Review Article

Evolving locally appropriate models of care for Indian sickle cell disease

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The sickle cell gene in India represents a separate occurrence of the HbS mutations from those in Africa. Sickle cell disease in India occurs against different genetic and environmental backgrounds from those seen in African patients and there is evidence of clinical differences between the populations. Knowledge of the clinical features of African disease was drawn from the Jamaican Cohort Study, based on prospective follow up of all cases of sickle cell disease detected by the screening of 100,000 consecutive newborns in Kingston, Jamaica, and supplemented by observations from the Cooperative Study of Sickle Cell Disease in the US. Defining the principal causes of early morbidity in African sickle cell disease led to successful interventions including pneumococcal prophylaxis, parental education in the early diagnosis of acute splenic sequestration, and the early detection by trans-cranial Doppler of cerebral vessel stenosis predictive of stroke but their success depended on early diagnosis, ideally at birth. Although reducing mortality among patients with African forms of SS disease, the question remains whether these interventions are appropriate or justified in Indian patients. This dilemma is approached by comparing the available data in African and Indian forms of SS disease seeking to highlight the similarities and differences and to identify the deficiencies in knowledge of Indian disease. These deficiencies could be most readily addressed by cohort studies based on newborn screening and since much of the morbidity of African disease occurs in the first five years of life, these need not be a daunting prospect for Indian health care personnel. Newborn screening programmes for sickle cell disease are already underway in India and appropriate protocols and therapeutic trials could quickly answer many of these questions. Without this knowledge, Indian physicians may continue to use possibly unnecessary and expensive models of care.

Key words India - models of care - public health - sickle cell disease - tribal people

Introduction

In the African continent, the sickle cell mutation occurs on three different DNA structures surrounding the beta globin locus, the site of the mutation for sickle haemoglobin (HbS). These are widely assumed to represent three independent occurrences of the HbS mutation and are named after the areas where these were first described, Benin, Senegal and the Central African Republic or Bantu haplotypes[1]. In North America and the Caribbean, the Benin haplotype predominates, and over the 40 years since the Sickle Cell Anemia Control Act was passed by the US Congress in 1972[2],

a great deal has been learnt about sickle cell disease. Spearheaded by the Cooperative Study of Sickle Cell Disease in the United States[3] and by the Jamaican Cohort Study[4], the clinical features of the different genotypes of the disease have been documented and interventions designed to address major problems. These interventions have included pneumococcal prophylaxis to prevent pneumococcal septicaemia, the reduction in mortality from acute splenic sequestration by teaching mothers splenic palpation, the use of transcranial Doppler (TCD) to detect cerebral vessel stenosis predictive of stroke and the prevention of primary stroke by chronic transfusion, and the use of hydroxyurea to reduce painful crises and acute chest syndrome. To be effective, these interventions require early diagnosis and the widespread implementation of newborn screening has been an essential component of the improved management. Overall, survival has significantly improved and it is likely that the quality of life is also better for most patients. However, these advances have been developed for sickle cell disease among peoples of African origin, predominantly of the Benin haplotype[5].

A fourth independent occurrence of the sickle cell mutation has been recognized around the Arabian Gulf and in central and southern India, known as the Asian haplotype[6]. The HbS mutation is assumed to be the same but it has occurred upon a DNA structure different from those observed in patients of African origin. It has also occurred against a different genetic and environmental background, factors which may influence expression of the disease. Deletional alpha thalassaemia occurs in 35-40 per cent of African patients but in over 50 per cent of those with the Asian haplotype[7-9]. The Asian haplotype is also associated with persistence of high levels of foetal haemoglobin (HbF). Both alpha thalassaemia and high levels of HbF inhibit polymerization of HbS and hence intravascular sickling suggesting that the disease should be milder than in African subjects.

This raises the question of whether the clinical course of sickle cell disease among Indian patients differs from that in African subjects and whether it is justified to assume that the interventions developed for African disease should automatically be applied to patients with the Asian haplotype? Concerns on this issue have been previously voiced[10] and the current paper seeks to expand these observations by examining the clinical features of African disease, usually of the Benin haplotype, and comparing these with data from Indian patients to determine the level of knowledge, whether these interventions are appropriate and whether the associated cost is justified.

The need for correct genotypic diagnosis

In many parts of India where the sickle cell gene is common, beta thalassaemia genes also occur giving rise to a spectrum of sickle cell-beta thalassaemia syndromes as well as homozygous sickle cell disease[11]. Although clinically this distinction may be considered academic, for scientific and other indications such as prenatal diagnosis and genetic counselling, the distinction may be important. If detailed prospective studies are to be based on populations defined by newborn screening, then family studies and molecular confirmation to define the precise genotype would add to the scientific value of these studies.

Splenic pathology

The spleen is central to much of the early pathology of sickle cell disease and although in African patients there is a progressive splenic fibrosis which occurs at different rates between patients, this process may be associated with episodes of acute red cell sequestration (acute splenic sequestration), chronic sequestration (hypersplenism) and the loss of the filtering function of the spleen rendering patients prone to overwhelming septicaemias.

Acute splenic sequestration (ASS): In the Jamaican Cohort Study[12], events of ASS were seen between three months and six years with most attacks occurring before two years, and a cumulative probability of 0.255 by two years and 0.297 by five years[12]. Events recurred in over 50 per cent children and after two attacks, subsequent attacks occur at shorter intervals. This complication was the most common cause of death in early childhood[13] and led to blood transfusion for the acute event and prophylactic splenectomy after two events. Teaching mothers regular splenic palpation allowed earlier detection of episodes and reduced the mortality from this complication by approximately 90 per cent[12].

What is known of the epidemiology of ASS in Indian patients? Does it occur and, if so, what are its features? Splenic sequestration was listed but without distinction of acute or chronic[14] and episodes of acute splenic enlargement with severe anaemia have been described[15,16] but without details of prevalence or natural history.

Chronic hypersplenism: Sustained splenic enlargement with evidence of red cell sequestration occurred in about five per cent in the Jamaican Cohort and was associated with lowered haemoglobin levels and retarded growth, both relieved by splenectomy[17]. Hypersplenism may commence with a clinical attack of ASS but generally the risk factors differed between acute and chronic red cell sequestration.

In Indian patients the spleen is often larger and persists for longer than in African patients and there is no doubt that hypersplenism occurs and may be relieved by splenectomy[16] but its prevalence, risk factors, and natural history is unknown.

Susceptibility to overwhelming blood infections: The loss of splenic function renders patients prone to overwhelming septicaemia especially with *Streptococccus pneumoniae*. In African patients the age-specific incidence of septicaemia with this organism falls sharply after three years[18] and so its incidence in SS disease is critically dependent upon the age at which splenic function is lost. In many African patients normal splenic function is lost in the first year of life[19] and this septicaemia is a major cause of early morbidity and mortality which has been successfully addressed by pneumococcal prophylaxis with a combination of pneumococcal vaccines (conjugate and regular) and penicillin by regular oral or monthly injections of depot penicillin until 4-5 yr of age[20,21]. This is an expensive and complex programme justified because of the established incidence of pneumococcal septicaemia in African patients.

But what of India? In the Asian haplotype, the commonly associated alpha thalassaemia and high levels of foetal haemoglobin allow splenomegaly to persist for longer and continuing splenic function is suggested in the Eastern Province of Saudi Arabia by pitted red cell counts[22] and technetium labelled spleen scans[23]. These data suggest that patients with the Asian haplotype may not be prone to pneumococcal septicaemia, and if so, the costs and logistical difficulties may not be necessary or justified in Indian patients. Discussions with Indian colleagues suggest that most patients with clinical septicaemia attend physicians and receive antibiotics without blood culture. A study of 20 blood cultures in children with acute febrile events revealed *Staphylococcus aureus* in eight and Gram-negative bacteria in 12, none had *S. pneumonia*[24]. While recognizing that the latter organism is fastidious in its growth and may fail to grow in suboptimal conditions, it is also possible that the persistence of splenic function beyond the age when the incidence of pneumococcal infection falls sharply has provided effective protection. Are we justified in assuming that febrile events are due to *S. pneumonia* and undertake expensive and complex pneumococcal prophylaxis or is there sufficient doubt to justify collecting convincing data? Proper documentation leading to appropriate interventions, must include blood cultures within the context of a carefully designed cohort study.

Other infections, malaria: In Jamaica, *Salmonella* has emerged as the second most common organism causing septicaemia and has a relatively high mortality[25] because of the assumption that the septicaemia is likely to be pneumococcal in origin and will respond to penicillin. Malaria does not occur in Jamaica so there are no useful contributions from the Cohort Study but the optimal prophylaxis and therapy of malaria requires careful documentation in both African and Indian patients with SS disease.

Stroke

Strokes, usually clinically manifest as hemiplegias and attributable to stenosis of major cerebral vessels, occurred in 8-17 per cent of hospital/clinic based studies[26,27] and in 7.8 per cent by the age of 14 yr in the Jamaica Cohort[28]. It is a predominantly paediatric manifestation with a median age of six year and 50-70 per cent subjects have recurrences within three years of the initial attack. This is the basis of chronic transfusion which aims to lower the proportion of HbS to below 30 per cent, and has significantly reduced this rate of recurrence[29]. Furthermore, transfusion therapy has also been shown to reduce the risk of initial stroke after detection of cerebral stenosis by transcranial Doppler (TCD)[30,31]. Programmes of early detection by TCD and subsequent transfusion are increasingly used in populations of African ancestry.

What is the scenario among Indian patients? Do strokes occur and, if so, what is their epidemiology, incidence and outcome; these questions have to be answered before the role of chronic transfusion and of TCD can be determined.

Bone marrow necrosis

This pathology accounts for the clinical spectrum of dactylitis (hand-foot syndrome), painful crisis and avascular necrosis of the femoral head.

Dactylitis: Painful swelling of the fingers and/or toes is a common early manifestation in SS disease of

African origin. It occurs as early as three months of age, is frequently recurrent and affected 45 per cent of children by the age of two years in the Jamaican Cohort[32]. It becomes rare after the age of five years when active marrow no longer occupies the small bones of the hands and feet but occurs in the juxta-articular areas of the long bones and spine. Risk factors include a low HbF level[32,33] and dactylitis appears to predict a severe clinical course[34].

Does dactylitis occur in Indian patients, and if so, what are its features? Does the persistence of high levels of HbF protect against this manifestation of the disease? Dactylitis occurred in 11 per cent patients in one study[24] of hospital admissions but this is likely to have underestimated the frequency of this relatively benign complication.

Painful crisis: At later ages, bone marrow necrosis affects the juxta-articular areas of the long bones, spine and sternum and the inflammatory response to dead bone marrow raises the intramedullary pressure causing severe bone pain. This is a major manifestation of SS disease in late adolescence and early adult life although events tend to ameliorate after the age of 30 yr. It was the cause of approximately 90 per cent of hospital admissions among patients in the US[35] and UK[36] although these figures may have decreased since the advent of hydroxyurea therapy. Precipitating factors include skin cooling exposure, exercise, dehydration, infections and psychological stress and avoiding these factors may prevent many painful crises. Risk factors include a high total haemoglobin[37,38] and a low HbF level[38].

In India, it is clear that painful crises are common, possibly associated with the high total haemoglobin level although some protection might have been expected from the correspondingly high HbF level. These events were more common during and soon after the monsoon[24] but more needs to be known about the epidemiology of these events, their natural history, duration and management. There is evidence that low dose hydroxyurea (10 mg/kg/day) may reduce painful crisis frequency[39,40].

Avascular necrosis of the femoral head: Continued weight bearing on a femoral head damaged by avascular necrosis of bone marrow may lead to articular surface disruption and secondary osteo-arthritic changes causing persistent pain and limitation of movement. The prevalence varies from 10-15 per cent and in the Jamaican Cohort, it occurred in 12 per cent by the age of 15 yr with a maximum incidence in the Cooperative Study in the 25-34 yr age group[42]. Risk factors include high total haemoglobin[37,41] and alpha thalassaemia[42].

In Indian patients both these haematological features characterize the disease suggesting that they may be at high risk of this complication. Little is known of the prevalence and epidemiology of this complication in India except for a personal review of 224 patients in central India[43].

Acute chest syndrome

Formerly assumed to be pneumonia, the term acute chest syndrome (ACS) refers to new pulmonary infiltrates with elements of infection, infarction, fat embolism, and acute pulmonary sequestration in its pathology. In African patients, it is a common cause of morbidity and in Jamaica, was the principal cause of death at all ages after two years[44]. In the Cooperative Study, the maximum incidence of 25.3/100 patients/yr in the 2-4 yr age group fell to 8.8/100 patients/yr in those aged over 20 yr[45] and in the Jamaican Cohort, the prevalence of ACS in SS children was similar to that of pneumonia in controls with a normal haemoglobin (AA) genotype until the age of eight months but then increased in SS patients to be four times greater by the age of four years[46].

In Indian patients, the acute chest syndrome occurs[15] but there is a lack of information on its epidemiology and natural history.

Anaemic episodes

Knowledge of the steady state levels in patients is essential to interpret the significance of haematological changes. Haemoglobins below steady state levels are common although only close and regular monitoring may determine whether the fall is acute of chronic. Red cell indices are helpful and reticulocyte counts are essential in their differential diagnosis. There is always a reason for falls in haemoglobin and eliciting the cause is important in determining the most appropriate therapy.

Aplastic crisis: In the Jamaican Cohort, reticulocyte counts of 0 per cent are almost always attributable to the aplastic crisis caused by human parvovirus B19 infection[47], which destroys the red cell precursors and haemoglobin levels fall by about 1 g/day. The natural history of this complication is for spontaneous recovery of the bone marrow after 8-10 days and blood transfusion is frequently performed as outpatients

in Jamaica[48]. In Jamaica, events occur in epidemics at 3-4 year intervals, there is a high risk of sibling involvement and serological confirmation is helpful because B19 induced aplasia never recurs[49].

Acute splenic sequestration: This is associated with the most precipitate falls in haemoglobin as much as 4-5g within hours. Classically associated with a reticulocyte response of 15-30 per cent, some events occur so rapidly that only increased counts of nucleated red cells appear in the peripheral blood.

Chronic hypersplenism: It is usually associated with gradual falls in haemoglobin, increased reticulocytes and a spleen at least 4 cm below the left costal margin. The increased metabolic demands of the greatly expanded bone marrow compete with the demands for growth and height often crosses growth centiles. Transfusion support may be necessary. Death may occur with superimposed ASS or coincident B19 infection and if there is no signs of spontaneous resolution within six months, splenectomy is performed in most Jamaican patients[50].

Iron deficiency: Iron released by haemolysis may be available for reutilization but iron deficiency may result from low dietary availability or increased loss from intestinal helminths. There is a very gradual and often well tolerated decline in haemoglobin, fall in reticulocyte counts, and microcytic red cell indices. Treatment with dietary advice, worm medicine, and oral iron therapy produces a good response and transfusion is rarely necessary (unpublished data).

Megaloblastic change: If the increased demands for folic acid are not met in the diet, then megaloblastic change may occur with reticulocytes below steady state levels, an increased mean cell volume and a very gradual decline in haemoglobin. Most commonly described from West Africa[51], megaloblastic change is unusual in Jamaica although an outbreak occurred following Hurricane Gilbert in 1988 when traditional sources of dietary folic acid were no longer available[52].

Infections especially septicaemias: These are usually associated with bone marrow suppression, falls in reticulocytes and haemoglobin level without any obvious change in red cell indices. Patients are usually febrile and have other clinical evidence of septicaemia and are treated by broad spectrum antibiotics pending the results of blood cultures, and possibly transfusion.

Chronic renal impairment: In Jamaica, chronic renal damage is common in SS patients over the age of 40 yr[53] and is associated with glomerular fibrosis, declining glomerular filtration rate and erythropoietin (EPO) levels. The lack of EPO driving the bone marrow results in falling reticulocyte counts and haemoglobin which may decline so gradually that surprisingly low levels are tolerated[54]. Treatment is by transfusion, dialysis and occasionally renal transplantation.

In India, there is no doubt that anaemic events or 'severe anaemia' are common but treatment is usually empirical with transfusion without detailed investigation or diagnosis. While recognising the high patient numbers, the lack of diagnosis seriously impairs a proper appraisal of this common complication and may lead to inappropriate treatment and unnecessary transfusions[55]. This is one of the most serious deficiencies in the management of sickle cell disease in India and the basic investigations of red cell indices and reticulocyte counts would do much to clarify this problem.

Role of transfusion therapy: In the absence of precise diagnosis for lowered haemoglobin levels, transfusion tends to be more widely used[55] compared to the practice in the Jamaican Cohort Study[56]. Furthermore, sickle haemoglobin within the red cell behaves with a low oxygen affinity and many patients in their steady state levels have near normal oxygen delivery. Blood transfusion is expensive and may cause complications, so there is an urgent need to define the role of transfusion therapy in Indian patients.

Leg ulcers

These are major cause of morbidity in African patients with SS disease especially in late adolescence and early adult life. Chronic leg ulceration reached a maximal incidence of 15-18 per 100 patients/yr in the Cooperative Study in the US[57] and a prevalence of 30 per cent in the Jamaican Cohort[58].

In Indian patients, chronic leg ulceration is much less common[59,60] but no formal studies on prevalence and risk factors are available in unbiased populations.

Priapism

Painful involuntary erection of the penis is a common problem among African patients especially in adolescence and early adult life. The prevalence is often underestimated because of embarrassment and the lack of realization that the complication is due to sickle cell disease but direct questioning in adults

indicates frequencies of 38-42 per cent[61,62], and in the Jamaican Cohort where direct questioning was routine, the cumulative incidence rose to nearly 60 per cent in those surviving to the age of 40 yr[63] (Serjeant & Hambleton - unpublished data). In Indian patients, this complication may occur[64] but appears to be rare.

Cumulative end organ damage

In African subjects, progressive tissue damage affects predominantly the lungs and the kidneys especially over the age of 40 yr, and these pathologies are major contributors to long term morbidity and mortality. The prevalence of chronic renal impairment rises steadily after 40 yr of age and studies in the Jamaican Cohort suggest that much lower levels of serum creatinine (70-80 µmol/l) reflect serious renal impairment in homozygous sickle cell (SS) disease[65] compared to the traditionally accepted values of 130 µmol/l in otherwise normal persons.

Conclusions

This brief comparison of features of SS disease in African and Indian patients necessarily condenses the great amount of clinical and pathological information available, but despite this shortcoming, major differences emerge and areas where more information is necessary are highlighted. Some manifestations of the disease such as leg ulceration and priapism are clearly less prevalent in Indian patients, some features such as painful crises and the acute chest syndrome are clearly shared by both populations, and occasionally some complications such as hypersplenism may be more common among Indian patients. Areas where limited or no information is available include the spectrum of bacteria in septicaemias, the cause of anaemic episodes, the prevalence of major cerebrovascular disease, the epidemiology of acute splenic sequestration and of chronic hypersplenism, and cumulative end-organ damage. This lack of information limits the development of locally appropriate models of clinical care for Indian subjects and without this information there will be a tendency to provide interventions such as pneumococcal prophylaxis[66] and transcranial Doppler detection of cerebral vessel stenosis which may be inappropriate and waste scarce resources.

There is a rapidly increasing literature on sickle cell disease in India but most of this is based on symptomatic patients attending clinics or hospitals which introduces many biases. If the desire is to record the true natural history of sickle cell disease, the frequency and outcome of complications and to devise therapeutic interventions, this would be most readily achieved by a cohort study based on newborn screening. Newborn screening is being increasingly performed in India[67-70] and although the disease affects predominantly the tribal population who are often scattered in rural communities with special social and cultural features, and have high levels of illiteracy, these special logistical problems can be addressed[71]. Designing protocols of close and intensive follow up of SS children diagnosed at birth along with regular assessments of their history by local health workers or by phone, and of haematology and the ability to provide special tests such as blood cultures will be vital to portray the true picture of sickle cell disease in India. These are formidable challenges but with the ingenuity of Indian colleagues, these can be addressed and overcome.

India is to be complimented on the rapid development of sickle cell programmes particularly in Gujarat, Maharastra, Chhattisgarh, and Odisha. These programmes have focused on population screening to get data on the prevalence and distribution of the sickle cell gene but extensive data are now available and there will be limited value in continuing to screen ever larger populations. Some programmes are being expanded to attempt prevention of the disease by prenatal diagnosis or by premarital screening and counselling carriers on the risk of having children affected by sickle cell disease[72,73]. These programmes are important but perhaps the time has come to use some of the resources destined for services to the sickle cell community to fund carefully planned studies of the natural history of sickle cell disease based on newborn screening. The resulting information will be invaluable for evolving locally relevant and appropriate models of care for sickle cell patients in India.

***Conflicts of Interest*:** None.

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