

Control of sickle cell disorder in Africa

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SUMMARY

Sickle cell disorder (SCD), understandably, concerns millions of Africans. There is no doubt that the prevalence of the condition is increasing, especially among the urban educated elite and in other communities who have access to effective basic health care. There is, however, a palpable lack of information and education about the disorder, which, with the increasing prevalence, has encouraged the growth of myths, misinformation, inappropriate treatment, frustration and stigmatization. The frustration has kindled the desire in many Africans to *do something about sickle cell disorder*. What needs to be done often appears to be deceptively easy, but it is usually not critically considered and therefore continues to be confusing and controversial even among health care professionals. In this regard, one frequently hears talk of eradication of the disorder by enactment of legislation while the wider context of control is invariably overlooked.

In this paper, I shall rely heavily on my experience in Nigeria and discuss some issues pertaining to the management and control of SCD in Africa in the hope that it will promote a better understanding of its complexities and help readers identify credible and effective strategies and solutions in their own

communities.

INTRODUCTION

Definition of Sickle Cell Disorder

The term sickle cell disorder is defined here as a lifelong ailment arising from the inheritance, from both parents, of sickle haemoglobin (Hb SS) or of Hb S from one parent and another variant pathological haemoglobin such as Hb C (Hb SC) from the other parent.

The disorder is characterized by premature breakdown of rigidly elongated or curved (sickled) red blood cells causing, in the case of Hb SS, constant anaemia and intermittent occlusion of small blood vessels. The latter event is believed to lead to pain crises and some other complications.

In Africa, the homozygous sickle cell disorder (Hb SS) also known as sickle cell anaemia is by far the commonest type of sickle cell disorder. Less common and usually less severe types include sickle cell-haemoglobin C disorder (Hb SC); sickle cell-beta thalassaemia (either $S\beta^+$ thal or $S\beta^0$ thal), sickle cell-haemoglobin D Punjab (Hb SD Punjab) and sickle cell-haemoglobin O Arab (Hb SO Arab).

SICKLE CELL TRAIT AND OTHER BENIGN HETEROZYGOUS STATES

It is important to recognize certain inherited variant haemoglobin states as benign and non-pathological so that the implication of their diagnosis is correctly explained to carriers to avoid unnecessary anxiety. The commonest is Hb AS which is the sickle cell trait. Others include Hb AC, Hb AD, Hb SD (Ibadan), Hb AG, Hb S-HPFP (hereditary persistence of fetal haemoglobin) and Hb SE. Although Hb AS can be responsible for sickling symptoms during severe hypoxic states (as in sudden depressurization in high flying aircraft) and for spontaneous haematuria, these complications are so rare that the condition is, to all intents and purposes, benign and the unlikely possibilities of these complications should, therefore, not normally be suggested to healthy carriers of the

trait.

MAGNITUDE

SICKLE CELL DISORDER

As said earlier, in Africa, sickle cell anaemia (SS) is by far the commonest type of SCD. Less common types include sickle cell-haemoglobin C disorder (SC), which is fairly common in central West Africa and the rare sickle cell - β^+ thalassaemia (S β^+ thal). As persons with Hb SC and other types have, on average, similar but milder syndromes, the rest of this paper will be based on our experience with the more severe sickle cell anaemia disorders.

About 1.5% of all babies born to indigenous tropical African parents would be born with sickle cell

care, and as most of these children are born into poor underprivileged families they hardly survive childhood. On the other hand, the survival of those with access to good care is steadily improving, at every stage of life.

SICKLE CELL TRAIT

It has been established that about 10-45% of the population of tropical sub-Saharan Africa are healthy carriers of the sickle cell trait.¹ The average carrier rate is about 20% of a total population of about 800 million. Consequently, the population of Africans who are healthy carriers of the sickle cell trait (Hb AS) could be about 160 million. On account of her large population, the largest Hb AS gene pool is in Nigeria, with about 40 million carriers of the sickle cell trait.

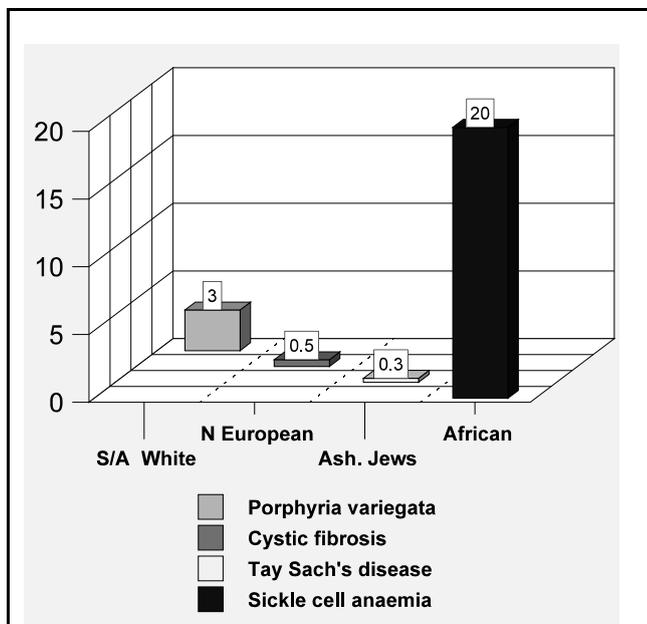


Figure 1. Some of the commonest genetic disorders (frequencies per 1000 births)

anaemia. This would translate to about 570,000 Hb SS affected children born every year, or a birth rate of 48 per 1000 of the total population. It is noteworthy that this prevalence is only at birth and progressively decreases through late childhood, adolescence and adulthood. This rate is very high when compared to the incidence of other serious inherited disorders that are commonly found in other races as shown in figure 1.

Survival of these babies beyond childhood is largely dependent on their access to good basic health

EPIDEMIOLOGY

The distribution of indigenous SCD coincides with the present or past distribution of endemic *Plasmodium falciparum* malaria. This is because possession of the sickle cell trait (Hb AS) confers a natural protection against a fatal episode of malaria. In any unprotected (non Hb AS) community, many children with Hb AA will succumb to malaria before the age of 5 years. Those with the sickle cell trait (Hb AS) will have milder malaria but will survive. Thus, a higher proportion of carriers of the sickle trait (AS) would live to reproduce and pass on the sickle gene to their offspring. Those who inherit Hb AS are thus better fitted for survival in this environment than those who inherit Hb AA.

Conversely, a study of population genetics has shown that the eradication of falciparum malaria, by eliminating the reproductive advantage of Hb AS carriers, predictably leads to a gradual dilution of the S gene pool within a population. Hence, in South Africa and southern Mozambique, both of which lie within the temperate non-malaria zone of sub-Saharan Africa, the S gene frequency is so low that sickle cell anaemia is not perceived as a problem. Carriers of the trait (Hb AS) do not exceed 0.3% of the Bantu population in these areas in contrast to the much higher prevalence among the Bantu in northern Mozambique and in countries lying to the north of the Zambezi River.^{2,3} The 2000-year-old migration of Bantus from western to malaria-free southern Africa is thought to have led to the remarkably low S gene frequency among the South

African Bantu. The same argument is advanced for the lower S gene frequencies in African-Americans (AS 8%) and African West Indians (AS 10%). Thus, the ultimate control of the S gene within a population is linked to the eradication of malaria in that population. The problem in the affected countries in Africa is that malaria is not being controlled. Luzzatto⁴ has estimated that, even if malaria were controlled, it would still take some 300 years for the gene frequency to be reduced by half. As a strategy for reducing the incidence of sickle cell anaemia, it is too slow to be appealing to countries in which SCD is a significant problem. Undoubtedly, the immediate beneficiaries from the control of malaria would be persons affected with sickle cell anaemia whose survival through childhood would be better assured.

Ironically, although carriers of the sickle cell trait can withstand deadly malaria, persons with sickle cell anaemia (Hb SS) being already moderately to severely anaemic, cannot. The invasion and destruction of their red blood cells by the malaria parasites simply increases the anaemia to critical levels. They are thus least fitted for survival in the hostile environment of malaria. Their survival in many African countries in appreciable numbers is a relatively recent phenomenon which reflects the improvement in standards of care, including effective prevention and treatment of malaria and other infections. Owing to their peculiar susceptibility to infection in childhood,⁵ the survival of children with sickle cell anaemia can be used as a sensitive barometer to assess the effectiveness of the basic health care programme in any community.

Many Africans find it hard to believe that the high prevalence of sickle cell anaemia in many of our communities is a relatively recent phenomenon. It is not fortuitous that despite a much higher incidence in sub-Saharan Africa, the first report of a patient with sickle cell anaemia was in Chicago in 1910.⁶ Over the next three to four decades, there were many other reports of affected patients in Europe and America, but surprisingly few in Africa. In the mid 1940's quite a few reports of a high prevalence of the sickle cell trait emanated from Africa.⁷⁻⁹ The low prevalence of sickle cell anaemia in indigenous African was therefore puzzling.

This led some workers to believe that sickle cell anaemia was indeed commoner in the African-American than in the indigenous African. In 1950, Dr

A B Raper wrote, *this essay has been directed to showing that the disease is of more importance to the American Negro than to the African.*¹⁰ Although Raper acknowledged a higher frequency of sickle cell trait (AS) in indigenous Africans, he suggested that the admixture of African and Caucasian genes was responsible for the higher incidence of sickle cell anaemia (SS) in African-American. With hindsight, he was, of course, totally wrong.

What he failed to realize was that very many more children with sickle cell anaemia were born in Africa than in America, but that very few of the former survived the hostile environment. The true incidence and public health importance of sickle cell anaemia in Africa was not widely appreciated until 1956 when Mabayoje¹¹ wrote:

sickle cell anaemia is a major disease of West Africa. It is a cause of distress in many families. It therefore deserves much better recognition than it gets at present. It should be treated as a major disease in schools of tropical medicine, textbooks and in all medical schools in tropical Africa.

Over two decades later, it was found in a community in northern Nigeria that although over 2% of all newborn children had sickle cell anaemia, there was no survivor with sickle cell anaemia in the adolescent or adult population in the community.¹² In fact, except for a 9-year-old child, no person with sickle cell anaemia was older than four years in the entire community of villages. Some years later, a significant improvement in the survival of persons with sickle cell anaemia was observed in the same community following the introduction of anti-malarial measures.¹³ In contrast, obstetricians in urban centres in Nigeria had, by the early 1970s, already reported many pregnancies and childbirths in women with sickle cell anaemia.^{14,15} This dichotomy in the survival of rural and urban dwellers clearly illustrates the critical sensitivity of persons with sickle cell anaemia to environmental factors.

THE NEED TO CONTROL SICKLE CELL DISORDER

Molineaux et al.¹³ in 1979 correctly summarized the situation when they wrote:

There is no other known inherited disorder present at such high frequency in a large population and of comparable severity as

sickle cell anaemia in Africa. With rising standards of living and control of malaria, sickle cell anaemia will become an immense medical, social and economic problem throughout the continent.

The need for control of sickle cell disorder in Nigeria and other tropical African countries is therefore unmistakable.

It is also clear that despite the uniformly high birth prevalence of SCD, the need for its control cannot be uniformly felt throughout any single African country. This is because of the remarkably low level of awareness in many communities in which deprivation has ensured a low prevalence of survival beyond early childhood of those with sickle cell disorder. Awareness is dependent on recognition of the condition, which in turn is dependent on the evident survival of affected persons. In the deprived areas, infant and child mortality rates are high enough to affect virtually all the children who are born with sickle cell anaemia.

Nonetheless, children with sickle cell anaemia in actual fact account only for a small proportion of infant or childhood deaths in the deprived areas and thus, do not, contrary to popular belief, solely account for the superstitious belief in the reincarnation of dead children known in Nigerian parlance as 'ogbanje' (*Igbo*) or 'abiku' (*Yoruba*). The work of Edelstein¹⁶ in Anambra State of Nigeria clearly refutes any significant connection between physically branded ogbanje children and sickle cell disorder. Therefore, the popular stigmatization of children with sickle cell anaemia as abiku or ogbanje is unjustified.

The felt need in the deprived areas is for the provision of the basic necessities of life, including effective health care. It would therefore be folly to attempt to introduce any specific programme to control SCD in these communities before their felt needs are met. It is only after the basic necessities of life have been provided and the quality of their lives improve that children with SCD and other non-communicable disorders will survive to merit special attention.

CONTROL OF INHERITED HAEMOGLOBIN DISORDERS

The approach to the control of inherited disorders is necessarily different to that of the control of

communicable or acquired disorders. Factors that must be taken into account are listed in box 1.

A control programme, as stated earlier, should be sensitive to the felt needs of the target community. In

Box 1. Factors impacting on the control of inherited haemoglobin disorders

- Political will
- Land size and terrain of the country
- Total population
- Level of literacy and education
- Severity of the disorder
- Magnitude of the disorder
- The infrastructure – water supply, communication and power supply

order to achieve maximum coverage, efficient utilization of resources, and sustainability, a control programme should be integrated into the health care system of the country and programme should also have been pre-tested for efficacy and acceptability. It should gradually decrease and certainly not increase the stigmatization and anxiety of SCD-affected persons – especially for carriers of the trait within the target population.

DEVELOPING A NATIONAL CONTROL PROGRAMME

Every country should develop an appropriate programme guided by strategies already shown to be effective in other countries (see box 2). There is no doubt that the task of designing and implementing an effective control programme for an inherited condition as prevalent and as complex as SCD, in the large and populous sub-Saharan region of Africa, would be immense. It would require meticulous planning, adequate research, and efficient mobilization-cum-co-ordination of resources within each affected country. It is important to appreciate the enormity of the task right from the outset so that the right attitudes and perspectives are adopted. The sickle cell problem in Africa is too immense to be amenable to quick-fix solutions. A frequently canvassed quick-fix 'solution' has been mass Hb genotype screening of the population and prohibition or discouragement of marriage between couples who both carry the sickle cell trait. The Military Administrator of Oyo State in Nigeria, had, in 1995, proposed a punitive edict aimed at prohibiting such marriages but the conference of the

solicitors-general in all the 36 states of Nigeria thwarted its introduction by declaring that it was unconstitutional and offended the human rights charter to which Nigeria is a signatory.

Box 2. Strategies for control of inherited haemoglobin disorders

- Accessible and effective treatment of affected persons
- Appropriate education of health care professionals
- Adequate supply of safe blood for transfusion
- Adequate and reliable laboratory diagnostic facilities
- Adequate numbers of trained counsellors
- Prenatal diagnostic programmes
- Effective community information and education
- Support for research - molecular, clinical and operational
- Constant monitoring and periodic evaluation of programmes

Although it is a popular belief that the implementation of this strategy would lead to the eradication of sickle cell disorder in the country, there is no evidence that it would. On the contrary, the indications are that it would not achieve that objective and would, instead, become disruptive and counter-productive. It is a well-known fact that, so far, enforced selective mating of couples has never been shown anywhere in the world to reduce the incidence of any inherited disorder. Attempts to introduce it in Cyprus for the control of thalassaemia, led to increased anxiety and stigmatization of people with thalassaemia and even of healthy carriers of the thalassaemia trait. This in turn led to widespread denial and falsification of haemoglobin genotype results among the carriers.¹⁸ There have also been reliable anecdotal reports of denial and falsification of Hb S status in Nigeria in reaction to the threat of some priests who had expressly stated that they will not join couples who are both Hb AS.

In Cyprus the initial strategy was therefore abandoned in favour of one comprising screening and optimal treatment of persons living with the disorder, education of members of the public and of health care professionals, genetic counselling and prenatal diagnosis. The Church in Cyprus no longer threatens not to join couples but only requires that they show evidence that they have been screened and counselled. This strategy has led to almost universal awareness and application in Cyprus of prenatal diagnosis of children expected by parents who both carry the

thalassaemia trait. It has been so successful that only 2 of the 71 unborn children diagnosed as having thalassaemia major were born in 1984.¹⁹

It is important to realize that in order to sustain a low birth prevalence of thalassaemia, the strategy has to be continuously applied given the persisting high prevalence of carriers in the population. The small size and population (670,000) of Cyprus, its excellent infrastructure, its high literacy rate, its excellent and free health and welfare services and the absence of abject poverty have all contributed to the successful outcome.

PRE-IMPLANTATION GENETIC DIAGNOSIS

The recent introduction of pre-implantation genetic diagnosis (PIGD) has made it possible to select the Hb genotype of the baby before implantation of the embryo into the uterus thus avoiding the need to test the unborn baby during pregnancy and the option of termination of affected pregnancies.

Invariably, persons who advocate selective mating strategies, have seriously under-estimated the complexity of the problem they intend to address and the resources and skills that would be required. Very little, if any thought, is given to the need to have adequate resources and facilities for the accurate laboratory diagnostic screening, the need for public and professional education, expert pre- and post-screening counselling of the target population and for pre-testing the strategy for efficacy and acceptability in the communities. A common misconception is that genetic counselling means marriage counselling aimed at directing carriers of the trait not to marry each other. In reality, this is not an objective of genetic counselling. In genetic counselling, full unbiased information is given and the client is encouraged to make informed decisions on reproductive and other choices. Sub-Saharan Africa has the largest pool of the sickle cell gene in the world and any facile talk of eradication must take this fact into account, and also the fact that the magnitude of the sickle cell problem is better determined by the size of the population carrying the trait than by the population living with sickle cell anaemia. The former would have at least 160 million S genes, while those with SCD can hardly boast of 2-4 million S genes. In the circumstances, eradication of sickle cell disorder is, at best, over-optimistic and would require unthinkable genocide or permanent banishment of all carriers to Alaska or

somewhere equally distant.

We have to appreciate that, as in war, attainable goals have to be set, the troops (health educators, counsellors and health care professionals) have to be trained in sufficient numbers, the resources have to be assembled and credible strategies and tactics researched and decided before engagement. It goes without saying that in the struggle against sickle cell disorder the structures for properly addressing the problem and finding effective and sustainable solutions must first be put in place. Embarking on inadequately planned and tested programmes will be disastrous and would have a good chance of jeopardizing or delaying the emergence or success of a future national programme.

The control of sickle cell disorder in Africa has occasionally engaged the attention of the World Health Organization (WHO). In 1987, WHO suggested the establishment of four pilot projects for testing the feasibility of certain strategies.²⁰ In 1994, WHO went further and recommended that:

In areas where haemoglobin disorders are common, special dedicated centres are required in appropriate numbers and appropriately situated, and with a high degree of autonomy.²¹

For various reasons including low priority, poor resources and capacity, conflict and political instability, the measures recommended have received scant attention in the affected countries. The WHO regularly responds to questions about the absence of programmes for SCD in Africa by stating that African Ministers of Health have never raised sickle cell disorder as a public health priority at their yearly meetings in Geneva. In the meantime HIV/AIDS has become rampant while malaria and tuberculosis have expanded considerably. Not surprisingly, all international aid is now targeted at these infections and not at sickle cell disorder. Superior professional advocacy is needed to sensitize African governments and the international aid agencies to the need of addressing sickle cell disorder.

In the circumstances, non government sickle cell organizations have emerged in several African countries and on May 10th 1996, eight of them, including the Federation of Sickle Cell Clubs of Nigeria (FESCCON), formed an international organization known as Federation des Associations de

Lutte Contre la Drépanocytose en Afrique (FALDA) in deference to the French speaking members who form the majority. A literal English translation is the Federation of Associations Combatting Sickle Cell Disorder in Africa. The membership now comprises 13 national associations from Benin, Burkina Faso, Cameroon, Chad, Côte d'Ivoire, Congo (*Brazzaville*), Ghana, Guinea (*Conakry*), Mali, Niger, Nigeria, Senegal and Togo. The formation of this continental body is an exciting prospect, which, hopefully, should ensure that the governments in the affected countries are sensitized to the magnitude of the problem and to the need to commit appropriate resources to it.

SUGGESTED WAY FORWARD

Sickle cell disorder presents a special challenge to sub-Saharan Africans. Sickle cell is not a hopeless condition. Research in the last two decades, has shown enough promise to suggest that many of the problems can be significantly reduced. In the last few years, the judicious use of a drug named hydroxyurea has reduced the frequency and severity of pain crises. Pneumococcal vaccination and daily oral penicillin, especially in children, have proven effective in preventing avoidable illness and death from pneumococcal infections. In Nigeria, we have demonstrated that attentive holistic care can drastically reduce morbidity and mortality rates.²²

Recently, the transplantation of stem cells derived from the bone marrow of compatible siblings has been used to cure sickle cell anaemia. Although this is a landmark in the treatment of sickle cell disorder, its rigorous pre-conditions and great expense make it, for now, unattainable to all but the fortunate minority. There is promise that the transplantation of stem cells derived from the umbilical cord blood in newborns would be much cheaper and would require less stringent pre-conditions. A cure through **gene therapy** is a promise on the horizon, although several more years of intensive research are required before this therapy will be available.

The way forward may be two-fold. First is for all health authorities and institutions to adopt, as soon as possible, the simple measures that have been shown to be effective in the management of sickle cell disorder. These include those listed in Boxes 2 and 3.

Box 3. Measures effective in the management of sickle cell disorder

- Establishing special sickle cell clinics
- Organising continuing education on SCD for health workers
- Continual training in counselling on SCD
- Employing trained counsellors
- Establishing prenatal diagnosis programmes
- Allocating funds to make these services affordable to all persons with SCD
- Monitoring and periodically evaluating outcomes

Second, a national sickle cell centre must be developed to facilitate the development of a rational, effective, co-ordinated and sustainable national control programme with the capacity to implement and monitor it through the National Health Service. The centre should appoint a national working group on haemoglobin disorders comprising experts in various relevant disciplines who will collate and analyse essential data, identify research priorities, promote research and collaborate with national health planners and international organizations in designing, monitoring and evaluating a national control programme.

The centre will accommodate essential workers and equipment; serve as a reference diagnostic laboratory, as well as a forum for relevant discussion, research and training of personnel. With the local wealth of clinical material, a functional sickle cell centre should attract foreign scientific interest and funding, stimulate research into all aspects of sickle cell disorder and encourage local participation and contributions to knowledge.

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