



Editorial

Comorbidities in sickle cell disease: Adult providers needed!

Sickle cell disease (SCD) is no longer a disease characterized by early childhood mortality. As patients with SCD live and age, comorbidities accumulate. The adult medical providers, unaccustomed as they were to taking care of these patients before, not only must become more aware of the care that these patients would generally require, but also now are being faced with patients with all the comorbidities and complications that can occur as a natural consequence of ageing in sickle. Acute conditions become chronic systemic disorders. Even accepted disease-modifying therapies may become more difficult to administer as renal, hepatic and cardiovascular issues may interfere with their use. Problems that were surmountable in youth become increasingly burdensome as patients try to maintain a quality of life. More adult providers must become more familiar with SCD and the comorbidities; they will be needed to manage this growing population and to take care of them throughout their adult lives.

SCD was first reported in the western literature in 1910 by Dr. James Herrick, however, it took almost 40 more years until, in 1949, Linus Pauling demonstrated that the disease originated from a mutated haemoglobin (Hb) and then another 18 years when, in 1957, Vernon Ingram discovered that a single amino acid substitution (glutamic acid to valine), due to a change in a single nucleotide (adenine to thymidine), was responsible for the disease^{1,2}. Under deoxygenated conditions, this mutated HbS undergoes polymerization, leading to intracellular tactoid formation and deformation of the red blood cells to an irreversibly sickled state. This causes an inflammatory activation of the vascular endothelium that upregulates cell adhesion molecule expression, stimulating leukocyte adhesion and leading to abnormal interactions between the sickled red cells, the endothelium, granulocytes and platelets³.

This series of events causes progressive organ damage and dysfunction, which is the hallmark of the disease.

SCD is an autosomal recessive disease which mostly affects the people of African, Hispanic, Caribbean and Asian descent. It is said to follow the 'malaria hypothesis', as it is believed that the abnormal sickle Hb (HbS) persisted due to conferred protection of the trait status against malaria. The sickle genetic mutation appears to have arisen independently in at least four different areas of these malarial regions, a testament to the efficacy of sickle cell trait as an inhospitable host for the parasite. Individuals with higher foetal HbF, Senegal or Arab-India beta-globin haplotypes, or co-existence of alpha-thalassaemia have a milder SCD phenotype, while those with lower HbF levels and the Bantu beta globin haplotype tend to have a more severe phenotype⁴. Doubly heterozygotes variants of SCD may also sometimes be milder; these include Hb S-beta thalassaemia, Hb SC, Hb SO-Arab, Hb SE, Hb SD-Punjab and other less common variants. Approximately 1000 children are born with SCD in Africa every day⁵.

The co-morbidities of SCD are numerous, can affect virtually any organ system in the body and increase with age. Acute comorbidities include vaso-occlusive crisis, acute chest syndrome (ACS), stroke, acute renal failure, priapism, splenic sequestration, hepatobiliary complications and acute ocular conditions; these can occur at any age. Chronic comorbidities such as avascular necrosis (AVN), leg ulcers, pulmonary hypertension (PH), diastolic heart dysfunction, gout, end-stage renal disease (ESRD) and ophthalmologic complications increase with age. The current options to prevent or mitigate these comorbidities include chronic transfusions, which increase oxygen carrying capacity, but repeated transfusions result in iron

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overload even with the best chelation therapy and over time, in the adult, this can lead to hepatic and cardiac hemosiderosis. Hydroxyurea, which induces Hb F production, decreases neutrophil production and increases nitric oxide and is currently the most effective therapy known but must be stopped in the adult during pregnancy or preconception. Doses may have to be reduced as renal function deteriorates in the adult. Myeloablative stem cell transplant, currently the only known 'cure' for SCD also carries the potential for sterility and graft versus host disease. Children are typically selected over adults due to less end-organ damage, resulting in lower risk for transplant-related morbidity⁶. Other potential modalities for cure, such as gene therapy, are in the experimental phases but will probably at least begin as a treatment for paediatric SCD.

Pain is the most common manifestation of SCD. Acute vaso-occlusive episodes are the most common presenting complaints and drive healthcare utilization in the emergency departments and inpatient settings. Pain can also be chronic, either due to actual organ/tissue damage, such as in AVN of bone and leg ulcers or due to idiopathic aetiology. Indeed, many patients experience pain daily throughout their lives. Over the years, opioids have become the mainstay of chronic pain management in SCD. In the older patient, repeated episodes of chronic opioid use can lead to opioid tolerance and, in some cases, abuse and addiction which in the older patient is less likely to be greeted with sympathy and understanding. With the current recognition of the opioid crisis, there is at last growing interest in alternative options to opioids such as acupuncture, meditation, relaxation therapy and medical marijuana for the management of chronic pain in SCD. These alternatives may be especially important for the many older patients whose job may be dependent on negative urine toxicology and who want to be more independent of addicting analgesia; however, their validation as effective agents in SCD has not yet been proven.

Although ACS can occur at any age and is a leading cause of death in SCD for both children and adults; chronic lung pathologies are more common in the adult with SCD^{7,8}. Early and aggressive management is required to prevent mortality, and repeated episodes can cause pulmonary arterial hypertension from the increased pulmonary vascular resistance and diastolic heart dysfunction.

Stroke is the main neurological comorbidity in SCD and is one of the few complications seen more often in children than in adults. More commonly ischaemic and affecting large arteries such as the middle cerebral and internal carotid arteries, strokes may be complicated by residual neurological deficits. Silent infarcts, which do not manifest overtly but can accumulate over time, have been shown to cause neurocognitive deficits in school-aged children and adults⁹.

Gastrointestinal comorbidities include cholelithiasis, cholecystitis, splenic sequestration and sickle hepatopathy. Progressive end-organ damage to the kidneys may result in ESRD with a growing fraction of adult patients becoming dialysis dependent. Priapism, a painful and sustained erection not brought on by sexual stimulation, remains a major source of distress for male patients. Repeated episodes of priapism can lead to erectile dysfunction and over time may require penile implants to restore function.

Leg ulcers are another major cause of morbidity in SCD. Often, the ulcers start in the late teens, or young adulthood and can last for years, despite adequate medical attention. The ulcer may limit the mobility of adult patients, who also develop a phobia of being around people or attending social events, especially if they have large ulcers and/or the ulcers have an emanating odour. Because of the stigma, they encounter from having a leg ulcer; these patients may limit their social interaction.

Other comorbidities include ophthalmologic issues such as sickle cell retinopathy, which can lead to vision loss if left uncontrolled in the adult, and AVN of bone, most commonly in the femoral head, with the need for total hip replacement. Hyperuricaemia and gout occur, particularly in the adult with poor renal function¹⁰. Mental health issues are prevalent in the SCD population, with one study reporting sleep disturbance in over 70 per cent of their cohort¹¹. Sleep disturbances, combined with the potential for ischaemia-induced cognitive decline, the increased employment absences that may result from frequent hospitalizations, the physical difficulties that may arise from a stroke, a collapsed hip or a large leg ulcer, all may contribute to clinical depression, estimated to be present in at least 20 per cent of the sickle population¹¹.

In resource-poor areas, it is estimated that more than 90 per cent of children with SCD do not survive to adulthood¹². However, in many industrialized countries, people with SCD now live well into adulthood. In

high-income regions, the current life expectancy for people living with SCD, is about 40-60 years⁷, an improvement that can be attributed to various factors such as improved healthcare infrastructure, delivery and preventative care such as penicillin prophylaxis and hydroxyurea therapy; however, it is also due to recognition and rapid treatment of these comorbidities and complications and improved long-term clinical management of these patients.

Globally, a pivotal point in the care of SCD patients is the transition from paediatrics to adults. This is usually a very difficult period for a variety of reasons. It marks the point where the individual assumes his/her care independently and coincides with the time where the complications of SCD and the comorbidities of end-organ damage develop, increase in severity and become more clinically significant. This has led to an emphasis on 'transition' programmes. However, the paucity of adult sickle cell providers to whom these patients can be transitioned to, when compared to the number of paediatrics providers, makes this period more challenging. With the increase in lifespan of patients with SCD, there is an increase in comorbidities but fewer providers to take care of these sicker patients. Typical ageing disorders of diabetes, atherosclerotic disease, degenerative joint disease, obesity and hypertension further complicate the already complex disease process. Emphasis must now be placed on recruiting adult sickle cell providers who can manage the comorbidities of this chronic disease. 'Adults are not just big kids' but come with all the issues of employment, child-bearing needs, care-taking responsibilities and complex relationships as they increase their end-organ damage and become less physically able.

In conclusion, the comorbidities in SCD are myriad and substantial and will only increase as the average lifespan increases. There is need to focus on management modalities that will help prevent or decrease the incidence of these comorbidities, so that as more patients live longer into adulthood, their quality of life is not dampened by the adverse outcomes of these comorbidities, but rather increases proportionately.

Conflicts of Interest: None.

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