Review article

Sickle cell disease in Britain

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SUMMARY Sickle cell disease is common in urban areas of Britain and it is estimated that in London alone there are nearly 2000 patients. One hundred and eighty four patients with sickle cell disease are known to the Central Middlesex Hospital, and 155 of those attend the sickle cell clinic regularly.

The commonest cause for admission to hospital is acute painful or vaso-occlusive crisis, which accounts for 80% of all acute admissions; 12% of admissions are for acute chest syndrome.

Comparison of clinical features in Brent and in Jamaica shows that the Brent patients with homozygous sickle cell anaemia are admitted with painful crises more frequently than Jamaican patients. However, the frequency of admissions for chest syndrome and priapism, and the incidence of splenomegaly are similar. Leg ulcers are uncommon in Brent. Patients with sickle cell haemoglobin C disease appeared more severely affected in Jamaica than in Brent.

During the past two years 3165 newborn babies have been screened for sickle cell disease at the Central Middlesex Hospital: five babies with homozygous sickle cell anaemia and three babies with sickle cell haemoglobin C disease were detected. The overall incidence of sickle cell trait was 3.2% and of haemoglobin C trait 0.8%. A significant number of babies with sickle cell disease are born in London every year. It is essential that such babies are detected at birth and offered prophylaxis against pneumococcal infection, which is one of the major causes of infant mortality.

Sickle cell disease is becoming an important blood disease in Britain and firm guidelines for the management of acute and chronic complications are required.

Sickle cell disease is a collective term for a group of blood diseases resulting from the inheritance of haemoglobin S. The four main genotypes of sickle cell disease found in Britain are: homozygous sickle cell anaemia, sickle cell haemoglobin C disease, sickle cell beta⁺ thalassaemia (S/Beta⁺ thal), and sickle cell beta⁰ thalassaemia (S/Beta⁰ thal).

The pathological process in sickle cell disease is caused by the sickling phenomenon: in the deoxy state haemoglobin S molecules aggregate into long polymers that are aligned to form liquid crystals called tactoids.¹ In the presence of tactoids the normal disc shaped, easily deformable red cell is transformed into the characteristic sickle shaped cell that gives this condition its name. The sickling phenome-

non damages the red cell membrane so that it becomes increasingly rigid. Such cells are sequestered in the reticuloendothelial system and rapidly destroyed, causing haemolytic anaemia. A second major disturbance in sickle cell disease arises as a result of altered flow properties of sickled red cells. There is an increase in blood viscosity associated with small vessel stasis and obstruction, which eventually lead to vasocclusive crises and ultimately to permanent organ damage. Furthermore, patients suffering from sickle cell disease have a propensity to bacterial infection owing to a combination of asplenia, defective opsonisation, and other, as yet ill defined factors.

Incidence of sickle cell disease in Britain

In the survey of sickle cell disease in England and Wales carried out in 1979 by postal questionnaire to

Table 1 Comparison of the results of newborn screening for sickle cell disease in five locations

Location	No of babies screened	% black births	% of all births				
			AS	AC	SS	SC	S/Beta ⁰ thal
Manchester ^a	7691	3.8	0.3	—	—	—	—
Birmingham ^a	43 500	10	1.1	0.4	0.006	0.006	—
Brent ⁷	3165	22	2.8	0.9	0.16	0.09	0.03
New York ^a	106 223	35	3.2	0.8	0.18	0.12	—
Kingston, Jamaica ^a	70 000	>98	10	3.6	0.31	0.20	0.03

AS = sickle cell trait

AC = C-trait

haematologists,² 1367 cases were identified; 862 were in London. The authors believed that the true number of cases was twice as large as that found by this approach. Recently, Weddell (personal communication) estimated the number of patients with sickle cell disease living in London, based on the 1979 National Dwelling and Housing survey.³ The predicted number of cases was 1836 in an estimated population of 288 000 West Indians and 65 000 Africans living in London. The accuracy of this estimate is difficult to prove. According to Weddell's estimate, however, there are 191 patients with sickle cell disease in the London borough of Brent. The Brent sickle cell register, started in 1979,⁴ now (1984) contains the names of 184 patients: 155 of them are regularly followed at the Central Middlesex Hospital. Thus the estimate is accurate for Brent.

The incidence of sickle cell disease in Britain is increasing because every year a number of babies with sickle cell disease are born to parents of Afro-Caribbean origin. The size of the increase is not known because there is no systematic screening of the newborn at risk. Table 1 compares the data from three British centres that screen the neonates⁵⁻⁷ with the USA⁸ and Jamaican⁹ experience. As expected, the number of babies with sickle cell disease increases with the increasing percentage of black births.

In Jamaica the prevalence per 1000 births is 3.1 for SS, 2.0 for SC, 0.34 for S/Beta⁺ thal, and 0.16 for S/Beta⁰ thal.⁹ The numbers screened in Brent are

at present very small, but if the present trend continues the prevalence will be higher than in Jamaica (at present 7.7 for SS, 4.3 for SC and 0.14 for S/Beta⁺ thal). This higher prevalence is almost certainly due to the high percentage of births to West African mothers (nearly 30% of all black births at the Central Middlesex Hospital). The high proportion of patients with sickle cell disease of West African descent among the London sufferers is well known: Murtaza *et al*¹¹ reported that 89 of 171 children attending the paediatric sickle cell disease clinic at King's College Hospital were of West African origin. In Brent, 44 of 155 regular attenders and 20 of 29 non-attenders are of West African descent. Between 30 and 50% of patients with sickle cell disease in London come from West Africa.

It is at present impossible to calculate the number of new cases of sickle cell disease in Britain every year, but on the basis of government statistics in 1979³ and the prevalence in Brent,⁷ it can be estimated that between 50 and 100 babies with sickle cell disease may be born in London alone every year.

Severity of the disease

COMPARISON OF GENOTYPES IN BRITAIN

The different clinical behaviours of SS and SC genotypes,¹⁰⁻¹² SS and S/Beta⁰ thal genotypes,^{13,14} S/Beta⁰ thal and S/Beta⁺ thal genotypes,¹⁴ as well as interaction with alpha thalassaemia,¹⁵ are well recognised. In the previously mentioned national sur-

Table 2 Genotypes observed in Brent in 1984

Genotype	Age (yr)						Total	
	<5		5-16		>16			
	M	F	M	F	M	F	M	F
SS*	3	4	9	10	19	23	31	37
SC	3	3	9	10	22	24	34	37
S/Beta ⁰ thal				2	2	2	2	4
S/Beta ⁺ thal		1	1		4	4	5	5
Total	6	8	19	22	47	53	72	83
							Total = 155	

*Two patients, a man aged 21 and a woman aged 22, are proved Hb SS/alpha thalassaemia 2 homozygotes.

Table 3 Age at diagnosis for SS and SC patients in Brent

Genotype	Age at diagnosis (yr)				
	<2	2-10	10-16	>16	Not known
SS	21	28	4	1	14
SC	8	19	18	21	5

Table 4 Method of diagnosis for SS and SC patients in Brent

Genotype	Method of diagnosis					
	Cord blood	1st admission	Symptoms*	Family study	Routine testing†	Not known
SS	5	47	5	2	1	8
SC	3	17	17	6	24	8

*Through general practitioner or outpatient department.

†Before anaesthetic for dental or other surgery, or in the antenatal clinic.

Table 5 Clinical features of SS and SC in Brent, 1964-1984

	Genotype	
	SS	SC
No of patients	68	71
No of patients never admitted	5 (8%)	16 (23%)
Total no of admissions*	415	95
Painful crises		
No of patients affected	63 (92%)	30 (40%)
No of admissions	332 (80%)	66 (82%)
Chest syndrome		
No of patients affected	18 (26%)	6 (8%)
No of admissions	54 (12.7%)	12 (12.6%)
No of proved infective episodes	9	2
No died	3	1
Splenomegaly	10 (14%)	23 (32%)
Splenectomy	3	2
Cholecystectomy	7	2
Peptic ulcer	5	1
Salmonella infections	1	1
Pneumococcal infections	8	3
Aplastic crises	5	3
Sequestration crises	3	0
Leg ulcers	3	0
Strokes	5	2
Priapism (cases/men)	7/30	2/31
No of pregnancies per women over 16	12/23	38/25
Fetal loss per pregnancy	3/12	5/38
Age of menarche in women over 16	14.4	13.5

*Excluding admissions in pregnancy.

Table 6 Admission rate in SS and SC, Brent 1964-1984*

Genotype	Under fives		5-16 years		>16	
	SS	SC	SS	SC	SS	SC
No of patients†	14	6	19	6	25	17
Total no of admissions	49	16	164	19	202	60
Years of follow up (mean and range)	3.6 (3-5)	4 (3-5)	8.7 (3-11)	6.6 (5-11)	5.8 (3-20)	8.2 (3-17)
No of admissions per year of follow up (mean and range)	1.03 0.25-2.0	0.64 0.25-1.6	1.02 0.25-2.25	0.44 0.20-0.75	1.67 0.25-6.5	0.39 0.20-1.33

*Excluding admissions during pregnancy.

†Only patients followed for 3 years or more included.

Table 7 *Some chronic complications of sickle cell disease in the over 16s*

	Genotype	
	SS	SC
No of patients over 16	42	46
Mean age $\pm$ SD	25.2 $\pm$ 7.1	31.3 $\pm$ 11.2
Renal failure	2	0
Aseptic bone necrosis		
Symptomatic	8	7
Asymptomatic	3	2
Proliferative retinopathy (cases/examined)	2/10	14/21

vey of sickle cell disease,² 58.5% of patients were SS, 29.9% were SC, and 9% were S/Beta⁺ or S/Beta⁰ thal. Combinations of haemoglobin S and other haemoglobins accounted for 2.6% of the cases. Table 2 shows the genotypes noted in Brent. The difference in the severity between SS and SC in Brent is best shown in Tables 3 and 4, which compare the age at diagnosis and the method of diagnosis for two genotypes. The number of cases of S/Beta⁰ and S/Beta⁺ thal is not sufficient to allow meaningful analysis.

It is clear from these tables that most patients with SS in London are diagnosed early in life, usually on first admission to hospital. Patients with SC are diagnosed later, often when seen in dental or antenatal clinics, or before minor surgery. Nevertheless, 17 of 71 patients (23%) with SC were diagnosed on first admission to hospital: in 16 cases the admission was for a sickle cell disease related or caused illness. Further data on the clinical manifestations of the two genotypes are shown in Table 5; these data confirm that SC is a milder disease than SS. Nevertheless, painful crises are not uncommon in SC, and the chest syndrome accounts for 12% of all admissions in both conditions. Infections and leg ulcers are rare in Britain. Few sequestration crises were seen, probably because the follow up did not

start until the second year of life or later in most patients (see Table 3).

The severity of the disease may also be assessed by the number of hospital admissions per year of follow up. This is shown in Table 6 for the under fives, school children, and adults. Patients with SS required on average one admission to hospital per year of follow up. Nine of the 25 adults accounted for 121 (59%) of 202 admissions, however, and required on average just over four admissions per year of follow up. No such severely affected subgroup was identified among the children with SS or patients with SC.

The incidence of common chronic complications of SS and SC is shown in Table 7.

COMPARISON OF CLINICAL FEATURES OF SICKLE CELL DISEASE IN LONDON AND JAMAICA

Sickle cell disease is affected by environmental as well as genetic factors. Cold climate, leg trauma, and exposure to infections may all affect the severity of sickle cell disease. Table 8 compares some clinical features in Brent and Jamaica.^{10 12-15}

Admissions for painful crises were required by more patients with SS in Brent than in Jamaica. The decision to admit is subjective and may not necessarily reflect the increased severity of vaso-occlusion. It is, however, interesting that fewer patients with SC needed admission for painful crisis in Brent than in Jamaica.

Similar percentages of patients with SS in both locations were admitted with chest syndrome; in SC chest syndrome was less common in Britain than in Jamaica. Leg ulcers were rare in Brent, but common in Jamaica. Splenomegaly was found in 14% of SS patients in England and in Jamaica, but was more common in Jamaican SC patients than in the Brent ones.

There were fewer pregnancies in Brent women with sickle cell disease than in their Jamaican coun-

Table 8 *Comparison of some clinical features in Brent and Jamaica*

Clinical feature	SS		SC	
	Brent	Jamaica	Brent	Jamaica
No of patients studied	68	88	71	90
No of patients requiring admission for painful crises	63 (92%)	35 (39%)	16 (22.5%)	35 (39%)
No of patients admitted with chest syndrome	18 (26%)	30 (37%)	6 (8%)	26 (29%)
Leg ulcers	3 (4%)	40 (45%)	0 (0%)	18 (20%)
Splenomegaly	10 (14%)	12 (17%)	23 (32%)	51 (57%)
Priapism (cases/men)	7/31	5/40	2/31	4/44
Retinopathy (cases/examined)	2/10	36/306	14/21	101/282
Aplastic crises	5	6	3	Not known
No of pregnancies	12/23	46/30	38/23	72/21
per women over 16	(0.52)	(1.53)	(1.65)	(3.1)
Fetal loss per pregnancy	3/12	9/46	5/38	7/72

Table 9 Deaths in sickle cell disease, Brent 1974-84

Genotype	Year of death	Age	Sex	Cause of death	Necropsy
SS	1974	9	M	Chest syndrome	Yes
SS	1974	15	F	Sudden death at home, cause unknown	Yes, coroner's
SC	1976	49	F	Chest syndrome, CVA	Yes
SS	1979	15	M	Chest syndrome	No
S/Beta ⁰ thal	1981	19	F	CVA in pregnancy	Yes, coroner's
SS	1982	19	M	Asthma, respiratory arrest	Yes, coroner's
SS	1983	22	M	Chest syndrome	Yes

CVA = cerebrovascular accident.

terparts, probably reflecting the altered social and reproductive pattern, as well as the relatively young mean age of the Brent group (21.9 for SS women and 26.3 for SC women).

The general impression is that the patients with SS in Britain have more vaso-occlusive crises but fewer cases of chest syndrome and leg ulcers. Patients with SC seem to be less severely affected in Britain than in Jamaica. The accuracy of these observations can be confirmed only by careful long term natural history studies, preferably on cohorts followed from birth. Such cohort studies are neither available nor planned in Britain.

Mortality

No data are available on the expected survival for patients with sickle cell disease in Britain. In the Jamaican cohort study Serjeant¹⁰ has shown a mortality of 10% in the first year of life, 5% in the second, and 3% in the third. He suggests that by the age of five the child may have survived the highest risk period and that the prognosis improves with age. Serjeant also states that "by the age of 20 years survival to 30 or 40 years may not be uncommon."

In the longitudinal study of 422 children in Los Angeles, Powars¹⁶ calculated a 10% death rate during the first decade and 5% during each subsequent decade of life. Mann¹⁷ followed 96 Birmingham children for 10 years and found an overall mortality of 1% per year. In the UK survey² 37 deaths were noted: 27 deaths were in SS patients (of the under 10s five died in the first two years of life and an additional 10 in the first decade) and 10 deaths were in SC patients (only in three under-10s: one at the age of 2.5, and two at 6 and 7 years of age).

Seven of the regularly followed patients in Brent died between 1974 and 1984. Another patient, a boy aged 18 with SS, died in September 1984 from chest syndrome. Their details are shown in Table 9. It is at present impossible to assess the mortality from sickle cell disease in Britain, but it is likely to be similar to that described by Powars for Los Angeles 10 years ago.

Future

There is an urgent need for good epidemiological studies of sickle cell disease in Britain. Most of the patients living in Britain are British born (97 of 155 Brent patients) and it is essential that their prognosis is established, not only for the patient's and his family's sake, but also to enable the health authorities to plan the appropriate health care.

It is a matter of utmost urgency that the British born babies with sickle cell disease are protected from the devastating infections and high early mortality. This has been successfully achieved in the USA^{7,18} and Jamaica¹⁹ through a programme of newborn screening, antibiotic prophylaxis, and parental education.

A more specific determination of the interaction of sickle cell disease, in particular SS, with other genes, such as homozygous alpha thalassaemia or heterocellular persistence of haemoglobin F, is essential if we are to offer antenatal diagnosis. At the same time a systematic campaign of educating the sufferers, the community at risk, and the health professionals must be undertaken. As for the other inherited debilitating diseases, health, educational and social needs should be recognised and eventually met.

The size of the problem in Britain is often underestimated. For example, in Brent nearly 40% of all acute admissions to haematology beds are for acute sickle cell disease manifestations. Roughly one third of the adults with sickle cell disease have a severe debilitating disease and require much effort and time in both inpatient and outpatient care. Others, although less severely affected, still need a meticulous follow up to prevent serious complications. In certain urban areas in Britain, sickle cell disease represents an important and increasing proportion of haematological workload.

The management of both acute and chronic manifestations of sickle cell disease is at present haphazard, with poor interdisciplinary cooperation and little or no coordination of effort; in many ways the situation is reminiscent of haemophilia 25 or 30

years ago. Although there are promising antisickling agents on the horizon, none is likely to be available immediately or to have a complete success in preventing all the manifestations of sickle cell disease. It therefore becomes increasingly important to establish firm guidelines for comprehensive management of sickle cell disease in Britain.

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