Early splenectomy in sickle cell disease: another piece of the puzzle

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Splenic involvement occurs very early in life in sickle cell anemia (SCA), which includes the SS and Sβ° genotypes, and later on in the SC and Sβ$^+$ forms of sickle cell disease (SCD). Slow blood flow and open microcirculation determine deoxygenation and sickling in the splenic vascular bed starting at six months of age.[1,2] Multiple mechanisms have been hypothesized to contribute to the damage in all the three histological areas (red pulp, white pulp, marginal zone) and to functional asplenia. Clinically, the main splenic complications are acute splenic sequestration (ASS) and splenomegaly, with or without hypersplenism. ASS is a frequent life-threatening cause of morbidity in SCA with a need for acute admissions and emergency red blood cell (RBC) transfusions; it also remains a significant cause of death under five years of age in recent newborn cohorts[3,4] in spite of early diagnosis of SCD and educational initiatives for parents. In France, among 4,682 children with SCD diagnosed through newborn screening and followed for 15 years in reference centers, 9 deaths occurred due to ASS (7 in SS/ Sβ° and 2 in Sβ$^+$); in Spain, data from the national registry show that three deaths occurred due to ASS, all in very young children (1 year of age). While the prevalence of ASS is between 10-25%, the recurrence rate after one episode of ASS can be as high as 67%, especially in younger children experiencing the first episode before one year of age,[5] with higher mortality rates after recurrence. Hypersplenism is the other main splenic complication in SCA and a possible indication for splenectomy due to high transfusion burden.[6]

The risk of pneumococcal invasive infection, especially in the short term after splenectomy, is one of the frequent and severe causes of death in high-income countries, and this has hampered the utilization of this procedure before the age of five years as a therapeutic measure for ASS.[6] The treatment of ASS is mainly supportive, while prevention strategies after a first episode utilizing RBC transfusion or hydroxyurea (HU) have limited efficacy. Hence the specific need to identify early splenectomy in SCD as a safe possible treatment and preventive strategy in order to avoid the high risk of recurrence and death in very young children.[5-8]

In this issue of *Haematologica*, Mechraoui *et al.*[9] present the results of an observational retrospective study investigating risks and benefits of early splenectomy in a large cohort of 1,167 SCA children followed from birth and diagnosed through neonatal screening in France. Among the 188 splenectomized patients, 123 (65.4%) patients underwent splenectomy after three years of age and 65 (34.6%) were under three years of age at splenectomy. The control group included the non-splenectomized patients of the newborn cohort.

The authors provide an answer to one of the challenging questions in the management of children with SCA: at what age is it safe to perform splenectomy? Does the benefit of splenectomy in managing life-threatening complications in very young children overcome the potential risks?

They demonstrate that, in the case of clinical indication, splenectomy can be safely performed as early as three years of age if the immunization schedule is complete and the antibiotic prophylaxis is continued with compliance. In fact, in their large cohort, with splenectomy performed at a median age of 4.1 years (range 2.5-7.2), with a high rate of full immunization and adherence to antibiotic prophylaxis continued until the age of ten, none of the children experienced life-threatening infections by capsulated bacteria during the follow-up period (mean 5.9 years; range 2.7-9.2), and the overall incidence of invasive bacterial infections and thromboembolic events was low (0.005/patient years [PY] and 0.003/PY, respectively).

Data from other high-income settings had shown worse outcomes, with death from severe infections and sepsis in the first year after splenectomy, even in children who had been splenectomized at an older age. Neither occurred in this cohort. The high rate of full immunization with the non-conjugate and conjugate vaccines, as well as the high compliance with penicillin administered until ten years of age, can surely have eliminated the infection

risk due to capsulated bacteria in this cohort, where only six cases of invasive infection occurred, but none from encapsulated bacteria. Continuation of prophylaxis for those children over five years of age, and even for their entire lifetime, is more common in European settings than in the United States, and can certainly be protective. The observation time after splenectomy in Mechraoui *et al.*'s cohort is still in the medium term (5.9 years of follow-up) with a median age at the time of study of 14.4 years; therefore, a longer follow-up is needed to confirm the low risk of infection throughout the patient's lifespan, even if splenectomy is performed as early as three years of age. Furthermore, the authors take into consideration the rate of occurrence of post-splenectomy sickle cell-related complications in relationship to HU treatment.

It is noteworthy that whereas vaso-occlusive events (VOE) were significantly lower in splenectomized patients who were not treated with HU, they were significantly higher in splenectomized patients who underwent HU treatment, in contrast to patients who were not splenectomized. Furthermore, there has been a growing trend in patients initiating HU due to clinical complications after splenectomy. Cerebrovascular events were more prevalent in splenectomized patients and, specifically, in those splenectomized before three years of age.

These findings raise a further question: does splenectomy increase the risk of sickle-related complications? Is the need for splenectomy in SCD simply an epiphenomenon of a more severe hemolytic disease? Or does splenectomy itself trigger or worsen the sickle crisis and vascular damage? This question is especially relevant for infants, who only have limited treatment options[10] and, therefore, the evaluation of the risk-benefit ratio of splenectomy requires not only the assessment of splenectomy-related complications, but also of the potential risk of disease progression and onset of sickle-related complications. The prevalence of VOE after splenectomy varied across studies, but the link between the surgical procedure and VOE remains elusive.[5-8]

Mechraoui e*t al.* report a worrying higher rate of cerebrovascular events (abnormal transcranial Doppler, stenosis on magnetic resonance angiography or overt stroke) post splenectomy in HU-treated patients and in children splenectomized before the age of three years. The authors' suggested hypothesis for this finding is that those children could be the ones with the most severe clinical phenotype and that spleen complications might serve as a marker of disease severity. However, the higher rate of cerebrovascular events post splenectomy in children who were symptomatic enough to warrant initiation of HU therapy post splenectomy also points towards the intriguing consideration of a link between the brain and the spleen with the involvement of the brain-spleen axis in SCA, as in inflammatory and cerebral disorders.[11] Further research on the anatomical neural circuits, and soluble inflammatory and immune mediators of the brain-spleen axis in SCA could enhance the understanding of severe phenotypes early in life and the risk of SCA-related complications post splenectomy.

In conclusion, Machroui *et al.* provide us with a new, important piece of the puzzle: if indicated, splenectomy should not be delayed until five years of age as long as there is good immunization and prophylactic coverage. Deeper understanding of the correlation between splenectomy and sickle-related complications will help clinicians plan comprehensive management of the disease and its evolution.

Disclosures

No conflicts of interests to disclose.

Contributions

RC and MC wrote the manuscript and reviewed it.

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