Sickle cell disease: looking back but towards the future

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Sickle cell disease (SCD) is a multisystem disease associated with episodes of acute illness and progressive organ damage, and one of the most common monogenic disorders worldwide, affecting an estimated 30 million people. SCD represents a major public health problem because of its associated morbidity and mortality[1,2].

Last year marked the 100th year since SCD was first described by James B. Herrick. The myriad clinical features of this hemolytic anemia result from a deceptively simple amino acid substitution of valine for glutamic acid in the sixth position of the ß-subunits of hemoglobin (Hb). The result is intracellular polymerization under conditions of hypoxia and dehydration, which triggers the characteristic sickle-shaped erythrocytes[3].

Modern advances in molecular and cellular biology have resulted in an accumulation of data on the sickle cell pathophysiology related to erythrocyte and extra-erythrocyte events[1]. Since the seminal discovery by Dr. Herrick, we have learnt that SCD is as much a disease of endothelial dysfunction as it is a hemoglobinopathy. Oxidative stress, chronic endothelial damage and hemolysis initiate a cascade of events that result in episodic vaso-occlusion, subsequent ischemia-reperfusion injury, inflammation and organ dysfunction[3].

Phenotypic heterogeneity and sub-phenotypes

SCD is characterized by anemia, severe pain and potentially life-threatening complications such as infection, splenic sequestration, acute chest syndrome, stroke and chronic organ damage[3,4]. However, the clinical phenotype of SCD varies widely, influenced by additional cellular and genetic factors, which could explain, at least partially, why some individuals have very severe disease with frequent vaso-occlusive complications and early morbidity and death at a very young age, whereas others can go unnoticed until adulthood. In addition, differences in frequency and severity of clinical events exist even within the same family[1,2].

Homozygosity for the sickle mutation (i.e., Hb SS disease) is responsible for the most common and most severe variants of SCD. However, a single sickle mutation is not sufficient to explain the heterogeneity of the disease phenotype that is observed clinically[3,4].

Two sub-phenotypes of SCD have recently emerged, one attributed to "viscosity - vaso-occlusion" and the other to "hemolysis – endothelial dysfunction". The vaso-occlusive sub-phenotype is manifested clinically by self-limited pain crises, acute chest syndrome and osteonecrosis, stroke, acute splenic sequestration, hepatic sequestration and organ failure such as renal disease and functional asplenia. Manifestations of the hemolytic sub-phenotype, mainly due to a proliferative vasculopathy, are pulmonary hypertension, priapism, leg ulcers, sudden death, and possibly stroke[1,3]. Although some overlapping between the sub-phenotypes is expected, clinical profiling to differentiate symptoms more typical for an individual patient with SCD is an innovative approach that may help direct personalized therapies for a specific sub-phenotype by targeting the predominant mechanism in this multifactorial disorder[3].

Predictors of disease severity

It has become clear that multiple cellular and genetic factors contribute to phenotypic heterogeneity. Hb F was identified as one of the first determinants of disease severity, with high Hb F associated with mild disease. Other studies later identified dactylitis, severe anemia, leukocytosis, childhood asthma and pulmonary arterial hypertension in patients with SCD as adverse prognostic parameters for the later development of frequent pain, recurrent acute chest syndrome, stroke, and death. On the other hand, a higher steady-state Hb concentration was associated with avascular necrosis and retinopathy[1-4].

Molecular studies have identified many disease-ameliorating factors such as co-inheritance of α-thalassemia, ß-thalassemia and ß-C gene interaction, specific ß-globin haplotypes, genetic determinants outside the ß-globin gene cluster and, most recently, the cMYB gene on chromosome 6p23, responsible for the variability in Hb F levels[1,3]. The

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α-thalassemia trait exists in up to 30% of patients of African origin with SCD. Its presence reduces the concentration of Hb in each erythrocyte, decreasing the tendency of Hb SS to polymerize, which results in increased Hb concentrations and decreased rates of hemolysis[2]. In addition to that, abnormal cerebral blood flow detected by transcranial Doppler (TCD) and polymorphisms in the proinflammatory TNF (-308) G/A promoter gene, were recently identified as risk factors for stroke[1].

Prevention and treatment improvements

Neonatal diagnosis, prompt treatment (vaccines, prophylactic penicillin) and guidance in respect to early recognition of splenic sequestration by mothers and caregivers have contributed to a reduction in the mortality rate of children in the first 5 years of life. Two other important factors were the identification of children at high risk for strokes with the adoption of a regime of chronic red blood cell transfusions aiming at preventing this serious complication, and the diagnosis and treatment of acute chest syndrome. These two conditions are currently the main causes of death in adolescents and young adults[5,6].

The introduction of hydroxyurea (HU) has also had an impact on the quality of life of SCD patients by reducing the number of vaso-occlusive crises, the number/length of hospitalizations and the occurrence of acute chest syndrome as well as noticeably reducing the mortality rate of SCD patients treated with HU, compared to those who do not take the drug[7,8].

Blood transfusions have been increasingly used as a therapeutic resource, in part because of improvements in the safety of this procedure, but above all, because transfusions prevent serious complications. In recent years, various therapeutic approaches have reduced the risk of stroke in SCD[2,9]. TCD followed by regular transfusions in children with high cerebral blood flow velocities has decreased the risk of stroke by 90%[10].

The SWiTCH trial tested HU as an alternative to transfusion for secondary stroke prevention in children with SCA and concluded that transfusions and iron chelation therapy remain the best way to manage children with Sickle cell anemia (SCA), stroke, and iron overload[11].

Recently, allogeneic peripheral stem cell transplantation, which is the only therapeutic option that provides a cure, has been recommended for this group of patients, especially for those who have more severe disease in the first years of life and who have an HLA-identical sibling[2].

Challenges

Neonatal diagnosis is fundamental, but not enough[5,6]. We know that the diagnosis needs to be linked to a wide ranging support program for SCD individuals which includes: easy access to quality medical services, an appropriate multidisciplinary approach to treatment with prevention of acute and chronic complications, continual education programs on the disease for different medical specialists and professionals in healthcare services, adequate genetic counseling, availability of educational activities for patients and families on the disease and specific programs to improve the patient's socioeconomic conditions[5,6].

In general, the clinical approach to SCD patients does not require complex or costly procedures. Up to the fifth year of life, the period of the highest rates of death and serious complications, prophylactic care is basically the essence of treatment. The follow-up and adequate treatment of these patients in state health clinics determine a better or worse prognosis following the occurrence of acute events[6].

Despite the evidence of safety, efficacy and tolerability of hydroxyurea (HU) in both pediatric and adult age groups, this important therapeutic advance has been underutilized in many countries around the world. Barriers to using HU are related to patients and parents, healthcare providers and health systems and are attributed mostly to fears about possible adverse effects on reproduction and growth and carcinogenic risk[1,2].

Recent human genetic studies have identified the gene encoding BCL11A as a locus that is important to control Hb F synthesis. Subsequent studies on mice and on human erythroid cell cultures have demonstrated that BCL11A is a transcriptional factor that represses Hb F synthesis. Studies of Xu et al. in the laboratory of Stuart Orkin at Harvard Medical School have identified the BCL11A as a pharmacologic target for the treatment of patients with SCD[12].

In Brazil, thanks to the effort of the Ministry of Health, through the *Coordenação Geral da Política Nacional de Sangue e Hemoderivados*, a care network has been organized for SCD patients in all Brazilian states and concrete measures have been developed, especially in regard to the enrollment of these patients in ongoing government programs and the education and training of the healthcare team needed to prevent disease by identifying clinical complications at an early stage; this will help to reduce morbidity and mortality rates and improve the quality of life of SCD individuals in Brazil[13,14].

This also emphasizes the need for concrete measures with the objective of decentralizing healthcare to safeguard medium- and high-complexity specialized centers as referral units for urgency and emergency care[14,15].

The issue of comprehensive healthcare for SCD individuals continues to be a political, social and economic challenge which requires the support of all: government bodies, referral centers, healthcare programs for the child, the woman and the family, healthcare professionals, patients and their representatives[14-16].

In this issue of the *Revista Brasileira de Hematologia e Hemoterapia*, Silva Filho et al. published a retrospective study of the clinical outcome of young SCD patients from the neonatal screening program in Rio de Janeiro[17]. The authors describe the most important acute clinical events and their correlation with genetic factors such as co-inheritance of α-thalassemia and specific β-globin haplotypes.

Conclusion

Advances in the knowledge of molecular, cellular and clinical aspects of the disease associated with early diagnosis and treatment have reduced morbidity, increased survival and improved the quality of life of individuals with SCD.

The major challenges facing the scientific community are the need for high-quality medical care with a continuing medical

education program and systematic follow-up of the patients in comprehensive healthcare centers for SCD individuals and the development of effective and safe treatments available to all affected patients worldwide.

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