Incidence of overt and covert neurological damage in children with sickle cell disease

P.C. Hindmarsh,¹ M. Brozovic,² C.G.D. Brook¹ and S.C. Davies²

Departments of ¹Paediatrics and ²Haematology, Central Middlesex Hospital, London NW10 7NS, UK.

Summary: We studied 25 patients with sickle cell disease (15 with HbSS; 8 with HbSC and 2 with HbSβ⁰) using neurological examination as a marker of overt and computed tomographic (CT) scan as a marker of covert neurological damage. Of the 25 patients, 5 (20%) had evidence of cerebral infarcts on CT scan, but only 4 of these 5 patients had neurological signs. Neurological problems were only seen in patients with HbSS. We could not identify any haematological risk factors, but in this small group of HbSS patients a crisis rate greater than 1 per year of follow up was associated with a significant risk of neurological damage.

Introduction

The clinical course of sickle cell disease (SCD) is characterized by repeated crises the commonest being vaso-occlusive. These events may occur anywhere in the body but the most debilitating manifestations occur in the nervous system.¹ They include cerebral infarction, subarachnoid haemorrhage, transient ischaemic episodes and spinal cord syndromes.² Several investigators have studied the neurological complications of SCD but patients have been selected on the basis of neurological dysfunction.^{3,4} The overall incidence of covert, as opposed to overt, ischaemic cerebral damage, therefore, remains unclear.

Blood transfusion regimens to suppress haemoglobin S production have been employed to reduce mortality from cerebral sickling events but they are not without complications.^{5,6} Knowledge of the incidence of overt and covert neurological damage is essential in order that permanent handicap may be avoided and methods of preventing cerebral sickling utilized in an effective manner. The purpose of this study was to establish the incidence in a population of children with SCD and to define any predisposing risk factors.

Methods

Twenty-five children with SCD aged between 6 and 17 years were studied; 15 have sickle cell anaemia (HbSS),

Eight have HbSC and 2 have sickle cell thalassaemia (HbSβ⁰). Children under the age of 5 were excluded from the study as they could not undergo computed tomographic (CT) scan without sedation. Parental consent was obtained and the study was approved by the Hospital Ethical Committee.

Patients underwent a full neurological history (with particular reference to such manifestations as convulsions or visual disturbance), clinical neurological examination and a CT head scan. The hospital records were reviewed with respect to precipitating and prodromal illness.

The EMI CT 1010S Scanner was used routinely and scans were interpreted by two neuroradiologists who were unaware of the clinical findings. In patients with overt neurological signs, a high resolution CT scan (GE8800) was performed.

Haematological variables [haemoglobin (Hb), PCV, MCV, MCHC, MCH, %HbF, %HbA₂] and the number of admissions for SCD-related crises per year (vaso-occlusive, sequestration, aplastic) were compared between the group of patients with no neurological damage and those with. Student's *t* test was used to test the significance between groups.

Results

Twenty-five children took part in both neurological and radiological aspects of the study. Five out of 25 (20%) children had evidence of cerebral infarcts on CT scan but only 4 of the 5 had neurological signs on physical examination. All 5 children had sickle cell anaemia (HbSS). Details of these patients and their

Correspondence: P.C. Hindmarsh M.R.C.P., Paediatric Department, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK.

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Table 1 Details of the 5 SCA patients with neurological damage

	Case no				
	1	2	3	4	5
Age	6.8	10.3	12.9	13.3	13.7
Sex	M	M	F	F	M
No of admissions/year	1.8	1.6	1.8	1.8	4.0
Neurology	Right hemiparesis Occipital epilepsy Special School	Poor long & short term memory	Normal	Right hemiparesis	Left hemiparesis Epilepsy Special School
Age at diagnosis of neurological problems	1.3	10.3	12.9	11.3	4.5
CT scan	Yes	Mild	Mild	Yes	Yes
Cerebral atrophy	Yes	Yes	Yes	Yes	Yes
Multiple cortical infarcts	15.8	5.1	3.1	6.5	1.56
% HbF					

neurological and radiological findings are shown in Table 1.

The CT scan abnormalities detected consisted of multiple cortical infarcts and cerebral atrophy. In cases 2 and 5 the cerebral atrophy was particularly marked (Figure 1). The majority of infarcts were in the watershed between the area supplied by the anterior and middle cerebral arteries.

There was no significant difference in haemoglobin, PCV, MCV, MCH, MCHC, HbA₂, HbF, α :non α globin chain synthesis ratio and platelet count between the groups of children with cerebral complications and those without. However, case 1 had a high HbF, 14.8%, at the time of his acute hemiplegia (age 16 months) which was probably age related.

The children without overt and covert neurological damage averaged 0.43 hospital admissions per year (range 0–1.2), while those with neurological damage experienced a greater number of hospital admissions for vaso-occlusive crises, 2.0 per year (range 1.0–4.0), prior to presentation with neurological complications. This difference was statistically significant ($P < 0.001$).

Discussion

This study has demonstrated a median age of onset from neurological problems of 6.8 years with neurological involvement in 20% of the clinic population, confirming previous reports.^{2–4} In addition, we have demonstrated significant differences in admission rates between the affected and non-affected groups. This difference may not be maintained in adult life⁷ which may explain why Powars *et al.*⁴ were unable to demonstrate any association with an increased crisis rate. It is also possible that our findings differed because the group studied by us were haematologically more homogeneous with the α thalassaemia interactions excluded.^{8,9}

Decreased levels of HbF are thought to be a risk factor for the development of cerebrovascular disease in SCD.^{4,10} This relationship is not linear and a threshold level exists somewhere between 10–15% HbF above which the risk is very low.¹¹ Although the percentage HbF of those with neurological deficit was low the difference was not statistically significant from the other children studied. Other haematological variables were not of predictive value in patients with HbSS as has already been established.⁴

All patients with evidence of neurological deficit had SCA but neurological problems have been documented in patients where the β gene interacts with other β gene variants and β thalassaemia such as HbSC disease.¹² It is apparent, therefore, that a more sophisticated haematological assessment of these patients is essential particularly in view of the haematologically and genetically distinct forms of SCA seen in southern

Figure 1 High resolution CT scan of Case 5 showing multiple cortical infarcts and cerebral atrophy.

and west Africa¹³ and also in Saudi Arabia.¹⁴

Our studies on this small group of children confirm that there is a high prevalence of overt and covert

neurological complications in patients with homozygous HbSS. In this subgroup high crises rate per year of follow up appeared to be associated with neurological damage. Acute hemiplegia seemed to be the major presentation in our group, as it is in children suffering with strokes in general.¹⁵ Patients with homozygous HbSS and high crisis rate should undergo regular neurological examinations at six monthly intervals with psychometric testing at yearly intervals. Implementing psychometric testing should reduce the need for regular CT scans but these are indicated if change is detected in any of the parameters already outlined. Blood transfusion regimens should be instituted promptly with the aim of keeping the % HbSS below 15–20.

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