SICKLE CELL DISEASE IN SIERRA LEONE: A NEGLECTED PROBLEM

G. T. ROBERTS[1], A. E. GABBA[1], T. L. ROBERTS[1], G. DEEN[1,2] and I. WURIE[3]

[1]Sierra Leone Sickle Society, 25 Thomas Street, Freetown, Sierra Leone, [2]Connaught Hospital, Freetown, Sierra Leone, [3]Ramsy Laboratory, 14 Liverpool Street, Freetown, Sierra Leone

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Corresponding Author: *George T. Roberts* ***Email:*** *gtr@sleonesickle.org*

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SUMMARY

Background: Sickle cell disease (SCD) is common in Sierra Leone although its exact prevalence, incidence and clinical spectrum are unknown.

Methods: Using a statistical package, StatsDirect (Altrincham, United Kingdom) we analyzed the demographic characteristics, presentations, acute events, treatments and clinical outcomes in a cohort of SCD patients attending sickle cell clinics in Freetown, Sierra Leone between February 2007 and August 2010.

Results: There were 446 patients, median age of 13 years. Of these, 435 were homozygotes (HbSS), median age 13 years also. There were 248 females, median age 12.5 and 198 males, median age 14, resulting in a male:female ratio of 0.79. Eleven (2.4%) were Sickle Cell-HbC disease, median age 14 years. Patients demonstrated many of the typical features of SCD. The most common reason for hospital admission was bone pain crisis associated with an infection, followed by severe anemia. Aseptic necrosis of the femoral head, leg ulcers, septic osteomyelitis and gallstones were seen in 0.22% of patients, but strokes and acute chest syndrome were not observed. The death rate was 2.51/100 patient years observation with an estimated mean survival of 3.6 years (CI 3.2-3.7). Severe anemia was implicated in the death of 8 patients (50%), whereas only 2 deaths (12.5%) were attributable to bone pain crisis. One death (6.25%) was associated with pregnancy complicated by severe anemia and another with an adverse blood transfusion event.

Conclusion: The clinical outcomes in this series highlight the need for a more comprehensive provision of care for SCD patients in Sierra Leone.

Keywords: Sickle cell disease, Sierra Leone, survival, anaemia, haemoglobinopathy

INTRODUCTION

One hundred years ago, Dr J.B. Herrick, a physician practicing in the American city of Chicago, published the first description of sickle cell disease (SCD) in the western medical literature.[1] His patient, Walter Clement Noel, a native of the West Indian Island of Grenada had been a student at the city's College of Dental Surgery between the years 1904 and 1907. In the century since that first report, a considerable body of knowledge has been amassed on the biology, epidemiology, management and treatment of SCD throughout many regions of the world. However, even though Sierra Leone lies within the equatorial belt in Africa, where the highest estimates of the sickle gene have been recorded, [2] very little information on the disease has been published from the country. The only significant work in the century since Herrick's first report was that of Knox-Macaulay who, in 1983, published his observations on a series of 121 Sierra Leonean patients whom he had been following prospectively.[3]

One hundred and six of Knox-Macaulay's patients were homozygous SCD (HbSS) with a small minority of 15 (12.4%) sickle cell/hemoglobin C or HbSC disease. Interestingly, Knox-Macaulay observed that 55% of his patients were descendants of African slaves who had regained their freedom and had been repatriated from North America and the West Indies, as well as others directly from other countries in Western Africa who had been liberated from ships that were taking them across the Atlantic Ocean to slavery.[4] These freed slaves were all landed at the port of Freetown, now the capital city of Sierra Leone. It goes without saying, therefore, that the descendants of those freed slaves, who are now called "Creoles," but more correctly, "Krios,"[5] have strong ethnic and genetic relationships with Black West Indians and African-Americans, closing the circle back to that foundation paper by Dr Herrick.

Ethnic diversity is of course an important factor in understanding some of the clinical aspects of SCD because haplotype diversity, occurring among ethnic groups can distinguish one community of sickle gene carriers from another .[6] By the same token, this type of diversity can mediate clinical manifestations of the disease, for better or for worse.[7] Notwithstanding this, however, it was not surprising that Knox-Macaulay was unable to detect any significant clinical differences between Sierra Leonean "Creoles" and "non-Creoles." It is not surprising because of a number of reasons. Firstly, the numbers were too small for statistical power to accrue in the cohort. Secondly, the Creole ethnic group is extremely diverse in its African, Afro-American and Afro-Caribbean origins as we have already seen.[5] Slaves, landed in the West Indies and America came from a variety of African sources.[8]

Some of those who were taken to America, in particular, came originally from the Sierra Leone hinterland.[9] Those who had come from elsewhere would have, inevitably, during the hundred or so years before eventual repatriation to Sierra Leone, inter-married, not only among themselves, but probably also with slaves who had been taken directly from Sierra Leone. Further diversity in the Creole group would have occurred, as explained previously, as a result of individuals introduced into the early community directly from various West African sources (including Sierra Leone) during the early to mid-nineteenth century.[9] This latter group of "liberated Africans" as they were called, eventually integrated and intermarried with the returnees from across the Atlantic Ocean, and indeed other Sierra Leoneans.[9]

When Knox-Macaulay compared Sierra Leone sickle cell patients with other groups of sickle cell patients elsewhere in the world, both similarities and divergences were observed. For example, vaso-occlusive events were similar to those in American, Jamaican, Ghanaian and Nigerian patients. [10,11] And whereas the frequency of leg ulceration in Sierra Leonean sickle cell patients was relatively low (13.2% SS, 13.3% SC) when compared to patients in the United States (73.6% SS) and Jamaica (63.3% SS), it was relatively high in comparison to Nigerian and Ghanaian patients.

On the other hand, avascular necrosis of the femoral head (ANFH) was more common among Sierra Leonean patients as a whole (8.5% SS, 20% SC) than in Ghanaians (2.8% SS, 6.6% SC), although similar to frequencies in Jamaican patients (8.2% SS, 18% SC).

Although Knox-Macaulay considered that these differences in complication rates could probably be attributed to environmental factors, they are only likely to be fully understood if haplotype and other biological elements are factored in.

As far as environmental factors go, they not only influence clinical outcomes but, at least one, malaria, in addition to potentially provoking acute painful episodes in the sickle cell patient, underpins the high prevalence rates the sickle gene demonstrates wherever it occurs.[12] Half a century after Herrick's report, it was hypothesized that the high prevalence of beta-thalassemia trait was the result of a balance between the red cell abnormality and *Plasmodium falciparum* malaria.[13] This hypothesis was subsequently extended to include other red blood cell polymorphisms among which, HbS is preeminent.[14]

The protection against severe malaria that the sickle trait (AS) and other mild RBC abnormalities afford provides a survival advantage for individuals who carry them.[15] Consequently, the hypothesis goes, individuals who carry the traits enjoy a relatively robust resistance to malaria and survive to adulthood, whilst homozygotes, on the other hand, die early, succumbing to a variety of environmental challenges.[16] In Sierra Leone, where *P. falciparum* malaria is hyperendemic, [17] it can be expected, therefore, that the prevalence of the sickle gene would be high.

Two reports, one in the mid-fifties and the other, four decades later, examined the prevalence of the trait among blood samples in two separate series. In the earlier report, Rose and Suliman examined the prevalence of sickle cell trait (SCT) among individuals of the Mende ethnic group, [18]whilst in the later publication Wurie et al reported a sickle cell positive rate of 22% among 3274 sodium metabisulfite-tested specimens processed in their laboratory during the early 1990's.[19]

Although these reports are useful, they do not, however, address some of the important questions about prevalence among communities in Sierra Leone. Nor do they begin to tackle the magnitude of the SCD burden and its consequences among Sierra Leoneans. Moreover, the only report focusing on clinical features was published in 1983.[3] The rationale for undertaking this study, therefore, is to update information about the disease in Sierra Leone and to re-evaluate its clinical features in patients in this country. Furthermore, a study such as this could provide a basis for greater insight into the factors that influence clinical outcomes.

METHODS

The patients

The patients in this study were registered at the clinics of the Sierra Leone Sickle Cell Society (SLSCS) in Freetown, from 1st February, 2007 to 31st August 2010. Patients consisted predominantly of children under the age of 18 years. At the clinics, they received intensive counselling about the nature of SCD and its complications and how to prevent and manage crises. In addition, they were given basic medications to assist nutrition (folic acid) and prevent complications (Penicillin V, Amoxicillin). Anti-malaria prophylaxis is provided with weekly Pyrimethamine supplemented with advice to sleep inside an insecticide-treated bed net. Painful crises, when mild, were managed at home and at the clinics with mild analgesics including Paracetamol, Ibuprofen and Diclofenac plus oral rehydration solutions.

Patients with complicated and more severe pain, not controlled by these measures, were referred on to hospital for more intensive care. Other symptoms that could not be managed at the clinics were also referred to hospital. Patients were followed up on regular monthly visits, and non-attendance at specified appointments was investigated by mobile telephone and, where feasible, home visits to patients who continue not to show up.

Procedures

We retrieved the records of patients in the clinics of the SLSCS and extracted the demographic data of date of registration, age first seen at the clinics, gender, clinical features and date of death and age at death. The data on hemoglobin phenotype, determined by alkaline electrophoresis on cellulose acetate medium was also extracted. Data of ethnic group, as reported by the patient or parent, was also obtained. Records of landmark clinical events as well as reasons for onward referral were also retrieved. Causes of death were evaluated from clinical observations in the terminal events that preceded death.

Statistical analysis

Retrieved data was analyzed using the statistical package Stats Direct (Altrincham, United Kingdom, WA14 4QA) that provided descriptive characteristics as well as survival analysis. ANOVA was used to compare ages of the various categories of patients and survival characteristics were estimated by the Kaplan-Meier method. Start date of analysis was taken as the date at which the patient was registered. All surviving patients were censored at the same date, 31 August 2010.

RESULTS

There were 446 patients, representing 637 patient-years. The median age of the entire cohort was 14 years. The demographic data of age, gender and ethnic distributions are shown in Tables 1-3 and in Figure 1.

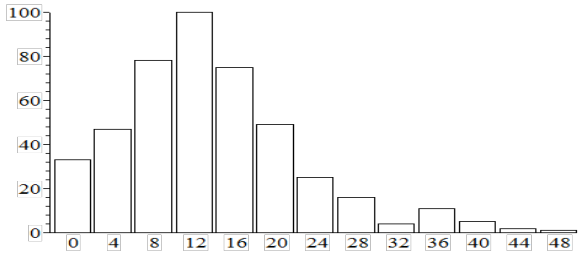

Figure 1 Age structure of Sickle Cell Disease Patients in Sierra Leone

Table 1 Sex and Age distribution of Sickle Cell Disease Patients

Phenotype	Number	Percent	Median Age (years)
All SCD Patients	446		14
All SCD – Females	248	55.6	13
All SCD – Males	198	44.4	14

Table 2 Sex and age distribution of HbSS and HbSC Patients

	Number	Percent	Median Age (years)
SS only	435	97.5	13
Female	240	55.2	12.5
Male	195	44.8	14
HbSC	11	2.5	14
Female	7	63.6	-
Male	4	33.4	-

Table 3 Distribution by Tribe compared with Census Distribution

Ethnic Group	**Number**	**Percentage**	**Census Percentages**
TEMNE	102	30	30
MENDE	51	15	30
KRIO	44	13	10
OTHERS	40	12	30

Homozygous sickle cell disease (HbSS) constituted the vast majority of patients, accounting for 435 (97.5%), whilst HbSC disease, the only other phenotype detected consisted of only 11 patients. ANOVA was used to compare the ages among all patient categories but no significant differences were revealed. Also, we could not detect any differences in ethnic distribution between HbSS and HbSC patients.

Clinical features

Clinical features encompassed some of the typical complications of SCD, with painful crises being the most frequent departures from the steady state. For the twelve month period when adequate figures were available, 48 (10.8%) patients required hospital admis-

sion. Of these, 16 were children under 10 years of age. Most admissions were for painful crises, associated with an infection episode.

Causes of the infection were not determined although some were attributed to malaria. However, 13 patients were admitted because of severe anemia. Three patients underwent surgical procedures, of which 2 were Caesarean sections. The third was for drainage of septic osteomyelitis. The organism involved was not determined. Thirteen patients received non-elective inpatient blood transfusion. One case each, of ANFH and leg ulcers, were observed.

There were no cases of stroke in the series, although 1 patient (0.22%) had neuropsychiatric disorder that impaired his societal interactions. One patient (0.22%) reported gallstones which she passed per rectum and an adolescent male reported priapism. Three pregnancies were recorded, one of which resulted in maternal and foetal death (33.3% mortality).

Survival

The majority of patients continue to live relatively active lives, attending school and, for adults, holding down jobs. However, a total of 16 (3.6%) patients have died, all with HbSS phenotype. The age at death ranged from 7-27 years, with a median of 17 years. Using the date of first registration as base, an attempt was made to calculate survival by Kaplan-Meier analysis (Figure 2), but the median survival (ordinate, in days) was too extended to be determinable. The mean incidence of death, however, was 2.51 per 100 patient-years. Estimated mean survival was 3.6 years (95% CI, 3.2 – 3.7 years).

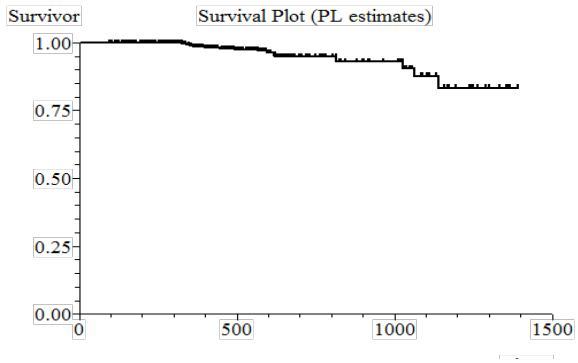

Figure 2 Survivals in 446 Sickle Cell Disease Patients

Causes of Death

The causes of death were not easy to determine. There were no autopsies. However, based on clinical events immediately preceding the deaths, causes of death were assigned, as indicated in Table 4 in which patients are identified by their unique patient numbers*. Significantly, 8 patients (50%) died of complications associated with severe anaemia and one patient (6.25%) had an adverse transfusion incident consistent with over-transfusion and/or haemolytic reaction during treatment for severe anaemia, and another patient died with anaemia complications associated with pregnancy.

Table 4 Causes of Death

Patients*	Age	Sex	Survival	Cause of Death
185	18	F	398	Severe anaemia
97	7	M	361	Unknown
254	3	M	493	Unknown
37	12	F	1064	Unknown
84	16	M	351	Severe anaemia
42	19	F	616	Bone pain crisis
175	11	M	595	Severe anaemia
85	7	M	569	Unknown
142	26	M	326	Bone pain crisis
199	9	M	342	Unknown
64	6	F	817	Severe anaemia
87	10	M	161	Severe anaemia
48	19	M	1029	Unknown
41	20	F	449	Pregnancy & anaemia
144	19	F	623	Severe anaemia
7	27	F	1141	Transfusion incident

DISCUSSION

The prevalence and incidence of SCD in Sierra Leone is unknown. However, based on limited survey results, the frequency of the trait is probably in the region of about 20-25%, [18,19] which would result in approximately 10-16 SS cases per 1000 live births annually. Using this figure and an estimated population of 6.4 million, [20] and with an annual birth rate of 44.7/1000, [20] it is likely that between 2816 and 4400 HbSS babies are born every year. To this should be added babies that are compound heterozygotes, the incidence of which is entirely unknown. However, their number is not likely to be less than 344 and could exceed 546, using data from Knox-Macaulay.[3]

Thus, the total number of new additions of sickle cell haemoglobinopathy to the population could be in the region of 3160 to 4946 annually. Determination of how many of these newborns survive to beyond 5 years could be fraught with difficulty as has been noted elsewhere.[21] However, subtracting the under-fives infant mortality of 154/1000 live births reported for Sierra Leone, [20] will result in a survival of between 3006 and 4792 babies. These numbers will add to their predecessors already surviving in the population. Determination of this cumulative number is, again, difficult[21] and only a well-structured population survey can elucidate it.

However, it can be assumed that this number is probably in the tens of thousands per generation, even if subsequent cumulative mortality is huge.

The patients we present in the current study, therefore, are likely to represent only a tiny fraction of SCD patients in the country. With that caveat, the cohort illustrates a number of features. Firstly, it confirms that HbSS disease predominates, although in this series, the proportion of the only other phenotype, HbSC, was, at 2.5%, smaller even than the 12.4% that Knox-Macaulay had observed in 1983.[3] Then, as in the current series, no other phenotypes were observed.

The reason for this is not known, but, in our view, is likely to be due to technical factors because, the only procedure applied for diagnosis is cellulose acetate electrophoresis, in which other variants could be missed. There is anecdotal evidence, however, of the presence of compound heterozygotes for beta-thalassemia (HbS Beta-thalassemia) in at least 2 unrelated Sierra Leonean families, diagnosed elsewhere. Furthermore beta-thalassemia trait frequencies of 9% have been reported from Liberia, with which Sierra Leone shares its eastern border.[21]

Another possible reason that could account for the apparent paucity of phenotypes other than HbSS is that other phenotypes may be milder than HbSS and therefore, do not seek medical attention or may get their treatment and management advice from traditional providers. The age structure of the cohort (Figure 1) is interesting in that median age is only 14 years, compared to 17 for the population at large.[20] This finding suggests that survival beyond childhood may be relatively reduced among SCD patients, as has been well-recognized elsewhere.[23]

This interpretation is reinforced by the fact that under 14's represent more than 59% of the group, in contrast to only 44.5% in the general population.[20] However, these observations should be interpreted with caution, as it is possible that older patients do not present themselves for a variety of reasons, one of which is that older, surviving patients may have milder disease and so do not seek medical attention.

The ratio of male to female is massively against males (198:248, or 0.79). In the general population this ratio is about 0.9 in the age sector under consideration.[20] The cause for this disparity is unknown. When Knox-Macaulay published his series in 1983, he observed that the Krios predominated over the other ethnic groups.[3]The proportions are reversed in the current series (Table 3), consistent with a demographic shift in this part of the country. In any case, the country-wide distribution of ethnic groups currently stands at, Temne 30%, Mende 30%, Krio 10% and other 30%.[20] Our series reflects these current trends, certainly with respect to Temnes and Krios. On the other hand, the situation in other parts of the country, where ethnic distribution may be more homogenous, is unknown. This is an important point to unravel, because provision of sickle cell care services in the future would depend partly on disease prevalence within communities.[20]

Clinical manifestation of SCD in the current series indicates that some features are not as severe or frequent as reported from other countries and indeed, in Knox-Macaulay's series. For example, ANFH was seen in only one patient (0.22%), contrasting with a 2.9% incidence reported from elsewhere in Africa.[24] However, apart from symptoms or physical signs, no systematic imaging techniques were used to assess the presence of hip joint disease. It would be important to ascertain the rarity of ANFH in this and similar groups of patients and to determine what underlies it.

Leg ulcers were also uncommon among our patients. Only one patient, a 19 year-old HbSS male had this complication, equivalent to a rate of only 0.16 per 100 patient years of observation, unlike elsewhere in Africa.[25] Here again, the reason for this rarity is unclear.
Gallstones, detected by imaging techniques, have shown, depending on age, prevalences as high as 58% in series from Jamaica, for example,[26] although they appear less frequent in African series.[27] In ours, where imaging techniques were not used, we observed only 1 case, in a 25 year old female, who passed the stone per rectum, without symptoms. Clearly, this is an area that needs further investigation.

The reasons why patients were admitted to hospital varied, but the most common was for pain crisis associated with a febrile episode. Although some of these patients reportedly had malaria, the causes for fever in others were not determined. Neither was the causative organism identified in the single patient with septic osteomyelitis. Bacteriological cultures were not available. Lack of microbiological detail is a major defect in our programme, since infection is a recognized risk factor for morbidity and mortality in SCD. For example, malaria was a principal cause for morbidity in Kenyan SCD patients.[28] On the other hand, the organisms involved in bacterial sepsis remain a cause for debate probably because of the lack of adequate identification procedures.[29] This is another area of research that requires attention.

In Nigeria, neurological incidents have been reported in varying frequencies among patients with SCD. For example, Fatunde et al, in Ibadan, found that, over a 15 year period, 5.4% of under-6 year-olds attending a

sickle cell clinic developed strokes.[30] Therefore, the absence of overt stroke in our series is surprising although a single case of neuropsychiatric disorder was observed in our patient with bilateral ANFH. It may be that stroke-affected patients are seen at stroke clinics elsewhere, where they receive treatment and follow-up.

But an alternative reason might be that SCD patients with stroke may have had severe disease to which they had succumbed before having an opportunity to present at out clinics. No systematic study of potential neurological impairment either by Doppler and/or by formal neuropsychiatric testing has been undertaken, nor were we able to conduct imaging studies such as CTI or MRI that could have revealed asymptomatic neurological lesions.

Some patients presenting with severe anemia required emergency blood transfusion usually attended by crises in blood procurement. When such crises were resolved, the clinical outcome was mainly satisfactory. However, in other instances, lack of appropriate blood apparently contributed to a fatal outcome. In one case, in contrast, a serious transfusion reaction was apparently a contributory factor to a fatal outcome in a 27 year-old female.

Sickle cell disease is a well-recognized risk-factor for poor outcomes in pregnancy.[31] In our series, three pregnancies occurred, resulting in good outcomes for both mother and child in two. However, in a third case, both mother and baby died during a Cesarean section in the severely anemic mother. Although this series of 3 is meager, a 33% mortality deserves close scrutiny to ensure better outcomes.

Priapism, another potential cause that could impair reproductive competence, was rare in this series, recorded in only 0.5% of males, a remarkably low incidence when compared to other series. An international study of priapism in SCD demonstrated a prevalence of 35% among males aged 4-66 years, with the earliest manifestation reported at age 12 years.[32] Of 46 patients reporting priapism, 21% reported having erectile dysfunction. Why our series contained only one case is unclear, even though 62.5% of cases were 12 years and older. However, reluctance to report the symptom because of embarrassment could be a factor. A more rigorous attempt to determine the extent of priapism needs to be made in order to minimize improper management that could contribute to subsequent erectile dysfunction.

Determining the cause of death in the 16 deaths has been difficult, principally because of the lack of autopsies. Nevertheless, using clinical information immediately before death, provisional causes could be assigned, bearing in mind, however, that autopsies remain the gold-standard for determining cause of death, especially in clinical studies. Nonetheless, with this proviso, the most frequent cause of death was "severe anemia," accounting for or involved in 8 (50%) of the deaths, one of which was associated with pregnancy and delivery.

The next most frequent cause of death was "bone pain crisis," which was recorded for 2 patients. A transfusion reaction that occurred during the transfusion of a second unit of blood after the uneventful transfusion of a prior unit for severe anemia was implicated in the death of one patient.

The Kaplan-Meier 50% survival estimate, taken from the date of registration, could not be determined as it was too extended (Figure 2). The incidence of death, however, stands at 2.51 per 100 patient years. The observation period, at 637 patient-years is relatively short, but even so, this death incidence is extremely high when compared to other countries.[23] If this alarming figure is confirmed, it would constitute a call for urgent action. Similarly, the mean survival time, estimated at slightly more than 3½ years emphasises the dire outlook for SCD patients in this country.

Many implications arise from this study. Firstly, the patients studied constitute a very narrow spectrum of SCD patients in the country. To know more about the nature of SCD in Sierra Leone, studies like the present one need to be repeated or expanded. Another important consideration is that our patients are young with relatively few adults in the cohort, which could be interpreted in a number of ways, including that SCD patients do not survive beyond early adulthood. Although there might be an element of self-exclusion among the older patient, extremely high death incidence in the cohort is consistent with a high rate of loss among SCD patients of all ages.

Whatever the case, a formal examination needs to be carried out to obtain more reliable survival data. In addition, there is a need for better information about the clinical features of SCD and, especially, the risk factors for hospital admission and for death.

Malaria has been implicated as a risk factor elsewhere on the continent,[28] and there is, currently, debate about the role of bacterial infections, especially *Streptococcus pneumoniae,* in morbidity and mortality in African SCD.[29] Risk factors and causes of death in SCD are not

known for this country in contrast to other African countries,[33] so an improved method of death reporting up to and including autopsies is mandatory.

That 50% of the deaths were attributable to anaemia, not treated with blood transfusion, signifies that access to blood transfusion services require upgrading. Similarly, improved microbiological services are required to manage febrile illnesses appropriately and help in defining preventive measures such as immunizations and chemoprophylaxis. It is of interest that the rates of complications seen in this study are much less than those observed when Knox-Macaulay studied SCD patients in the Freetown community thirty years ago.

Why there are these differences is unknown, but since 1983 there have been significant population shifts because of civil instability in spite of which, however, some beneficial changes in social amenities have occurred. It is certainly relevant that patients followed in a clinic setting, where advice about sickle cell coping strategies is given, does have a beneficial effect on clinical outcomes.[34]

Finally, there is no data relating to ethnic or regional patterns of SCD in the country, although it is likely that differences will be trivial. In any event, it would be important to establish gene frequencies and disease burden in the various districts in order to set priorities for service provision.

CONCLUSION

Although the challenges seem daunting, the best way to answer the questions this study has raised would be in a new-born screening study protocol in which all or the majority of new-borns with SCD in an area or district are identified and subsequently followed systematically and cared for in a structured way. Given the findings in our study, instituting such a protocol should be considered urgent.

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