parvovirus induced aplastic crisis, which can often be associated with fever,[16] and in one case of dengue haemorrhagic fever. Highly suggestive of viral illness but unconfirmed serologically were two cases of varicella and mumps. The low frequency of blood cultures reflected the relative wellbeing of many of the children with clinical diagnoses of otitis media or upper respiratory tract infections (totalling 17 of 21 events without blood cultures), and it is possible that a prospective study with routine blood and urine cultures would disclose more bacterial infections. All possible causes for high fever combined (bacteraemia, confirmed or suggestive viral infection, local bacterial infection, and acute chest syndrome) accounted for 114 (69%) of the events, leaving 51 (including 20 with painful crisis) without explanation.

Despite the paucity of invasive bacterial disease in this study, it is probably wise to treat all highly febrile children with sickle cell disease with antibiotics pending the results of blood culture. Although the greatest concern has traditionally been *S pneumoniae*, effective prophylaxis has reduced its incidence, and enteric Gram negative organisms, especially *Salmonella* species, are of particular importance in Jamaica. Lack of awareness of *Salmonella* septicaemia has been associated with a high death rate,[15] and any seriously ill febrile child in whom sepsis is suspected should receive coverage for *Pneumococcus* as well as *Salmonella*. The incidence of invasive Hib infection has been greatly reduced through vaccination. Policies of pneumococcal prophylaxis may need modification because of the rapidly emerging penicillin resistance, but trials of a conjugated vaccine which may be effective when given at 2, 4, and 6 months may in the future simplify prophylaxis. In addition to broad antibiotic coverage in any potentially septic child, the incidence and limited clinical signs of acute chest syndrome in some children make routine chest radiography a wise precaution.

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