The spleen: Neglected but essential - Section 3

The spleen in sickle cell disease

Valentine Brousse1,2

1Reference Centre for Sickle Cell Disease, Pediatrics Department, Hôpital Universitaire Necker-Enfants Malades, Paris; 2UMR_S 1134 Integrated Biology of the Red Cell, Université Sorbonne Paris Cité/Université Paris Diderot/INSERM/INTS/Laboratoire d’Excellence GR-Ex, Paris, France

Introduction

The spleen is a major lymphoid organ branched to the blood stream. It serves two interrelated immune and filtering functions to clear the blood of senescent or damaged cells and infectious agents. In sickle cell anemia (SCA) a fraction of circulating red blood cells (RBCs) are rigid and abnormally adherent, thus prone to sequestration in the spleen. Chronic or acute splenic sequestration of RBCs leads to early spleen injury in SCA and ultimately to spleen destruction (autosplenectomy). Consequences of spleen injury in SCA include potentially life-threatening clinical manifestations in childhood but, most importantly, loss of function in infancy results in an increased infectious susceptibility to encapsulated bacteria, notably Streptococcus pneumoniae. Indeed, T-independent clearance of polysaccharidic germs requires both an intact splenic filtration and an efficient opsonization by IgM, antibodies preferentially produced by splenic memory B-lymphocytes. In high-income settings, the increased risk of invasive pneumococcal infection is well tackled by early diagnosis, penicillin prophylaxis, immunization and aggressive antibiotic treatment, so that infection-related mortality in childhood has drastically decreased. By contrast, in sub-Saharan Africa, where over 300,000 babies with sickling disorders are born annually, more than half of them will die by age 5, infection and malaria being presumably the major contributors.

Current state-of-the-art

The spleen’s microarchitecture is highly organized to support its combined immunological and filtering function. The filtering function of red blood cells (RBC) takes place mainly in the splenic red pulp, which accounts for 80% of the spleen’s volume. In this compartment, blood elements are not contained in conventional endothelialized vessels but rather circulate slowly and interact directly with resident cells and splenic macrophages that are responsible for culling and recycling abnormal or senescent RBCs. “Removal signals” on the RBC’s membrane such as PS exposure, opsonins or natural Ab5 are recognized by these specialized macrophages. Alternatively RBCs can be pitted i.e. groomed of damaged or unwanted content and recirculate. In addition, to return to the circulation, RBCs are forced through a narrow inter endothelial slit, a supplemental checkpoint where rigid or parasitized RBCs are blocked or pitted. In SCA, the spleen is normal at birth, both in size and function. Splenomegaly is frequent in the first year of life but less so thereafter. In contrast, splenomegaly is present in older SCA patients in India or in the Arabian Peninsula, in relation with a higher HbF level and coinheritance of alpha-thalassemia. In sub Saharan Africa, higher prevalence of splenomegaly in older children is thought to be related to malarial immunological stimulation of the white pulp. Importantly in SCA, there is no correlation between spleen size and/or volume and spleen function. The presence of a spleen without function defines functional asplenia. In a previous study, 94 % of SCA children at 5 years had a level of pocked red cells at or above 3.5%, a level associated with splenic hypofunction for this splenic biomarker. However, the mean age at which the state of total irreversible fibrotic atrophy of the spleen occurs is still unknown and most probably variable. In other sickling genotypes like SC or S beta+ -thalassemia, functional asplenia is delayed to the second decade of life. Guidelines regarding antibiotic prophylaxis in childhood are therefore merely derived from SCA, with no clear evidence of any benefit.

The occurrence of splenic injury secondary to repetitive ischemia is in the vast majority of cases clinically unnoticeable. The sequestration of RBCs in the spleen may be either acute or pro-

Take Home Messages

- The spleen is the first organ injured in sickle cell anemia (SCA) and undergoes progressive ischemia, fibrosis and atrophy during childhood resulting in life long susceptibility to invasive infection with encapsulated bacteria.
- One major life-threatening complication is acute splenic sequestration occurring mostly in infancy in SS or S-beta+ genotypes.
- In SCA, there is no correlation between spleen size and/or volume and spleen function.
gressive. Acute splenic sequestration (ASS) is characterized by a sudden onset of anemia with spleen enlargement and may result in death. Symptoms include pallor, tachycardia, lethargy, pain, and abdominal fullness, in relation with intravascular volume depletion and acute anemia. ASS is seen in 10% to 30% of SCA children at a median age of 16 months, with 75% of first episodes occurring before 2 years of age. Over 60% of children may experience recurrence. Infection may be a triggering event and is found in almost half of the cases. Mortality related to ASS has drastically declined following neonatal screening and parental education. Although rare after the age of 5, ASS, including massive splenic sequestration, has been reported in older children and adults, particularly in other sickling genotypes such as SC or S-beta thalassemia or in SCA with high HbF levels. Urgent transfusion is warranted to correct anemia and may reverse acute sequestration. To date no strategy is established to prevent recurrent attacks but chronic blood transfusion may be an option to avoid life threatening attacks, until splenectomy can be performed. Subacute recurrent splenic sequestration may be difficult to differentiate from hypersplenism but transfusion efficiency is usually reduced in the latter case. Although the spleen’s natural fate in SCA is to disappear, partial or total splenectomy may be necessary to prevent recurrent ASS in children or to alleviate symptoms of hypersplenism. Preservation of splenic function or reversal of splenic hypofunction has been evaluated following hydroxyurea treatment, transfusion therapy and hematopoietic stem cell transplantation (HSCT). Preserved splenic function in infants treated by hydroxyurea at a fixed dose of 20 mg/kg/d was not evidenced. The same drug at maximum tolerated dose was associated with preserved or improved splenic filtration function measured by liver-spleen scan but the majority of treated children had continued evidence of a nonfunctioning spleen. Blood transfusion, likewise, may preserve splenic function and delay the natural history of autosplenectomy. HSCT may also improve splenic function for pediatric patients with SCA, although only 8/53 children (15%) had normal uptake on liver-spleen scans at a median 2-year post HSCT.

Future perspectives

Many issues remain unresolved concerning spleen dysfunction and its management in SCA. For instance, measuring splenic function is still challenging and an easily reproducible high throughput assay would be helpful. Such an assay, by assessing the residual splenic function in very young children with ASS, would facilitate decision-making on the timing and best surgical procedure to offer i.e. total versus partial splenectomy in order to avoid recurrence and preserve immune function. In sub Saharan Africa, an easy and cheap assay would allow the evaluation of splenic immune function in a malaria endemic setting which is thought to influence both the size and the function of the spleen. Studies to determine the best strategy for the prevention of recurrent ASS are also urgently needed. Importantly, the protective role of the spleen in vascular homeostasis and autoimmunity needs to be further explored to better understand the multiple consequences of a non-functional spleen, beyond SCA patients.
References

1. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood 2010;115:3447-52.
2. Piel FB, Hay SI, Gupta S, et al. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med 2013;10:e1001484.
3. Grosse SD, Odame I, Attrass HK, et al. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 2011;41(6 Suppl 4):S398-405.
4. Ramakrishnan M, Moisi JC, Klugman KP, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:329-37.
5. Mebius RE, Kraal G. Structure and function of the spleen. Nat Rev Immunol 2005;5:606-16. *A thorough review on the microarchitecture and function of the spleen in antibacterial and antifungal immune reactivity, mainly based on studies in rodents.*
6. de Back DZ, Kostova EB, van Kraaij M, et al. Of macrophages and red blood cells: a complex love story. Front Physiol 2014;5:9.
7. Buffet PA, Milon G, Brousse V, et al. Ex vivo perfusion of human spleens maintains clearing and processing functions. Blood 2006;107:3745-52. *A recent review on the spleen in SCA.*
8. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol 2014;166:165-176. *The first review focusing on the interactions between SCD, malaria and the spleen in malaria-endemic areas.*
9. Tubman VN, Makani J. Turf wars: exploring splenomegaly in sickle cell disease in malaria-endemic regions. Br J Haematol 2017;177:938-46.
10. Rogers ZR, Wang WC, Luo Z, et al. Biomarkers of splenic function in infants with sickle cell anaemia: baseline data from the BABY HUG Trial. Blood 2011;117:2614-7. *This paper has yielded important updated data on splenic function in SCA infants.*
11. Brown AK, Sleeper LA, Miller ST, et al. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Cooperative Study of Sickle Cell Disease. Arch Pediatr Adolesc Med 1994;148:796-804.
12. Brousse V, Elie C, Benkerrou M, et al. Acute splenic sequestration crisis in sickle cell disease: cohort study of 190 paediatric patients. Br J Haematol 2012;156:643-8.
13. Al-Salem AH. Massive splenic infarction in children with sickle cell anemia and the role of splenectomy. Pediatr Surg Int 2013;29:281-8.
14. Owusu-Ofori S, Remmington T. Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease. Cochrane Database Syst Rev 2017;11:CD003425.
15. Al-Salem AH. Indications and complications of splenectomy for children with sickle cell disease. J Pediatr Surg 2006;41:1909-15.
16. Nickel RS, Seashore E, Lane PA, et al. Improved splenic function after hematopoietic stem cell transplant for sickle cell disease. Pediatr Blood Cancer 2016;63:908-13.