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EDITORIAL

Sickle cell disease: challenging the past, looking to the future☆

Enfermedad falciforme: desafiando al pasado, mirando al futuro

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With more than 1300 cases of sickle cell disease (SCD) in children and adults documented in the Spanish Register of Haemoglobinopathies and Rare Anaemias (known by its Spanish acronym, REHem-AR) of the Sociedad Española de Hematología y Oncología Pediátricas (Spanish Society of Paediatric Haematology and Oncology, SEHOP) (information shared by the SEHOP), this disease is infrequent in Spain, but is present at every level of care of the health system due to its multisystemic manifestations.[1]

Universal newborn screening for SCD was first introduced in 2003 in the Community of Madrid, in 2011 in the Basque Country, in 2012 in the Valencian Community, and gradually extended to the rest of Spain from 2015. As the number of cases detected by newborn screening and at later ages increased, the SEHOP started keeping track of diagnosed cases, leading to the creation of a register (the REHem-AR) in 2014, which gradually started to record not only the cases of sickle cell disease, but also of thalassaemias and other rare anaemias. In addition, the efforts made to provide holistic care to patients, including preimplantation genetic diagnosis, prenatal diagnosis, genetic counselling, newborn screening, specialised paediatric and adult haematology care, health education, primary care, multidisciplinary cooperation for the management of complications and psychosocial support reinforced a natural structuring process in care programmes: paediatric and adult clinical practice guidelines have been published since 2015 with specific recommendations for diagnosis and treatment in addition to the organization of care in primary care centres, general hospitals and higher-care or more specialised hospitals. Specialised hospitals should evaluate every patient periodically, treat severe acute and chronic complications, standardise treatment protocols and referral criteria, coordinate the training of specialists, promote joint care team meetings and conduct cohort studies and clinical trials. In Spain, the Ministry of Health designated 2 hospitals in 2018 as reference centres for hereditary red blood cell disorders (in the framework of the centres, services and reference units system, or CSUR) that are required to meet experience criteria based on the number of managed patients, although these designations are reviewed annually and may change (Hospital Sant Joan de Deu de Barcelona y Hospital Gregorio Marañón de Madrid).

Sickle cell disease is a global public health problem. In Spain, the public health care system has invested on improving outcomes and survival, but while this decreases the morbidity and mortality associated with the disease, the number of affected patients continues to grow.

Sickle cell disease is caused by a structurally anomalous form of haemoglobin, haemoglobin S, that results from a point mutation leading to the substitution of valine for glutamic acid in position 6 of the beta globin chain. In Spain, early diagnosis combined with adequate treatment has achieved a reduction in mortality, turning SCD into a chronic disease in children and adults. The 2 distinctive

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features of the disease are haemolytic anaemia and vaso-occlusive events, which, if localised in bone tissue, cause the most salient complication, vaso-occlusive bone pain. However, both haemolysis and generalised vaso-occlusive crisis contribute to cumulative damage overtime.

From the earliest description of the disease in 1910 by Herrick of a young man with anaemia, chronic ulcers, jaundice and frequent pain crises, the cytological description of elongated, sickle-shaped cells was enhanced with the discovery in 1949 of the structural abnormality in haemoglobin and its molecular underpinnings by Pauling. In the past 10 years, there have been advances in the knowledge of the pathophysiology of SCD that have allowed us an understanding of the change from foetal to adult haemoglobin, with identification of some key regulators, such as *BCL11A*, that now make it possible to approach therapeutic interventions based on gene therapy.

The current issue of this journal includes 3 studies on the subject of SCD. Cieza-Asenjo et al.[2] analysed SCD-related admissions in paediatric intensive care unit. In 3 years, 11 patients (0.8% of total admissions) required care in the intensive care unit. Although the fact that the study was conducted in a reference centre for SCD could be a source of bias, it still demonstrates that it would be relevant to conduct multicentre studies analysing severe complications in order to develop a standardised approach to their management.

On their part, González-Pérez et al.[3] reviewed the effect of hydroxyurea in the 64 episodes of acute chest syndrome developed by 23 of the 48 children with SCD followed up in their hospital. While this was a retrospective study that covered a long period of time, and therefore there were changes in the therapeutic recommendations throughout this period, its findings support the current approach of providing this drug to all patients unless it is expressly contraindicated.

Lastly, Reparáz et al.[4] described 71 hospitalizations in 25 patients out of a cohort of 35 children followed up for SCD. The diagnoses at admission did not differ from the previous literature, but the study reminds us that 70% of patients require hospital admission despite receiving the best possible care (early diagnosis, adequate prophylaxis).

Therefore, even under the best circumstances, in health care systems with newborn screening, early initiation of antibiotic prophylaxis and disease-modifying treatment with hydroxyurea and/or transfusions, early management of acute and severe emergencies, attenuation of chronic complications and an increase in life expectancy, SCD continues to be a harrowing condition. Still, in the past decade, 2 key promising fronts have emerged: on one hand, a potential cure with bone marrow transplantation and gene therapy. On the other, combination therapy mostly in addition to maintenance therapy with hydroxyurea.[5,6]

The drawback of haematopoietic stem cell transplantation is the scarcity of adequate donors, usually HLA-identical siblings. Trials are underway to study alternatives, such as haploidentical or unrelated donors. It was first used in 1984 in a child with myeloid leukaemia, and the patient was cured of both diseases. At present, the outcomes of transplantation of stem cells from an HLA-identical sibling are excellent.

Gene therapy is also bearing fruit as an alternative treatment approach, although it is only in its early stages. It uses the stem cells of the patients modified genetically in vitro, which theoretically sidesteps the possibility of graft rejection or graft-versus-host disease. Three main modalities are used: (1) lentiviral vectors expressing anti-sickling genes or gamma globins that increase the concentration of foetal haemoglobin, (2) lentiviral vectors expressing erythroid-specific short-hairpin RNA to downregulate expression of *BCL11A*, thus increasing foetal haemoglobin, and (3) editing of the *BCL11A* gene to delete the regulatory element allowing its expression.

Combined treatments will probably be the cornerstone of management for a large number of patients in upcoming years. Hydroxyurea should be given to all patients with the SS or SBeta0 phenotypes from age 9 months. Simple transfusions or chronic automated red blood cell exchange are indicated in every child with pathological transcranial Doppler Ultrasound findings or for secondary prophylaxis of stroke in those that have already had one. But in recent years, other molecules have been developed that have disease-modifying effects. Crizanlizumab is an IgG2 kappa monoclonal antibody that binds to P-selectin in endothelial cells and platelets, inhibiting their interactions to red and white blood cells. It is administered intravenously every 4 weeks at a dose of 5 mg/kg. Voxelotor is a haemoglobin S polymerization inhibitor and achieves increases in total haemoglobin. It is administered orally in the form of 500 mg tablets, usually at a dose of 1500 mg/day. Although they are at different stages in the authorization process in Europe for its use in different age groups (the results of trials in children aged less than 16 years are still pending, and trials in children under 12 years are still underway), crizanlizumab and/or voxelotor are expected to be used in patients that had had 2 or more vaso-occlusive crises in the previous year or for other clinical indications still to be determined.

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