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Editorial

Sickle cell disease: More than a century of progress. Where do we stand now?

Over 110 yr ago, the first description of a West Indian student with sickle cell disease (SCD) was reported by Dr Herrick in Chicago, USA, opening the way to deciphering the disease from its molecular basis to its complex systemic and multicellular pathophysiology[1]. SCD is characterized by a single mutation in the gene encoding for β-globin chain of haemoglobin which, in the homozygous state, results in a cascade of events starting with the polymerization of the mutated haemoglobin (HbS) when deoxygenated. Multiple downstream and interrelated biological processes contribute to the clinical expression of SCD, among which chronic inflammation, hypercoagulability, ischaemic injury, functional nitric oxide deficiency, endothelial, platelet and leucocyte activation and oxidative stress play important roles. Painful vaso-occlusion, chronic haemolytic anaemia, susceptibility to infections and systemic vasculopathy are among the main clinical consequences of the disease[2]. Patients with SCD experience considerable morbidity from both acute and chronic complications that lead to end-organ damage and reduced life expectancy. In addition, disease-related complications starting in infancy significantly impair physical, mental and psychosocial aspects of health-related quality of life[3].

Today, SCD is the most common severe monogenic disorder in the world, with a high prevalence in sub-Saharan Africa, parts of Mediterranean, India and in the Middle East[4]. In South Asia, the highest prevalence of the disease is in India, where over 20 million patients with SCD live. SCD prevalence in India has been quantified through various approaches, including village-level prevalence surveys as well as State-wide screening programmes[5], focussing on groups with a high prevalence of the β^S allele. Screening generally relies on Hb solubility test at the point of care, but this test does not distinguish sickle cell trait (HbAS) from SCD and therefore requires further testing[2]. Pilot projects of new-born screening programmes for SCD in the States of Gujarat, Maharashtra and Chhattisgarh resulted in figures of HbAS prevalence ranging from two to 40 per cent[2]. The highest frequency of the β^s allele is found across Central India (up to 10%), from South-Eastern Gujarat to South-Western Odisha[4]. Altogether, India has been ranked the country with the second highest numbers of predicted SCD births, with 42,016 [interquartile range (IQR): 35,347-50,919] newborns estimated to have been born with sickle cell anaemia in 2010[4].

SCD is characterized by considerable variability in clinical severity. This variability can partly be explained by genetic modifiers, including factors that affect HbF level and co-inheritance of α-thalassaemia. The Arab–India haplotype is associated with high HbF levels and found in an area extending from the eastern coast of Saudi Arabia and East Africa to India[2]. It is usually associated with a milder phenotype than that associated with the four African haplotypes (Benin, Bantu, Cameroon and Senegal haplotypes) and is prevalent in the tribal populations in India[6]. Early descriptions of SCD in India were focussed on these tribal populations and hence, SCD in India was initially thought to be milder than in other countries[5,6]. However, the latter data suggest that the severity of the disease can be compared to that in African countries. In a study of 833 paediatric SCD patients in Nagpur, common SCD-related complications, including acute pain, severe anaemia, stroke, splenic sequestration, acute chest syndrome and meningitis, were more frequent[6] than in the Cooperative Study of SCD, which prospectively investigated the natural history of SCD in the United States between 1978 and 1988[7].

Early, simple, cost-effective measures can change the prognosis of SCD in childhood but are challenging in low-income, high-burden settings. Neonatal screening for early diagnosis, penicillin prophylaxis

and immunization to control the infectious risk along with parents and medical community education have dramatically decreased SCD-related childhood mortality in high-income countries, where more than 90 per cent of children with SCD survive to adulthood[8]. Such measures are however, not widely implemented, particularly in low-income countries, where 50-80 per cent of children with SCD die before reaching five years of age[9]. In places without new-born screening programmes, the initial diagnosis of SCD typically occurs at approximately 21 months of age[2]. The initial presentation is often a fatal infection or acute anaemia, resulting from an acute splenic sequestration crisis. In a study performed in Gujarat, India, around 20 per cent of children with SCD died by two years of age and 30 per cent children from tribal areas died before they reached adulthood[10]. In India, there is important regional variation in the implementation of follow up strategies including penicillin prophylaxis, immunization against pneumococcus and comprehensive care. Additional basic health measures include access to safe transfusion and opioids for pain relief. Both are needed for SCD patients who suffer, among other complications, from recurrent painful vaso-occlusive episodes and exacerbation of chronic anaemia.

Blood transfusion is established as an important treatment in some acute situations, such as severe anaemia and acute chest syndrome, and also to prevent some chronic complications, such as cerebrovascular disease. The availability of blood transfusion varies widely across South Asia, as only a few patients have access to a safe and reliable supply of blood. There are State-run blood transfusion services in Sri Lanka, Bhutan and the Maldives, but most blood is supplied by charitable and private blood banks in Bangladesh, India and Pakistan. As per a modelling study, India is estimated to have the biggest unmet need for blood units in the world[11], with important implications for the treatment of SCD. Making reliable blood transfusion services available would improve the standard of care for patients with SCD and facilitate the development of curative treatments, including gene therapy and bone marrow transplantation.

Hydroxyurea (HU) was the first licensed disease-modifying therapy for SCD. Clinical studies were first undertaken more than 30 yr ago in the USA and Europe and have shown convincing and consistent evidence of benefit, both for acute (reduced incidence of acute pain, acute chest syndrome and blood transfusion) and chronic complications (reduced risk of progressive cerebrovascular disease, improved hypoxia and prolonged survival)[2]. In low-income countries in malaria-endemic sub-Saharan Africa, the safety and efficacy of HU have also been demonstrated[12]. In India, prospective trials of HU therapy, mostly using a fixed low-dose (10 mg/kg/day) regimen, demonstrated a significant reduction in vaso-occlusive crises and transfusion requirements[13]. A dose-dependent effect was also shown in sub-Saharan Africa, opening the prospect of additional benefits of higher dose in other settings, like India[14]. Randomized studies in India are still needed to replicate these results given the many genetic and environmental differences that may influence outcomes[15].

Irrespective of the question of optimal dosage, HU is underutilized both in low- and high-resource countries because of healthcare infrastructure deficiencies, poor compliance and fear of toxicity. In a review by Jain and Mohanty[6], poor compliance with HU in India was attributed to physician's concerns of potential long-term neoplastic effects and lack of experience of primary attending physician with HU therapy. HU-related carcinogenicity, teratogenicity and reduced fertility have not been confirmed by follow up studies, and no report of increased risk of neoplasia has emerged[16]. In particular, worries about the toxic effect on spermatogenesis may have triggered patients to decline HU[17]. Recent reassuring data on fertility have shown that the effect on spermatogenesis is reversible, including when HU is given to pre-pubertal boys[18]. Altogether, the benefit/risk ratio of HU in SCD argues very strongly for its wider use. Strong evidence-based guidelines in India could reassure primary attending physicians and increase the knowledge on the beneficial effect of HU in SCD.

Beyond sickle haemoglobin polymerization, the unravelling of many aspects of SCD pathophysiology, such as the increased adhesion of red cells to the vascular endothelium or platelet activation, has resulted in an increasing number of pre-clinical and clinical drug trials registered every year. Many products that target one or more of the mechanisms of the disease process are currently in phase II or phase III trials[19]. Most of these trials are multicentric and international but face the challenge of low enrolment, resulting in early termination. The recent completion of large, multicentre, multinational clinical trials has resulted in the marketing in high-income countries of new drugs for the treatment of SCD such as P-selectin blockers, L-glutamine and voxelotor[19]. These drugs are however,

available to date at unaffordable costs for patients living outside high-income countries and currently seem to have a limited efficacy. Given the complexity of SCD and the wide range of possible complications, a tailored multidrug approach will probably be the best option for SCD patients, posing again the question of drug access in low- and middle-income countries in the future.

The only curative therapy in SCD so far is the replacement of the genetic defect in the haematopoietic stem cells (HSCs). This can be achieved either through allogeneic HSC transplant from an HLA-matched sibling (with or without myeloablative conditioning), through HSC transplant using a haplo-identical donor or through auto-HSC transplant using gene therapy. Although HSC transplant may be performed in high-burden, low-income areas[18], the accessibility of curative therapies still needs to be addressed. In the short term, improving the availability of proven therapies, such as penicillin prophylaxis and HU, is the quickest and easily achievable way to increase the life expectancy of patients with SCD and, importantly, quality of life.

Irrespective of the genetic influence on disease expression, evidence suggests that poverty and low socio-economic status may result in adverse outcomes in the disease[20]. Environmental factors, home environment, nutrition and access to care influence the severity of the disease. In India, SCD is particularly prevalent in Scheduled Tribe and Scheduled Caste populations, which constitute the most socio-economically disadvantaged communities in the country[5]. When the COVID-19 pandemic has been tackled, in India and elsewhere, addressing the survival and quality of life of the many patients with SCD will be a priority.

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

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