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Editorial Haematologica

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 6 months of age. 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 need of acute admissions and emergency red blood cell transfusions; it remains also a significant cause of death under 5 years in recent newborn cohorts (3-4) in spite of early diagnosis of SCD and parent education. In France, among 4682 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 3 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, which have hampered the utilization of this procedure before 5 years of age as a therapeutic measure for ASS (6). The treatment of ASS is mainly supportive, while prevention strategies after a first episode utilizing red blood cell 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 result of an observational retrospective study investigating risks and benefits of early splenectomy in a large cohort of 1167 children SCA followed from birth and diagnosed through neonatal screening in France. Among the 188 splenectomized patients, 123 (65.4%) patients underwent splenectomy after the age of 3 and 65 (34.6%) were younger than 3 years 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 to manage life-threatening complications in very young children overcome the potential risks?

They demonstrate that, in case of clinical indication, splenectomy can be safely performed as early as 3 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 10, 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/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 10 years of age can surely have

eliminated the infection risk due to capsulated bacteria in this cohort, where only 6 cases of invasive infection occurred, but none from encapsulated bacteria. Continuation of prophylaxis above 5 years of age and even for the entire life is more common in the European settings compared to the United States and can surely be protective. The observation time after splenectomy in Mencherou's cohort is still in the medium term (5.9 years of follow-up) with a median age at the study of 14.4 years, therefore a longer follow-up is needed to confirm the low risk of infection throughout the lifespan, even if splenectomy is performed as early as 3 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 (VOEs) 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 of patients initiating HU due to clinical complications after splenectomy. Regarding cerebrovascular events, they were more prevalent in splenectomized patients and, specifically, in those splenectomized before 3 years of age.
These findings raise a further open issue: 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 sickle crisis and vascular damage? This question is relevant especially for infants, who can benefit from 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 the potential risk of disease progression and onset of sickle-related complications. The prevalence of VOEs after splenectomy varied across studies, but the link between the surgical procedure and VOEs remains elusive (5-8).
Mechraoui et al report a concerning higher rate of cerebrovascular events (abnormal TCD, stenosis on MRA or overt stroke) post splenectomy in HU treated patients and in children splenectomized before age 3. A possible hypothesis for this finding, suggested by the authors, 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, points also toward 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 and relevant piece of the puzzle: if indicated, splenectomy should not be delayed until 5 years of age as far as good immunization and prophylactic coverage is present. Deeper understanding of the correlation between splenectomy and sickle-related complications will help clinicians to plan a comprehensive management of the disease and its evolution.

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