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Perspective

Sickle cell disease in India: A perspective

Sickle cell disease is an inherited blood condition which is most common among people of African, Arabian and Indian origin. In disease of African origin, research has led to models of care which prevent serious complications, improve the quality of life, and increase survival[1]. In India, the disease is largely undocumented. Thus, there is an urgent need to document the features of Indian disease so that locally appropriate models of care may be evolved.

The sickle cell mutation affects the beta chain of adult haemoglobin which changes the behaviour of sickle cell haemoglobin. Possession of a single *HbS* gene results in the generally harmless sickle cell trait (AS genotype) but inheritance of the *HbS* gene from both parents results in homozygous sickle cell (SS) disease which is often a severe condition destroying red blood cells rapidly and blocking flow in blood vessels with painful and often serious complications[2]. The HbS mutation has occurred on at least three occasions in Africa, named after the areas where these were first described[3], Benin, Senegal and Bantu (Central African Republic) and referred to as the beta globin haplotypes. A separate and fourth occurrence of the mutation was seen around the Arabian Gulf and India and designated the Arab-Indian or Asian haplotype[4].

Significance of different haplotypes

Sickle cell disease in North and South America, the Caribbean and much of Europe occurs in people of African origin. This is mostly of the Benin haplotype and this form of the disease has been well documented, is relatively severe, and successful interventions have been developed to improve outcome of the disease. The disease of the Asian haplotype is generally milder because the mutation has occurred against a background of genetic features likely to inhibit sickling.

Sickle cell disease in patients of African origin

The spleen is central to much of the early pathology of African SS disease since the rapid development of intravascular sickling compromises splenic function in the first year of life[5]. Patients with African forms of SS disease often develop symptoms at 3-4 months and the greatest chance of dying is between 6-12 months of age[6]. Common causes of early death include pneumococcal sepsis[7], acute splenic sequestration[8], and stroke[9]. Hypersplenism[10] occurs at later ages but contributes to both morbidity and occasionally mortality. Interventions which have successfully addressed some of these complications include pneumococcal prophylaxis[11], teaching parents to detect acute splenic sequestration[8], chronic transfusion to prevent secondary stroke[12] and transcranial Doppler to detect the stenosis of cerebral vessels preceding stroke[13] (Table).

Sickle cell gene in India

First described in the Nilgiri Hills of northern Tamil Nadu in 1952[19], the sickle cell gene is now known to be widespread among people of the Deccan plateau of central India with a smaller focus in the north of Kerala and Tamil Nadu[20]. Extensive studies performed by the Anthropological Survey of India[21] have documented the distribution and frequency of the sickle cell trait which reaches levels as high as 35 per cent in some communities.

Sickle cell disease in India

Early studies[22] described SS disease with higher levels of foetal haemoglobin, more frequent alpha thalassaemia, higher total haemoglobin and lower reticulocyte counts and persistence of splenomegaly compared to Jamaican SS disease. Several patients were first diagnosed by family study, some adults denying

Table. Early complications in sickle cell (SS) disease of African and Indian origin

Complication	African disease			Indian disease	
	Frequency (%)	Intervention	Cost	Frequency (%)	Observations
Pneumococcal septicaemia	6-8	Pneumococcal prophylaxis[11], penicillin for 4 years, conjugate and regular vaccine	High	Unknown	Not described
Acute splenic sequestration	30	Teaching parents to check spleen size at home[8]	Low	?10	Events occur[15,16] but natural history and optimal treatment unknown
Chronic hypersplenism	5	Chronic transfusion or splenectomy[14]	Moderate	?5	Hypersplenism occurs[10] and trials of optimal management needed
Stroke	10	Chronic transfusion to prevent secondary stroke[12], transcranial Doppler (TCD) and transfusion to prevent primary stroke[13]	Very high	Unknown	Stroke occurs[17,18] but natural history unknown and TCD may not be justified

specific symptoms. These features were similar to the mild disease reported from the Eastern Province of Saudi Arabia[23] and were believed to characterize the Asian haplotype of SS disease. Persistence of splenomegaly and of presumed splenic function were important since the age-specificity of invasive pneumococcal disease falls sharply after the age of five years[24] and if a functioning spleen persists beyond this age[25], the risk of pneumococcal septicaemia may be markedly reduced. In contrast to this benign picture, studies from Central India report severe disease (defined as >3 bone pain crises, >3 transfusions/year) in 30 per cent children[17] and supported by an analysis of 85 under five children hospitalized[18]. The latter study included 20 bacteraemic events due to *Staphylococcus aureus* and Gram-negative bacteria but no pneumococci. The pneumococcus is a fastidious organism, readily overgrown by other bacteria and possibly underestimated because of antibiotics preceding blood cultures; however, there is much information on nasopharyngeal carriage in India[26] and since this usually precedes invasive disease, the apparent lack of pneumococcal septicaemia in Indian sickle cell disease may reflect persisting splenic function.

The coincidence of large tribal populations with the 'sickle cell belt' of Central India and northern Kerala and Tamil Nadu has given rise to the assumption that tribal people are more prone to the *HbS* gene although this seems widely distributed among tribal and non-tribal people[27]. Sometimes striking differences have been reported, a tribal population in Valsad having milder disease than a non-tribal population in Nagpur[28] and attributed to extremely high frequencies of alpha thalassaemia in the tribal group. The apparent disparity in clinical severity between different reports in India reflects to some extent the mode of ascertainment of patients, studies of hospitalized cases[17,18] not surprisingly revealing severe disease compared with the studies in Burla[22] which focused on outpatient attendance. Addressing the question of intrinsic severity of patients in Central India was the focus of a study recently completed in Akola Medical College, Maharastra, where 40 per cent of patients with sickle cell disease were found to have sickle cell-beta thalassaemia and of the 54 per cent with SS disease, alpha thalassaemia occurred in only 16 per cent[29] compared with over 50 per cent observed in Odisha[22] and 86 per cent in Valsad[28].

Newborn screening

It is becoming clear that a great deal remains to be learnt about Indian sickle cell disease (Table) and the best way of achieving this is by studies based on newborn screening which removes the bias of symptomatic selection. Newborn screening is already underway in India[30-32] and the robust nature of dried blood samples means that this need not be confined to hospital deliveries but could be extended to domiciliary deliveries. Follow up from birth with regular assessments of haematology, clinical features, and growth would provide the knowledge base needed

for development of locally appropriate models of care and would also provide populations for therapeutic trials. The data generated by such studies would allow definition of the role of hydroxyurea therapy, of blood transfusion, of bone pain crises, of stroke and priapism, the nature of infections, and the possible role of infection prophylaxis.

Future directions

Who would be responsible for these studies? Multicentre studies pioneered by the Indian Council of Medical Research have begun the process of systematic documentation of the disease[17,18,32]. The National Rural Health Mission, created in 2005, is making major contributions with their programmes in south Gujarat but also at Burla Medical College, Sambalpur University in western Odisha[33]. The Gujarat Sickle Cell Anaemia Control Society was formed in 2011 to coordinate the many activities in Gujarat State. State sickle cell programmes, especially those in Gujarat[32], Maharastra and Chhattisgarh[34,35] focus on extending population screening to detect the sickle cell trait with a view to offer genetic counselling and to identify patients with sickle cell disease for referral to clinics and follow up. Much resources and goodwill are directed towards the problem of sickle cell disease in India but studies of the clinical features and natural history are urgently required to generate locally appropriate models of care. Studies based on newborn screening should be a priority[35] and without this information, Indian physicians may feel coerced to use models of care developed for patients of African origin[36]. This information will also be necessary to define the role of premarital screening and the need and acceptability of prenatal diagnosis in the prevention of disease. The increasing sophistication of laboratory and molecular services renders these technologies available to Indian patients but their role in Indian sickle cell disease is critically dependent upon a greater understanding of clinical severity and its determinants[37]. This knowledge is also essential for the development of appropriate genetic counselling[38,39].

Conclusions

Assuming that models of care developed for African disease should be followed in India may be inappropriate and waste limited resources. Studies based on newborn screening will avoid symptomatic selection and provide the best clinical data.

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