

## Editorial

### Sickle cell disease: Status with particular reference to India

Sickle cell disease (SCD) continues to be a serious, widespread disorder with only a few effective treatments. The characteristic abnormally shaped red cells were first recognised and named in 1910<sup>1</sup>, and knowledge about the condition has steadily accumulated since then. Haemoglobin polymerization was identified as the primary event, causing red cell dehydration and damage, leading to vaso-occlusion and a cascade of pathologies, including infarction, anaemia, inflammation, hypercoagulability, oxidative stress, haemolysis and vascular-endothelial dysfunction. The clinical course is characterized by intermittent episodes of acute illness on a background of chronic vasculopathy and organ damage, resulting in premature organ failure and death<sup>2</sup>. There are > 15 different genotypes which are known to cause SCD, although three predominate in most populations: HbSS (often called sickle cell anaemia, SCA), HbSC, and HbS/ $\beta$ -thalassaemia; the latter is a variable condition depending on the severity of the co-inherited  $\beta$ -thalassaemia allele<sup>3</sup>.

In Europe, Jamaica and the USA, childhood mortality is only slightly increased above the background rate, although mortality increases rapidly in early adulthood, and median life expectancy is shortened by 30-40 years<sup>2</sup>. Less is known about the natural history of SCD in Africa, although emerging studies suggest that the majority do not survive childhood, with up to 80 per cent dying before the age of 5 yr from infections, including malaria, anaemia and unknown causes<sup>2</sup>. Even less is known about SCD in India with no reliable estimates of life expectancy.

Despite increasing data on the complex pathophysiology of SCD, treatment options remain very limited. Penicillin prophylaxis has reduced childhood

mortality in the northern hemisphere, and may well also be beneficial in tropical countries, although data are lacking<sup>4</sup>. Blood transfusion has an established role in acute anaemia, acute chest syndrome and stroke prevention, but is not safely available to most patients with SCD. Hydroxyurea is the only drug which has been shown to modify the natural history of SCD, with good evidence that it reduces the severity and frequency of acute complications, and, more recently, may be effective in primary stroke prevention in high-risk selected children<sup>5</sup>. In the USA it is currently recommended that it is offered to all children with SCA<sup>6</sup>, although the long-term safety of such an approach is unknown. Hydroxyurea is relatively cheap and widely available, but still unaffordable in much of Africa; additionally, all studies have involved regular monitoring with blood tests for neutropenia, and there is very little evidence on its efficacy in low-income and tropical countries<sup>7</sup>. There is potential for its use at low doses without the need for blood monitoring in some countries, although as yet there is no evidence that this is either safe or effective. There is increasing evidence for the benefits of haematopoietic stem cell transplantation, and emerging protocols for transplanting older patients with alternative donors, which may make this more widely applicable, although it is likely to continue to be expensive and require intensive medical support. Similarly, trials of gene therapy are starting, although it seems likely to be many years before this is affordable in all but the richest countries.

SCD was first described in India 64 years ago in Tamil Nadu, and has subsequently been identified in many locations across the country. It was initially thought to be a particular feature of tribal peoples, but it has now been found in all populations. The

distribution is very uneven even across small areas, although it seems to be more prevalent in western and central areas<sup>8</sup>. This variability in prevalence makes any estimates of patient numbers very approximate, but there may be more than 120,000 patients with SCD, with most found in Madhya Pradesh<sup>8</sup>. It has also been estimated that 44,000 children are born per year with SCA in India, with possibly a similar number having HbS/ $\beta$ -thalassaemia, which is the third highest birth rate in the world, after Nigeria and the Democratic Republic of the Congo<sup>9</sup>.

Relatively little is known about the natural history of SCD in India, although more information is now starting to emerge. The earliest studies showed that typically SCD patients in India had high foetal haemoglobin (HbF) levels, which has long been associated with higher total haemoglobin levels and fewer clinical complications. Fairly small studies suggested that the high HbF levels were linked to the presence of the HbS mutation on the Arab-Indian  $\beta$ -globin haplotype, and the *XmnI* polymorphism<sup>10</sup>, although the exact mechanism of high HbF in Indian populations is still not understood<sup>11</sup>. Similarly early reports also identified frequent co-inheritance of  $\alpha$ -thalassaemia with SCD, which in African populations has been linked to more episodes of pain, but fewer life-threatening complications<sup>10</sup>. Based on this largely laboratory-based information, it was often stated that Indian patients with SCD followed a mild clinical course, although newer studies are beginning to challenge this idea. A recent study of 91 patients from Maharashtra State<sup>12</sup> confirmed the presence of high HbF levels, but found that  $\alpha$ -thalassaemia was less common than in previous studies at 16 per cent; the authors also found that more patients than expected were compound heterozygotes with HbS/ $\beta$ -thalassaemia. Clinical complications were common: more than 90 per cent of the patients had suffered bone pain, with 16 per cent having acute chest syndrome. More than 70 per cent had received at least one blood transfusion, and more than 90 per cent had been admitted to hospital. The figures for blood transfusion and hospital admission are higher than for most studies of SCD in populations of African origin in Europe and the USA<sup>2</sup>, although the authors express concern that some patients may be transfused inappropriately. Hydroxyurea prescription rates were also high in this study, with 45 per cent HbSS and 53 per cent HbS/ $\beta$ -thalassaemia receiving the drug, although the doses used were low (10 mg/kg); again the authors were

concerned that there were no clear guidelines on the use of this drug, and some prescriptions were possibly inappropriate. However, despite these concerns, the picture emerges of significant morbidity associated with SCD in India, more than would be expected based on the high HbF levels<sup>12</sup>.

Many questions remain unanswered about SCD, particularly in India. Stroke is one of the major causes of morbidity in children with SCA in populations of African origin and little is known about its prevalence in India. In high-income countries the prevalence of stroke has fallen greatly with the introduction of transcranial Doppler screening and prophylactic transfusion, and it is unclear what role this might play in India. Similarly, little is known about many other aspects of SCD in India, including which infections are important, and the role of antibiotic prophylaxis. Studies in India are starting to emerge which begin to answer some of these questions; in particular, newborn screening programmes in various areas offer the potential for the identification of birth cohorts, and are already starting to define the natural history, and confirm the severity of SCD in India<sup>13</sup>.

Despite the United Nations declaration, and the celebration of World Sickle Cell Day, SCD is undoubtedly still neglected, as recognised by its designation as an orphan disease in some countries, such as the USA. This reflects that SCD is still relatively rare in most high-income countries, with approximately 10,000 affected births annually in the USA and Europe combined<sup>9</sup>. Because the numbers of patients are much less than those with diseases such as cancer, heart disease and dementia, relatively little funding is available for research from government, charitable and pharmaceutical sectors, and no new treatments have been licensed to specifically treat SCD for the last two decades. The majority of children with SCD are born in low- and middle-income countries, with approximately 250,000 births per year in Africa and 30,000 per year in South Asia<sup>9</sup>. Although these numbers are vast, and childhood mortality rates are very high, SCD is still seen as relatively unimportant in these countries, compared to the numbers dying from infectious diseases, malnutrition and trauma. As deaths from infections, particularly malaria, fall in some countries, SCD and other inherited disorders are becoming relatively more important, and are starting to be recognised as problems by individual governments and States. The main manifestation of this is the

increasing number of neonatal and other screening programmes for SCD in many countries, which open the doors for improved clinical care and research<sup>14</sup>.

Collaboration between high- and low-income countries is probably the most important way to make progress in this area. Various important north-south partnerships are emerging which may offer benefits to both sides, with the potential for improved understanding of SCD and better treatments for all patients. Hopefully World Sickle Cell Day will continue to grow, with celebrations bringing the condition to the notice of governments, policy makers, medical charities and the pharmaceutical industry, leading to significant improvements in the quality and quantity of life for patients with SCD over the next decade.

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