Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London

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ABSTRACT

Background and Objectives

We investigated outcomes in a UK neonatal cohort as a benchmark for care of children with sickle cell disease (SCD).

Design and Methods

Two-hundred and fifty-two children (180 with hemoglobin [Hb] SS, 64 with HbSC, and 8 with HbS/β thalassemia), identified during 1983-2005 by universal birth screening in East London, were followed in a hospital and community-based program which included penicillin V prophylaxis from 3 months of age, 23-valent pneumococcal polysaccharide vaccine from 1993, conjugate pneumococcal vaccine from 2002 and transcranial Doppler screening from 1991.

Results

At the end of 2005, there were 2158 patient years of observation. The median age of the patients was 7.8 (interquartile range 3.3-13.0) years, and 2.8% of those enrolled had been lost to follow-up. The estimated survival of children with HbSS at 16 years was 99.0% (95% confidence interval, CI, 93.2 to 99.9%) and pneumococcal sepsis rate was 0.3 (95% CI 0.1-0.8) episodes per 100 patient-years. The risk of overt stroke was 4.3% (95%CI 1.5 to 11.4%) and could be further reduced by transcranial Doppler screening from infancy and transfusing all children with high-risk scans. No deaths, strokes or episodes of pneumococcal sepsis were observed in children with HbSC or HbS/β thalassemia. The mortality rates from HbSS were significantly lower than those in other reported cohorts.

Interpretation and Conclusions

Mortality in childhood SCD can virtually be eliminated in a well-resourced health service setting linking community-based care with a specialized, hospital-based center. SCD continues to cause substantial morbidity from acute complications and chronic organ damage. We recommend setting up of clinical networks to optimize the management of SCD.

Key words: neonatal screening, sickle cell, mortality, infection, cerebrovascular disorders.

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Sickle cell disease (SCD) is an important cause of morbidity and mortality in childhood.[1,2] The natural history was well described in the Jamaican cohort[3-6] and USA Co-operative Study of Sickle Cell Disease (CSSCD),[7-12] which demonstrated that early identification of affected infants by neonatal screening and careful follow-up, coupled with relatively simple interventions, substantially reduced morbidity and mortality.[4,6,13] These studies enrolled >25 years ago but two recent studies from the USA have documented further improvement in survival rates.[16,17] In addition, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that stroke risk can be reduced by screening children with transcranial Doppler ultrasound (TCD) and transfusing those with internal carotid/middle cerebral artery velocities >200cm/sec, who otherwise have a 40% risk of stroke over the following 3 years.[14,15]

In the UK, there are no comparable data, but these are essential for planning clinical services, counselling parents on prognosis, and making decisions regarding high-risk therapies, such as bone marrow transplantation. The newborn bloodspot screening program for SCD was developed from a recommendation in the National Health Service (NHS) plan for a linked antenatal and neonatal hemoglobinopathy screening programme in England.[18] By October 2006 the program had been implemented across the whole of England, and initial statistics gave an estimated incidence of affected births of approximately 1 in 2000, indicating that SCD is now the commonest serious inherited disorder in England.[19] In order to provide best care for affected children, standards of care for SCD have recently been published[20] and a target mortality rate of <4 deaths per 1000 patient-years in under 5-year old children is expected by 2010.[21]

Hospital laboratories in some high prevalence areas in England had previously initiated local neonatal screening programs, using cord blood collected on the labor ward. One of the longest established of these programmes is based in the London Borough of Hackney, one of the areas with the highest prevalence of SCD in England, with over 25% of the population being of Caribbean or African origin.[22,23] A joint hospital and community approach to SCD management has evolved over 23 years of continued screening. We wished to analyze outcomes of affected births to provide figures for SCD morbidity and mortality in a UK setting, and to determine whether there are significant differences in outcomes of these patients compared to those in the USA and Jamaica.

Design and Methods

Follow-up of affected infants

From October 1982, umbilical cord blood samples from all babies born in maternity hospitals in the London Borough of Hackney were analyzed for hemoglobin variants. From 1998, the program was expanded to include children from the adjacent London Borough of Tower Hamlets, and continued until replaced in 2004 by the newborn bloodspot screening programme for SCD.[18] Results indicating a major hemoglobinopathy were fed back to the general practitioner (GP), pediatrician and to the Hackney Community Sickle and Thalassaemia Centre (HCSTC). Parents were visited by a community nurse specialist to explain the results, and to arrange confirmatory testing. The infant was then referred to the consultant pediatric hematologist in the Children's Sickle Cell Clinic, initially at Queen Elizabeth Children's Hospital, Hackney, and after 1998, at The Royal London Hospital. If the child resided outside Hackney, cord blood results were transmitted to the child's GP and the local Sickle Cell Clinic, with no further follow-up in Hackney. Children were seen 3-monthly for routine clinic visits. Parental education in the management of the disease was reinforced by the hospital and community nurse specialists and by the distribution of specific literature. Parents were systematically questioned about a range of symptoms associated with SCD, including dactylitis, painful episodes, and infections. They received instruction in splenic palpation, in the management of common complications, and how and when to access acute hospital services. Clinic non-attendance for more than one visit was addressed by writing to the GP, and by visiting the home. All children received oral penicillin V starting at 3 months of age and continued indefinitely, with adherence monitored and re-enforced at routine clinic visits. Vaccination schedules included 23-valent polysaccharide pneumococcal vaccine (Pneumovax®) from 1993, conjugate vaccine for *Haemophilus influenzae* type B from 1993, conjugate meningitis C vaccine from 2000 and 7-valent conjugate pneumococcal vaccine (CPV, Prevenar®) from 2002. From 1991, TCD screening for schoolchildren, mainly with HbSS, was undertaken in the clinic by three experienced operators (Deborah Hewes, PT, and FK) using the TCD64B or Companion II portable systems (Nicolet). Hydroxyurea was recommended to children with recurrent painful crises (more than three admissions per year) or recurrent chest crises (more than two episodes per year) after 1999.

From 2000, routine screening for adolescents and adults (at the age of 15 and 5-yearly thereafter) included pulmonary function tests (FEV1, FVC, KCO), echocardiography (for assessment of pulmonary hypertension), analysis of 24-hour urine samples (protein quantitation, creatinine clearance), and retinal examination. Boys were instructed about priapism and asked to report any episodes at routine clinic visits. A diagnosis of chronic complications (avascular necrosis, chronic sickle lung syndrome, nephropathy, retinopathy, priapism) required the presence of significant symptoms together with the characteristic abnormalities detected by examination and by investigation.

Children were considered lost to follow-up if not seen for more than 2 years. For children who had not been seen for more than 1 year, information was obtained by contacting the last known GP by letter and telephone, and the family at the last known address. When a child transferred to another pediatric clinic, or an adolescent transferred to an adult clinic, the new clinician was contacted for information about major events. Crises were defined according to previously published criteria.[7-12] The definition of a painful crisis required admission to hospital for analgesia. The definition of dactylitis was pain and swelling of the digits and/or dorsum of one or more hands or feet, which was judged clinically not to be due to infection. Admission to hospital for analgesia was not usually required.

Ethical considerations

This study was approved by the Institutional Medical Ethics Committee, who decided at the time of application (October 2004) that, since the study had the characteristics of an internal *audit*, individual written informed consent was not required.

Statistical methods

Data were extracted from hospital records and entered into a database by two of us (*SC,OW*), and independently checked by a third person (*PT*). Statistical analyses were performed in STATA 9.0. Data were censored at 31/12/05, or at last clinic visit for those lost to follow-up, except for the data on pain and chest crises, which were censored at the time patients started regular transfusions or hydroxyurea, or on transfer to another hospital. Error bars for crisis incidence rates were estimated at 95% Poisson confidence intervals. Survival estimates were plotted as Kaplan-Meier curves. Relative risk calculations were performed using the STATA implementation command *ir*.[24]

Results

Patients

Between 1st November 1982 and 31st December 2005, 252 children diagnosed with SCD by neonatal screening were referred to the clinic and seen at least once. One hundred and eighty had HbSS, 64 HbSC, and 8 HbS/β thalassemia. Three of the latter had severe β^+ thalassaemia mutations (IVS 1-110 in one case and IVS 1-5 in two cases), the remainder were milder mutations. Twenty-eight additional children were excluded from the analysis. Twenty-one were identified by cord blood screening, but not referred to the clinic and never seen. Five cases of HbSS were only diagnosed after presenting with a crisis. Four of these five cases had not been detected by the screening program because no neonatal sample had ever been received in the screening laboratory. One case was incorrectly diagnosed as having HbAS, due to maternal contamination of the cord blood sample. These five children are currently alive and well. Two infants with HbSS died before being seen in clinic. The first had a univentricular heart and died of heart failure at the age of 3 months. The second had a congenital polyneuropathy, developed respiratory failure soon after birth and died of respiratory failure at the age of 6 months.

There was a trend for an increase in the annual number of diagnoses during the follow-up (Figure 1), and an increasing proportion of patients of African or Caribbean origin. Further demographic data are shown in Table 1.

Clinic entry, follow-up and retention

The median age at clinic entry was 2.7 months and 149 (59%) of the patients were seen by the age of 3 months. Two-hundred and twenty-five (89.3%) are under continuing follow-up at The Royal London Hospital in pediatric or adult clinics, and 20 (7.9%) are being followed-up elsewhere. There was a total of 2158 patient-years of follow-up: 1542 for patients with HbSS, 541 for those with HbSC and 75 for those with HbS/β thalassemia. Seven (2.8%) patients were lost to follow-up for more than 2 years at a median age of 3.8 (interquartile range [IQR], 1.7-14.4) years; the median time since these patients were last seen was 3.5 (IQR 2.0-4.3) years.

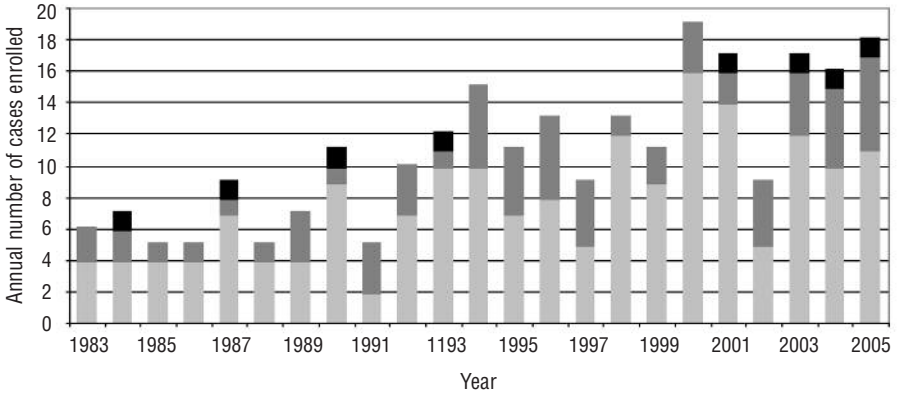

Figure 1. Number of cases enrolled in clinic annually from 1st January 1983 to 31st December 2005, stratified by genotype: HbS-β-thalassemia (black bars), HbSC (dark gray bars) and HbSS (light gray bars).

Table 1. Demographic and follow-up data for the neonatal cohort.

	HbSS N=180	*HbSC n=64*	*HbS/β thalassemia n=8*	*Total n=252*
	Number (%)	*Number (%)*	*Number (%)*	*Number (%)*
Sex				
Male	101 (56)	33 (52)	2 (25)	136 (54)
Female	79 (44)	31 (48)	6 (75)	116 (46)
Family origin				
Caribbean	36 (20)	21 (33)	4 (50)	61 (24)
Africa	144 (80)	43 (67)	2 (25)	189 (75)
Other	0 (0)	0 (0)	2 (25)	2 (1)
Follow-up at end of study				
Pediatric clinic, RLH	138 (77)	46 (72)	6 (75)	190 (75)
Other pediatric clinic	10 (6)	8 (13)	0 (0)	18 (7)
Adult clinic, RLH	18 (10)	4 (6)	1 (12.5)	23 (9)
Other adult clinic	5 (3)	5 (8)	1 (12.5)	11 (4)
Lost to follow-up	6 (3)	1 (2)	0 (0)	7 (3)
Dead	2 (1)	0 (0)	0 (0)	2 (1)
BMT	1 (1)	0 (0)	0 (0)	1 (0)
Median age (Interquartile range)	7.4 (4.0, 12.6)	8.9 (2.9, 13.0)	8.6 (2.4, 15.6)	7.8 (3.3, 13.0)
Follow-up (patient-years)	1542	541	75	2158

RLH: Royal London Hospital; BMT: bone marrow transplant.

Mortality

Two patients, both HbSS, died; one was a boy who died of acute chest syndrome (ACS) in 1990 at the age of 6 years, the other was a man who died of a cerebral hemorrhage at the age of 22 years. Mortality rates in the age range 0-16 years are shown in Table 2. There were no deaths in the under 5-year old age group or in children with HbSC or HbS/β thalassemia. The overall mortality rate for patients with HbSS was 0.13 (95% confidence intervals [CI], 0.02 to 0.47) per 100 patient-years. The estimated survival for HbSS patients at 10 and 20 years of age is 99.0% (95%CI 93.2-99.9%). If the two infants who were identified as having HbSS but who died before being seen in clinic are included in the survival analysis, the estimated survival at both 10 and 20 years is 97.9%, and the overall mortality 0.27 per 100 patient-years of follow-up.

Acute sickle crises

Age-specific rates for acute sickle events are shown in Table 2, and Kaplan-Meier curves showing time to first crisis in Figure 2. Crises were more frequent in cases with HbSS than in those with HbSC. Before their second birthday, 33.2% of patients with HbSS had had at least one documented episode of dactylitis. Painful crisis

Table 2. Crisis rates.

Age range	*Age 0-2*	*Age 3-4*	*Age 5-6*	*Age 7-8*	*Age 9-10*	*Age 11-12*	*Age 13-14*	*Age 15-16*	*Age 0-16*
Patient years follow-up									
Total HbSS	475	265	211	166	140	106	77	57	1498
HbSS without therapy*	475	264	205	161	133	99	68	51	1456
HbSC	163	88	79	70	54	37	27	14	532
HbSS Crisis rates/100 patient-years									*Rate (95% CI)*
Pain crisis	27.8	53.1	52.1	83.1	118.4	117.5	149.9	81.8	63.9 (58.2- 66.2)
Acute chest syndrome	16.4	21.2	15.6	12.4	18.1	18.2	22.0	11.7	17.1 (14.6- 18.8)
First stroke	0.0	0.8	0.5	0.6	0.0	0.9	0.0	0.0	0.3 (0.1- 0.8)
Acute splenic sequestration	6.3	1.9	1.4	0.6	0.7	0.0	0.0	0.0	2.7 (1.9- 3.6)
Aplastic crisis	0.8	1.9	1.9	1.8	2.1	0.9	0.0	0.0	1.3 (0.8- 2.2)
Pneumococcal sepsis	0.6	0.0	0.5	0.0	0.7	0.0	0.0	0.0	0.3 (0.1- 0.8)
Death	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.1 (0.0- 0.4)
HbSC crisis rates/100 patient-years									*Rate (95% CI)*
Pain crisis	3.7	15.9	20.4	18.6	23.9	18.9	11.1	14.0	13.9 (10.9- 17.4)
Acute chest syndrome	3.7	4.6	6.4	7.2	1.8	2.7	0.0	0.0	4.1 (2.6- 6.2)
First stroke	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0- 0.7)
Acute splenic sequestration	0.0	0.0	2.5	0.0	1.8	0.0	3.7	0.0	0.8 (0.2- 1.9)
Aplastic crisis	0.0	0.0	0.9	0.0	0.6	0.0	0.0	0.0	0.4 (0.0- 1.3)
Pneumococcal sepsis	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0 (0.0- 0.7)
Death	0	0	0	0	0	0	0	0	0.0 (0.0- 0.7)

**Patient-years on hydroxyurea or regular transfusion excluded.*

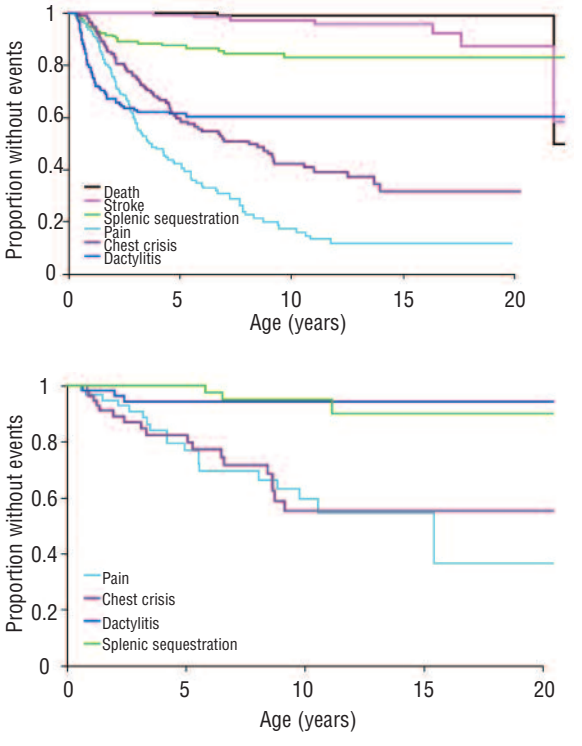

Figure 2. Kaplan-Meier curves indicating time to first event for common sickle crises. A. Hb SS. B. Hb SC.

was the commonest event in all age groups, reaching a peak incidence in early adolescence in patients with HbSS, while there was a suggestion of a bimodal trend in the incidence of ACS. Acute splenic sequestration was relatively common in the first 2 years of life, while aplastic crises were documented up to the age of 10 years.

Pneumococcal and other bacterial infections

Sixty-one of 62 (98%) children born after the introduction of CPV in January 2002 were vaccinated. Five children had an episode of pneumococcal sepsis with a positive microbiological isolate; in four case this occurred before the introduction of CPV (Table 2). Three children had bacterial meningitis, all due to *Streptococcus Pneumoniae*. Six patients had septicemia, with *Streptococcus pneumoniae* isolated in three (one with concomitant meningitis), *Escherischia coli* in one, and *Salmonella typhimurium* in two. There were eight episodes of osteomyelitis in seven children; *Salmonella typhimurium* was isolated in three cases.

Stroke and TCD screening

Seven children had a total of 11 overt strokes, two intra-cerebral hemorrhages and nine infarcts. The incidence of first stroke among HbSS patients up to 16 years of age was 0.3 (95% CI 0.1-0.8) per 100 years. The estimated risk of stroke was 0.7% (0.1-5.0%) at 5 years; 2.7% (0.9-8.3%) at 10 years; 4.3% (1.5-11.4%) at 15 years; and 12.8% (4.8-31.3%) at 20 years. Four of the five first infarcts occurred in the absence of a precipitating cause and all had large vessel cerebro-vascular disease on magnetic resonance angiography. The fifth occurred during a severe episode of ACS requiring exchange transfusion and ventilatory support. All are receiving regular transfusions for secondary stroke prevention but two had recurrences despite this management. Two-hundred and seventy-five TCD scans were attempted in 124 children, including 79.8% of those with HbSS aged >3 years. The mean age at the first scan was 6.4 years. Fifty-sevenof the patients had more than one scan (average 2.2 for scanned children with HbSS). TCD results (most severe result per child) are shown in Table 3. Seven, all with HbSS, had high-risk velocities: four were transfused as primary prophylaxis and are currently stroke-free, one diagnosed at the age of 9 in 1992 was observed and suffered recurrent cerebral infarcts, and the other two, both pre-school age, were scanned only after suffering their first cerebral infarct. Four children had an overt stroke despite a standard-risk TCD scan. Two had an intracerebral hemorrhage, the third suffered extensive bilateral infarction during an ACS, already referred to, and the fourth was a 16-year old with a cerebral infarct in whom low velocities had been previously documented.

Table 3. Results of transcranial Doppler screening classified according to Adam's criteria.[15]

	HbSS Number (%)	*HbSC Number (%)*	*HbS/β thal. Number (%)*	*Total Number (%)*
High risk	7 (6)	0 (0)	0	7 (6)
Conditional	11 (10)	0 (0)	0	11 (9)
Standard risk	87 (79)	13 (100)	1	101 (81)
Inadequate	5 (5)	0 (0)	0	5 (4)
Total	110	13	1	124

For children screened more than once, the most severe finding. (high risk>conditional>inadequate>standard risk) has been used.

Chronic complications

Three children with HbSS (two boys, one girl) developed symptomatic avascular necrosis of the hip between the ages of 9 and 11 years old. Four boys had recurrent episodes of stuttering priapism but none required surgery. Two young women with HbSS had vitreous hemorrhages. There were no cases of ankle ulceration, renal impairment, chronic lung disease or symptomatic pulmonary hypertension.

Treatment

One boy with HbSS underwent matched sibling allogeneic bone marrow transplantation aged 5 years, and is crisis-free with stable engraftment after 6 years of follow-up. Twenty-six HbSS patients had 32 transfusion

Table 4. Comparison of mortality data in cohort studies of HbSS children.

Reference	*Setting*	*Duration of enrollment*	*Method of enrollment*	*Number of patients*	*Patient-years of follow-up*	*Number of events*	*Mortality per 100 patient-years years follow-up (95% CI)*	*Estimated survival (95% CI)*	*Relative risk compared to E London cohort (95%CI)*
Gill *et al.*[8]	CSSCD infant cohort	1978-1988	Recruitment of infants <6 months old	427	1781 to age 10	20 to age 10	1.1 (0.7-1.7)	Not given	14.1 (8.6-21.9)*
Lee *et al.*[5]	Jamaica (most recent cohort)	1979-1981	Neonatal screening	105	Not given	16 to age 15	Data not available	84.0% (77.0-91.0) at 15 years	Data not available
Quinn *et al.*[16]	Dallas cohort	1983-2002	Neonatal screening	431	3571 to age 18	22 to age 18	0.6 (0.4-0.9)	85.6% (73.4-97.8) at 18 years	9.4 (5.9-14.2)°
This study	E London cohort	1983-2006	Neonatal screening	180	1257 to age 10 1517 to age 18 1542 to age 23	1 to age 10 1 to age 18 2 to age 23	0.1 (0-0.4) 0.1 (0-0.4) 0.1 (0-0.5)	99.0 (93.2-99.9) at 20 years	

**E London cohort data up to age 10; °E London cohort data up to age 18.*

episodes (regular transfusion for >3 months) starting at a median age of 10.9 (range, 0.8-18.8) years with a median duration of 0.7 (range, 0.3-7.6) years. Eighteen children have been treated with hydroxyurea, initiated at a median age of 13.3 (range, 5.0-19.7) years with a median duration of 2.37 (range, 0.2-5.4) years; there were 42.6 patient-years of treatment follow-up. Ten children (all with HbSS) have undergone splenectomy, and ten (nine with HbSS and one with HbSC) had a cholecystectomy.

Discussion

This study is the first to report on a cohort of children with SCD identified in a UK universal neonatal screening program. Although the setting is one of the most socially deprived parts of London, most children have remained under local care, and the rate of loss to follow-up is similar to that in the Jamaican cohort,[4] and substantially less than that in the CSSCD infant[8] and Dallas neonatal cohorts.[16] The program continues to accrue patients who remain under follow-up in a health service setting, in contrast to the Jamaican and CSSCD surveys, which were conducted in a research setting, and are no longer recruiting patients.

The overall mortality in this study was 0.13 per 100 patient years. There were no SCD-related deaths in under 5-year olds and in the age range 0 to 16 years, the only death was due to ACS; this occurred early in the study and would probably have been prevented with modern management. The National Haemoglobinopathy Screening Programme has set a standard for the newborn bloodspot screening for SCD of <4 deaths per 1000 patient-years in under 5-year olds in England by 2010.[21] This target is achievable if the standard of care in a specialized center, such as ours, can be transferred to smaller clinics with less experience and expertise.

Since the method of statistical analysis and the duration of follow-up are not identical in the different SCD cohort studies, (the CSSCD infant cohort study only reported comprehensively up to the age of 10, the Jamaican cohort only reported survival analysis, and the Dallas cohort followed-up only until the age of 18), we have had to use subsets of our data to make comparisons. However, Table 4 makes clear that the mortality rates in our cohort are significantly reduced, and comparable to those in California, Illinois and New York during 1990-1994 (0.35 per 100 patient years).[17]

In our analysis of mortality rates, we included deaths of all causes, but excluded two infants who were found to be positive for HbSS by screening tests, but died of causes unrelated to SCD before being seen in our clinic. The criteria for inclusion in our cohort were the same as those in the Dallas cohort (*seen at least once in our center*). Deaths of all causes were included in our cohort, however, we excluded two infants who were screen positive for HbSS, and died of causes unrelated to sickle cell before being seen in the clinic. The criteria for inclusion in the cohort were the same as in the Dallas cohort ('*seen at least once in our center*'). In the Dallas cohort and the Jamaican cohort, the authors did not present data on deaths in screen-positive infants who were never seen in the programme. The CSSCD infant cohort was not linked to a specific neonatal screening programme, and entry into the study was at the discretion of the individual centres. From these considerations, we do not believe that survival data is artificially improved compared to these studies. If these two infant deaths are included, mortality rates compared to the E London cohort are still significantly increased in the CSSCD infant cohort (relative risk 4.7, 95% CI 2.9-7.3) and in the Dallas cohort (relative risk

3.12, 95% CI 2.0-4.7).

One possible explanation for the difference in outcomes observed in this UK center compared to those in the US studies is a difference in genetic background between the study subjects. Twenty-four per cent of the childrens' families in our cohort originated from the Caribbean, and 75% from Africa, the majority of these from Nigeria and Ghana. One might expect a more complex genetic mix in the Caribbean and North American population, due to increased interbreeding with native Americans and Europeans. Social and cultural differences certainly exist, but we suspect that the good outcomes observed in our study are largely due to the benefits of a comprehensive SCD program run from within the UK National Health Service which is free and available to all.

It is possible that the children lost to follow-up have died, and have not been included in our survival estimate, but this is unlikely; if they had died while in our area, the information would have been passed on to us from local GPs or from the community Sickle Cell Center. Most of these children were at the mild end of the spectrum of disease severity, and it is more likely that they are asymptomatic and see no need to access medical care. With regard to the screened-positive infants who were not referred to our clinic, the reasons for non-referral were mainly related to moving out of the local area or returning to the country of origin soon after the birth of the child. This is relatively common in immigrant Africans who have not obtained full residency status in the UK. It is difficult to make any comment on the outcome of these children if there are no records of their being followed in clinics. For the national newborn screening program in England, such cases will need to be tracked as far as possible, in order to determine whether they are still resident in the UK and managed in another clinic, or have left the country altogether.

As in other studies, we observed lower than expected mortality and morbidity from pneumococcal sepsis. This suggests that the pneumococcal prophylactic measures adopted during the program have been beneficial. The documented infection rates are about ten-fold lower than those in cohorts not given without penicillin prophylaxis,[13] and less than half the rates reported in the era of penicillin and polysaccharide vaccine alone.[25,26]

The risk of first stroke in HbSS patients of 0.3 also compares favorably with rates of 0.4 to 0.9 per 100 patient-years previously reported during childhood.[5,11,16,27,28] In a study of Californian children, the incidence decreased during 1998-2000 to 0.17 per 100 patient years, probably due to the implementation of the STOP protocol after publication of the results of this trial.[28] We introduced screening[29] before evidence of the efficacy of transfusion became available,[15] so the one high-risk child identified was only observed; including this patient, three of our five cases of cerebral infarctions might have been prevented by fully implementing the STOP protocol from infancy. The incidence of first stroke for HbSS patients would then be 0.13 per 100 patient-years, similar to the Californian estimate.[28] However, in addition to the two hemorrhagic strokes, two infarcts were not predicted by TCD screening, and two patients suffered recurrent infarction despite regular transfusion, suggesting a need for further research into risk factors for primary and secondary strokes.

The rates of acute and chronic complications for which there is no universally applicable means of primary prevention, were similar to, or higher than, previously reported rates. Pain crises in our series were more frequent than in the CSSCD study,[10] possibly because access to the UK NHS care is free, and parents are more inclined to bring their children to hospital rather than trying to manage at home. Hydroxyurea may have a beneficial effect on survival in SCD[30] but we are not yet in a position to test this hypothesis in our cohort because of the low overall mortality rate, the small proportion of patients treated and the short duration of follow-up. There remains a substantial morbidity from acute complications of SCD, and a burden of chronic disability, apparent in this study with cases of brain damage, stuttering priapism, retinopathy and avascular necrosis of the hips.

In conclusion, compared with previously published data, mortality and morbidity from some of the most severe complications of SCD in childhood are substantially lower in this program incorporating collaboration between community-based and hospital-based care. These data will help to inform discussions with parents about the longer term outcome when their child is newly diagnosed with SCD. For these results to be replicated throughout the UK, we endorse the establishment of clinical networks linking specialized centers with smaller clinics in areas where the prevalence of SCD is low, and implementation of the national standards of care for this disease.[20]

Authors' Contributions

PT planned the study, participated in managing the patients, and data collection and wrote the manuscript; JE participated in planning the study, managing the patients, collecting data and revising the manuscript; DR participated in planning the study, managing the patients, collecting data and revising the manuscript; SC participated in planning the study, managing the patients, collecting data and revising the manuscript; OW participated in managing the patients, and collecting data; HN participated in managing the patients, and collecting data; PC participated in planning the study, undertook the statistical analyses and revised the manuscript; BS participated in managing the patients, data collection and revising the manuscript; RA planned the laboratory screening and participated in data collection and revision of the manuscript; AS planned the laboratory screening and participated in data collection and revision of the manuscript; FK planned the study, participated in managing the patients, data collection and revision of the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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