

Commentary

Morbidity pattern of sickle cell disease in India: A single centre perspective

Sickle cell disease (SCD) is the most prevalent inherited blood condition worldwide resulting from single DNA mutation within the beta globin gene¹. Due to recent population movements, there is gene flow from high allele frequency areas of sub-Saharan Africa, the Middle East, and India to Europe and parts of America². This has led to sizeable sickle cell populations emerging in previously unaffected areas of the world. Each year approximately 300,000 children are born with sickle cell anaemia or one of its variants and nearly 80 per cent of these births occur in poor socio-economic countries^{3,4}. The incidence of most clinical complications varies markedly both with time in the same individual and between different individuals⁵. The same variability and unpredictability are seen with most other serious complications, including cerebrovascular disease⁶, acute chest syndrome⁷, renal failure⁸ and premature death⁹. Despite the complexity and multifactorial pathophysiology of vaso-occlusion, relatively straightforward interventions have been found to greatly improve outcomes for children with SCD. These include, (i) early identification by neonatal screening programme; (ii) education of parents and patients of medical complications and early recognition; (iii) preventive measures with prophylactic penicillin and pneumococcal immunizations; (iv) screening programmes for early signs of organ damage especially transcranial Doppler (TCD) examination; and (v) therapeutic intervention with transfusions, hydroxyurea, or stem cell transplantation. Although outcomes have improved significantly over the last 40 years in many countries, clinical management remains primitive particularly so in countries where the disease is most common, including Africa and India.

SCD is a variable condition. Despite all patients with sickle cell anaemia (HbSS) being homozygous for the same mutation, there is significant diversity in

clinical severity and the correlation between genotype and phenotype is poor¹⁰. Some of the phenotypic heterogeneity can be explained by the different sickle cell haplotypes as evidenced by the differences in the clinical characteristics. The Arab-Indian haplotype seen in Indian population is associated with higher foetal haemoglobin (HbF) levels and splenomegaly and fewer complications. Higher concentrations of HbF are associated with fewer episodes of acute pain and improved survival. The Senegal haplotype is also associated with fewer hospitalizations and painful episodes whereas the Bantu haplotype is associated with higher incidence of organ damage, and renal failure; both these predominate in populations of African origin¹¹. The co-inheritance of alpha thalassaemia is another important determinant of severity in SCD. Alpha thalassaemia, which is common in Indian populations, is associated with protection against life and organ threatening complications, but paradoxically may predispose towards more frequent episodes of acute pain. Other determinants of severity are not well characterized, but might include differences in red cell physiology caused by unknown genetic determinants, and environmental factors, such as climate and air quality¹². The importance of climatic factors as precipitants of acute pain has been recognized for more than 30 years and several studies have shown an increase in painful episodes in cold and rainy season, although the pattern varies. The enormous contribution of environmental factors is highlighted by the marked differences in outcomes between different countries, such as high infant mortality in many parts of Africa.

SCD has a high prevalence in India, especially in the central and western regions, and poses a considerable health burden^{13,14}. With increasing control of infant mortality and infectious diseases, genetic diseases are assuming a proportionately greater importance; the beta

thalassaemias, sickle cell disease, and haemoglobin E disease contribute significantly to morbidity and mortality in India. The natural history of SCD is not established. About 20 per cent of children with sickle disease died by the age of two as reported in one ICMR survey, and 30 per cent children with SCD among the tribal community die before they reach adulthood^{15,16}. The sickle cell mutation was first described in India among the tribal groups in south India¹⁷ but the prevalence of sickle allele is high in both tribal and non-tribal populations. The true incidence of SCD in India is still not known and most of our understanding and knowledge of the natural history of the disease comes from developed countries where effective interventions have resulted in significant reduction in mortality. There are reports that provide interesting insights into SCD in India but most of these are inconclusive based in a single institution or region¹⁸⁻²⁰. Although knowledge about SCD in India is increasing, yet it is very difficult to establish the burden of this problem accurately in the absence of screening programmes, nationwide reporting system or registries. As in other countries, the major clinical manifestation among homozygotes in India is vaso-occlusion²¹ with the highest incidence during rainy season followed by winter²². Priapism and leg ulcers are rare in the Indian population²³, although haemoglobin levels are relatively low and could be attributed to severe iron deficiency. Alpha thalassaemia is relatively common, and there is also increased number of patients with SCD due to the co-inheritance of the sickle mutation with different beta thalassaemia mutations²⁰. Overall, the manifestations of SCD in Indian population are milder than those seen in African populations, predominantly because of high HbF levels.

Perhaps simple interventions that work in the western countries can also work in India. Patients are usually diagnosed when they present with severe complications in hospital. Early diagnosis can lead to better management and reduction in morbidity and mortality. Interventions like neonatal screening, penicillin prophylaxis, pneumococcal immunization, transcranial Doppler screening as well as education regarding infection may reduce the morbidity and mortality significantly. Antenatal screening and prenatal diagnosis can provide more information to parents and help in reducing the number of children born with SCD.

The study by Jain and colleagues in this issue²⁴ is important in that it starts to elucidate the natural

history of the condition in India. The authors offer good descriptive information of clinical and laboratory characteristics of young children with SCD, specifically in the State of Maharashtra. The authors have looked at the seasonal variation in the incidence of hospital admissions and their observation of maximum admissions during monsoon season is in contrast to studies in temperate climates, which have shown no significant effect of rain or cold²⁵. Higher humidity is associated with fewer admissions for pain in the UK, the opposite of the tropical association. The increased incidence of acute febrile illness during monsoon season may be linked to high prevalence of water-borne infections and may explain some of the variations and differences. Similar findings were observed in a Nigerian study²⁶ which may be linked to poor socio-economic status and poor hygienic conditions. The study also highlights changing bacterial pattern and the increasing resistance to first line antibiotics. The high levels of HbF seen in the study are in keeping with the previous studies and may explain the reduced incidence of acute pain. The study highlights some important differences in the morbidity pattern between Indian population with SCD and equivalent patients in Europe and USA.

Though this study²⁴ provides valuable information about sickle patients in Maharashtra, there is a need for further, long term collaborative studies between different centres in India to get a complete picture of SCD in the country. This is essential because of topographical, climatic and socio-economic differences between different parts of country which may pose problems in generalization of findings. The role of pollution and climatic factors also requires further multicentre studies so that preventative measures can be applied to reduce the seasonal excess of complications related to SCD. As further studies elucidate the natural history of SCD in India, it will become easier to assess the role of interventions, such as hydroxyurea, which seems to be efficacious in affected infants and children²⁷ in Europe and the USA.

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