# Improved survival in homozygous sickle cell disease: lessons from a cohort study

Allison Lee, Peter Thomas, Lena Cupidore, Beryl Serjeant, Graham Serjeant

**Abstract**

***Objective*—To examine whether simple interventions in a sickle cell clinic improve survival in sickle cell disease.**

***Design*—Survival curve analysis and hazard ratios in a cohort study followed from birth.**

***Setting*—MRC Laboratories (Jamaica) at the University of the West Indies, and Victoria Jubilee Hospital, Kingston, Jamaica.**

***Subjects*—315 patients with homozygous sickle cell disease detected during the screening of 100 000 consecutive non-operative deliveries between June 1973 and December 1981 at the main government maternity hospital, Kingston, Jamaica.**

***Interventions*—Prophylactic penicillin to prevent pneumococcal septicaemia, parental education in early diagnosis of acute splenic sequestration, close monitoring in sickle cell clinic.**

***Main outcome measures*—Survival.**

***Results*—Survival appeared to improve, the log rank test for trend comparing the first, second, and last third of the study reaching borderline significance (P=0.05). Combined deaths from acute splenic sequestration and pneumococcal septicaemia-meningitis declined significantly (test for trend, P=0·02).**

***Conclusion*—Early diagnosis and simple prophylactic measures significantly reduce deaths associated with homozygous sickle cell disease.**

## Introduction

The debate on bone marrow transplantation in the treatment of homozygous sickle cell disease has highlighted the need for assessing alternative approaches.[1-3] Bone marrow transplantation is an expensive, high technology procedure applicable only to the approximately 20% of patients with an identical HLA matched sibling[4] and carries a short term mortality of around 10%. At a conservative cost of $100 000 per patient it is unlikely to be applicable on a population basis especially in countries with limited resources where most sickle cell disease occurs. An alternative approach is the assessment of simple measures to prevent the high early mortality of the disease.[5] These include prophylactic penicillin,[6,7] parental education of acute splenic sequestration,[8] better understanding of the pathogenesis and treatment of aplastic crisis,[9] more effective treatment of the acute chest syndrome,[10,11] earlier intervention after neonatal diagnosis, and coordinated management in dedicated sickle cell clinics. These measures are likely to diminish morbidity and improve survival, but their effects have not been documented until this assessment in the Jamaican cohort study of sickle cell disease.

## Patients and methods

The patients attended the sickle cell clinic of the University Hospital of the West Indies, Kingston, Jamaica, and participated in a cohort study of all people with sickle cell disease born among 100 000 consecutive non-operative deliveries at the government maternity hospital (Victoria Jubilee) between June 1973 and December 1981. Screening identified 315 babies with homozygous sickle cell disease, of whom eight failed to be admitted to the study. The 307 remaining patients were followed as described[12] and defaulting patients actively traced. Diagnostic criteria have been described previously.[13]

To assess changing survival the 315 children were divided into three equal groups of 105 children born between 25 June 1973 and 27 December 1975 (30 months), 28 December 1975 and 2 January 1979 (36 months), and 3 January 1979 and 28 December 1981 (36 months). Mortality was assessed with survival curve analysis by using the product limit method. Survival was examined from birth to the 15th birthday, and survival curves for each third were compared by using the log rank test for trend. Hazard ratios were calculated with Cox's proportional hazards model.

The cause of death was determined by necropsy in 54/61 deaths. Cases with multiple diagnoses were arbitrarily assigned to the perceived more serious event. Two cases with acute splenic sequestration and blood cultures that yielded positive results were attributed to septicaemia, and in one with the acute chest syndrome and acute splenic sequestration review suggested that the chest pathology led to death.

## Results

There were 61 deaths before 15 years of age, 28 in the first third, 17 in the second third, and 16 in the last third; the log rank test for trend being of borderline significance (P=0·05). Table 1 summarises the probability of cumulative survival in the three groups, and the figure shows the survival curves. The hazard ratio (95% confidence interval) for adjacent thirds was 1·37 (1·00 to 1·88).

**Table 1**—*Cumulative survival* in homozygous sickle cell disease according to date of birth. Figures are proportion surviving (95% confidence intervals)*

| Age (years) | First third (June 1973-December 1975) | Second third (December 1975-January 1979) | Last third (January 1979-December 1981) |
|---|---|---|---|
| 1 | 0·90 (0·85 to 0·96) | 0·97 (0·94 to 1·00) | 0·95 (0·91 to 0·99) |
| 2 | 0·86 (0·80 to 0·93) | 0·95 (0·91 to 0·99) | 0·94 (0·90 to 0·99) |
| 3 | 0·83 (0·75 to 0·90) | 0·93 (0·88 to 0·98) | 0·93 (0·88 to 0·98) |
| 5 | 0·81 (0·73 to 0·88) | 0·91 (0·86 to 0·97) | 0·91 (0·86 to 0·97) |
| 10 | 0·77 (0·68 to 0·85) | 0·85 (0·78 to 0·92) | 0·87 (0·80 to 0·93) |
| 15 | 0·73 (0·64 to 0·81) | 0·83 (0·75 to 0·90) | 0·84 (0·77 to 0·91) |

*Total deaths were 28 in first third; 17 in second third; 16 in last third.

The principle causes of death (table 2) in the first group were septicaemia-meningitis, the acute chest syndrome, and acute splenic sequestration. As acute splenic sequestration and pneumococcal septicaemia-meningitis were the two common complications in which specific interventions were used, these were combined for analysis and together showed a significant decline in mortality during the study (test for trend, P=0·02; table 3). The hazard ratio (95% confidence interval) for adjacent thirds of the study was 2·40 (1·11 to 5·19). No change was observed in the

**MRC Laboratories (Jamaica), University of the West Indies, Kingston, Jamaica**
Allison Lee, *medical student*
Peter Thomas, *statistician*
Lena Cupidore, *nurse practitioner*
Beryl Serjeant, *chief technologist*
Graham Serjeant, *director*

Correspondence to:
Professor G Serjeant.

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numbers with the acute chest syndrome. In seven patients without necropsy the cause of death was unknown and could not be assumed from the history by family interview. One child died aged 7 years, three years after splenectomy for hypersplenism, having defaulted without pneumococcal prophylaxis; the history of fever and premonition of death was consistent with septicaemia. Two others died with high fever and four suddenly but without known cause.

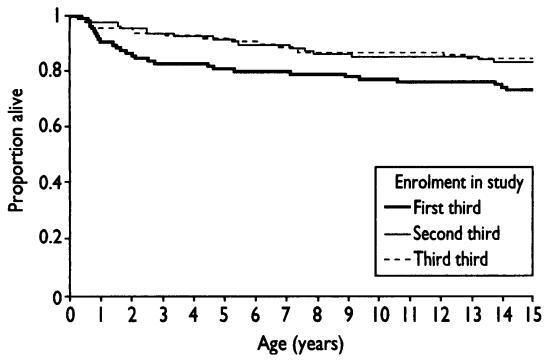
## Discussion

There seems to be a trend of improved survival of cohort study children with sickle cell disease and, in particular, a significant trend of reduced mortality from acute splenic sequestration and pneumococcal septicaemia-meningitis combined. The decreased number of deaths from pneumococcal disease followed an apparently successful trial of pneumococcal prophylaxis,[6] although mortality in the United States declined before widespread use of penicillin, possibly reflecting greater awareness, earlier diagnosis, and more prompt treatment.[14] Latterly, *Haemophilus influenzae* was a more common agent consistent with a recognised susceptibility[15] and suggesting the need for specific prophylaxis against this organism. Reduction in deaths from acute splenic sequestration probably resulted from both parental detection of the first episode[8] and prophylactic splenectomy after two serious attacks, which together have reduced mortality from this complication by about 90%. The acute chest syndrome remains an important problem and, although aggressive transfusion treatment may reverse acute pulmonary sequestration in some cases,[10 11] no decline in incidence was observed. Stroke has also shown no change and, although chronic transfusion may reduce the incidence of recurrence,[16] nothing can yet be done to prevent the initial stroke. The aplastic crisis is a cause of death where reduced mortality might be expected as the epidemiology is well known, the clinical course benign and predictable if oxygen carriage is maintained by transfusion, and virtually all cases are caused by human parvovirus infection, auguring well for a vaccine, which is currently under development.

In addition to the documented effects on acute splenic sequestration and pneumococcal septicaemia-meningitis, dedicated clinics with specialist knowledge to which the patients have easy access are likely to encourage patients to present earlier, allowing more time for effective treatment. These observations from the Jamaican cohort study show that simple readily implementable measures may improve survival in sickle cell disease, but to avoid the high mortality in the first year of life neonatal detection of sickle cell disease is essential. Early detection of sickle cell disease and implementation of these preventive measures is the most realistic and feasible approach to improving survival in sickle cell disease.

### Key messages

- Neonatal screening of 100 000 consecutive babies delivered non-operatively has identified a representative sample of 315 patients with homozygous sickle cell disease
- Long term follow up identified major early causes of death such as acute splenic sequestration, pneumococcal septicaemia, aplastic crisis, and the acute chest syndrome
- Specific interventions included pneumococcal prophylaxis to prevent pneumococcal septicaemia and educating parents about the early detection of acute splenic sequestration
- Survival significantly improved when the first, second, and last thirds of the patient group were compared
- Simple low technology interventions that are readily implemented significantly improve survival in homozygous sickle cell disease




*Survival of cohort with homozygous sickle cell disease followed up to 15th birthday by period of enrolment*

**Table 2**—*Causes of death according to date of birth*

| Diagnosis | First third (June 1973-December 1975) | Second third (December 1975-January 1979) | Last third (January 1979-December 1981) |
|---|---|---|---|
| Acute splenic sequestration | 5 | 2 | 1 |
| Acute chest syndrome | 5 | 5 | 6 |
| Gastroenteritis | 3 | 0 | 0 |
| Septicaemia-meningitis: | | | |
| Pneumococcal | 4 | 1 | 1 |
| Salmonella | 2 | 0 | 1 |
| *Haemophilus influenzae* | 0 | 0 | 3 |
| Unknown organism | 2 | 0 | 0 |
| Stroke | 4 | 2 | 2 |
| Aplastic crisis | 1 | 0 | 1 |
| Portal vein thrombosis | 0 | 1 | 0 |
| Unknown | 2 | 4 | 1 |
| Motor vehicle accident | 0 | 2 | 0 |
| Total | 28 | 17 | 16 |

**Table 3**—*Cumulative survival in homozygous sickle cell disease according to date of birth (deaths from acute splenic sequestration and pneumococcal meningitis-septicaemia only). Figures are proportion surviving (95% confidence intervals)*

| Age (years) | First third (June 1973-December 1975) | Second third (December 1975-January 1979) | Last third (January 1979-December 1981) |
|---|---|---|---|
| 1 | 0·96 (0·92 to 1·00) | 0·99 (0·97 to 1·00) | 0·99 (0·97 to 1·00) |
| 2 | 0·94 (0·89 to 0·99) | 0·98 (0·95 to 1·00) | 0·99 (0·97 to 1·00) |
| 3 | 0·93 (0·88 to 0·98) | 0·98 (0·95 to 1·00) | 0·99 (0·97 to 1·00) |
| 5 | 0·92 (0·86 to 0·97) | 0·98 (0·95 to 1·00) | 0·98 (0·95 to 1·00) |
| 10 | 0·91 (0·85 to 0·97) | 0·97 (0·93 to 1·00) | 0·98 (0·95 to 1·00) |
| 15 | 0·91 (0·85 to 0·97) | 0·97 (0·93 to 1·00) | 0·98 (0·95 to 1·00) |

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# Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease

A J Lees on behalf of the Parkinson's Disease Research Group of the United Kingdom

## Abstract

***Objective*—To compare effectiveness of levodopa and levodopa combined with selegiline in treating early, mild Parkinson's disease.**

***Design*—Open, long term, prospective randomised trial.**

***Setting*—93 hospitals throughout United Kingdom.**

***Subjects*—520 patients with early Parkinson's disease who were not receiving dopaminergic treatment.**

***Interventions*—Treatment with levodopa and dopa decarboxylase inhibitor (arm 1) or levodopa and decarboxylase inhibitor in combination with selegiline (arm 2).**

***Main outcome measures*—Assessments of serial disability, frequency and severity of adverse events, and deaths from all causes.**

***Results*—After average of 5·6 years' follow up, mortality ratio in arm 2 compared with arm 1 was 1·57 (95% confidence interval 1·09 to 2·30), and difference in survival between the two arms was significant (log rank test, P=0·015). Hazard ratio adjusted for age and sex was 1·49 (1·02 to 2·16), and after adjustment for other baseline factors it increased to 1·57 (1·07 to 2·31). Patients in arm 1 had slightly worse disability scores than those in arm 2, but differences were not significant. Functionally disabling peak dose dyskinesias and on/off fluctuations were more frequent in arm 2 than arm 1. During the trial the dose of levodopa required to produce optimum motor control steadily increased in arm 1 (median daily dose 375 mg at 1 year and 625 mg at 4 years), but median dose in arm 2 did not change (375 mg).**

***Conclusions*—Levodopa in combination with selegiline seemed to confer no clinical benefit over levodopa alone in treating early, mild Parkinson's disease. Moreover, mortality was significantly higher with combination treatment, casting doubts on its chronic use in Parkinson's disease.**

## Introduction

Levodopa in combination with a peripheral dopa decarboxylase inhibitor substantially improves the functional disability and quality of life of patients with Parkinson's disease, and 25 years after its routine introduction into clinical practice it remains the most effective palliative treatment. However, it fails to halt the underlying progression of disease, and the long term therapeutic response is compromised by the emergence of abnormal hyperkinetic involuntary movements, fluctuations in motor performance and mood, and psychiatric side effects.[1] Although there is no definitive clinicopathological evidence to suggest that exogenous levodopa might be harmful to surviving nigral neurones in Parkinson's disease, it has been shown to increase oxidative stress in tissue cultures, thus consolidating theoretical concerns about its potential neurotoxicity in patients.[2] It also now seems clear that levodopa does not substantially improve the life expectancy of patients with Parkinson's disease.[3]

Recently, there has been interest in the notion that the antiparkinsonian drug selegiline hydrochloride, a selective type B monoamine oxidase inhibitor, might protect failing nigral neurones in Parkinson's disease and improve life expectancy. The Parkinson Study Group in the United States reported that, in the early stages of the disease, selegiline delayed the emergence of parkinsonian disabilities and the need for symptomatic treatment with levodopa by around nine months.[4] In their initial publication they suggested that selegiline might have a beneficial effect on the natural course of Parkinson's disease through neural protective mechanisms. On longer follow up, however, they concluded that selegiline did have symptomatic effects, and a worsening of motor scores was seen two months after selegiline had been stopped.[5] It has been proposed that the putative neuroprotective effects of selegiline may not be due just to its inhibition of type B monoamine oxidase but that trophic effects and alteration of gene expression in damaged neurones may also occur.[6] However, the symptomatic antiparkinsonian effects of selegiline and the subjective end point of the DATATOP study confound the interpretation of its main findings.[7]

In 1985 the Parkinson's Disease Research Group started a study of the possible beneficial effects of combining selegiline with levodopa (with a dopa decarboxylase inhibitor) on the natural course of Parkinson's disease and the potential advantage of starting antiparkinsonian treatment with a dopamine agonist (bromocriptine).[8] The interim three year report indicated that all three treatment regimens led to improvement in baseline disabilities after one year of continuous treatment but that functional disability and physical signs had deteriorated after three years.[9] No significant differences were found between the two study arms with levodopa, but both treatments were significantly more effective than bromocriptine and produced fewer adverse reactions in the first three months of treatment. However, drug induced dyskinesias and motor fluctuations in performance

**Parkinson's Disease Research Group of the United Kingdom, National Hospital for Neurology and Neurosurgery, London WC1N 3BG**
A J Lees, *honorary secretary*

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