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Splenopathy in Patients with Sickle Cell Disease

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Abstract

Splenopathy with sickle cell disease refers to disorders that require medical care and surgical treatment. It is common in patients with sickle cell disease. The genotype of patients with sickle cell disease could affect the characteristics of splenopathy. Patients with sickle cell anemia genotype mainly experience auto-splenectomy, while those with sickle cell thalassemia have splenomegaly. Splenopathy requires careful observations by the hematologists and surgeons, especially in emergencies as it could prove fatal. Splenic infarction is the main reason for splenopathy in patients with sickle cell disease; however, it does not explain the unresolved important clinical issues. Research is still going on to explore more about the relationships between sickle cell hemoglobinopathy and splenopathy.

Introduction

Splenopathy refers to inflammatory, neoplastic, or traumatic anomalies of the spleen, and is a major complication of sickle cell disease (SCD) [1]. SCD refers to a group of inherited hematological disorders that affect different races across the geographical areas worldwide [2]. It is an autosomal recessive disorder of the beta (β)-hemoglobin chain. In normal adults, there are two alpha (α) and two β globin chains in hemoglobin A; however, in patients with SCD, a mutation in the β globin chain leads to sickle cell hemoglobin (HbS) [3]. This mutation was first discovered by Linus Pauling in 1949. He proved that this abnormal hemoglobin molecule causes detrimental pathology [4]**.** Normally, there are three different types of hemoglobin A, A2, and F. HbS in patients with SCD contains an abnormal β globin chain encoded by a substitution in chromosome 11 genes that result in valine instead of glutamic acid. α-Thalassemia (Thα) represents an autosomal recessive disorder with reduced production or absence of α-globin chains that result in anemia. β-thalassemia (Thβ) represents an autosomal recessive disorder with reduced production or absence of β-globin chains that also results in anemia. The main genotypes in patients with SCD are (1) homozygous HbSS sickle cell anemia (SCA) and (2) sickle cell thalassemia (SCTh) [5,6]. Further, SCTh includes either SC-Thα or SC-Thβ.

The genotype of SCD determines the size of the spleen [7]. In childhood, a patient with SCA has splenomegaly; however, in adulthood the patient has spleen atrophy [8]. In SCTh, the spleen progressively increases in size, which could require splenectomy in adulthood. There are many theories about how the deformed red blood cells (RBC) containing HbS cause the clinical manifestations of SCD. Traditionally, it has been considered that the distortion of the diseased RBC causes sickling crises. This distortion is precipitated by states of low oxygen tension including dehydration, surgery, trauma, physiological or pathological stresses and temperature extremes. Because of RBC deformity, blood viscosity increases leading to disruption of blood flow, consequent vascular obstruction, and even necrosis of the end organs [9]. Such affected organs can cause numerous systemic complications including body pain syndrome, neurological, pulmonary, ophthalmological, hepatobiliary, renal, genitourinary, musculoskeletal, and many other complications including splenic diseases [10]. New evidence shows that the pathogenesis of SCD is more complicated and is not limited to a simple distortion of the RBC and vascular occlusion. Such factors are related to the other hemoglobin variants along with HbS, which reduce polymerization potential and response to oxygen stress; moreover, they alter membrane lipids and adhesion molecules [11]. The spleen is one of the most commonly affected organs [12]. A wide spectrum of diseases can affect the spleen secondary to SCD, with new evidence surrounding their management, both medical and surgical. This article aims to review the recent literature regarding these important complications and their management.

Splenic Infarction

The repeated vaso-occlusive attacks in SCA can result in splenic infarction. Usually these infarcts are small and recurrent, resulting in subsequent auto-splenectomy [13]. In majority of the cases, the splenic infarcts are mild and self-limited. In a few cases, however, the infarcts can be severe and can result in acute splenic syndrome. In such cases, patients experience a triad of severe abdominal pain, splenomegaly, and left upper quadrant tenderness. Additionally, the patients can exhibit signs of peritonitis, guarding, abdominal rigidity as well as left pleural effusion and atelectasis. Most of these patients can be managed conservatively with proper hydration, pain control, oxygenation, and rest. However, splenic rupture may occur in severe acute splenic syndrome necessitating surgical splenectomy [14].

Hyposplenism and Functional Asplenia

Hyposplenism and functional asplenia are well-recognized complications of SCA and are characterized by impaired and loss of the reticuloendothelial function of the spleen, respectively [15]. This dysfunction is considered to be a consequence of splenic fibrosis caused by repeated vascular occlusion and infarction [16]. Hyposplenism can also result secondary to the surgical removal of the spleen following therapeutic splenic immobilization and as a complication of certain medical conditions [17]. The diagnosis of hyposplenism does not always correlate with a decrease in the spleen size per se; rather it has been shown to be related to decrease splenic

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vascularization. This condition can be diagnosed by assessing the filtering function of the spleen, as measured by the levels of the Howel-Jolly bodies in RBCs as well as by nuclear imaging [18]. Patients with hyposplenism and/or functional asplenia are at an increased risk of infection due to "impaired immunity [17]. These patients are particularly susceptible to infection by encapsulated bacteria, especially Streptococcus pneumonia, Neisseria meningitides, and Haemophilus influenzae. In addition, other factors have been found that predispose a patient to this overwhelming infection. These include dysfunction of immunoglobulin IgG and IgM response, defects in the alternative pathway of the complement system, and dysfunction of phagocytic opsonization [19,20]. The prevention of such infections is best achieved by proper immunization, antibiotic prophylaxis, and optimal patient education [21].

Acute Splenic Sequestration

Acute splenic sequestration is a life-threatening event and is a leading cause of deaths in children with SCD [22]. In patients, who are homozygous for HbSS, the incidence of acute splenic sequestration is reported to be between 7% and 30%. It can occur as early as 8 weeks of age with 76% of the cases as less than 2 years of age [23,24]. The pathophysiology remains unclear. However, it has been suggested that the diversion of the blood flow through the intra-splenic shunt causes splenomegaly, RBC retention, and capillary engorgement. Patients usually experience signs of hypovolemic shock, and a decrease of 2 g/dL or more is observed in their normal blood hemoglobin concentration along with evidence of reticulocytosis [23-25]. This condition can deteriorate and lead to death, if not treated adequately. Treatment of acute splenic sequestration mainly consists of early diagnosis, clinical support, and packed RBC transfusion [24]. In patients who survive an attack, subsequent splenectomy is usually performed to avoid the potentially life-threatening complications of recurrence [25,26].

Splenomegaly

Splenomegaly is a characteristic feature of SCTh. Splenomegaly occurs because of occlusion of the venules and sinusoids of the spleen due to trapping of sickled RBCs [27,28]. It usually occurs at 6 months of age and remains enlarged [29]. Splenic size is normally <12 cm; the moderately enlarged spleens are 12-20 cm in size, and the severely enlarged spleens are >20 cm in size. Special attention should be given to spleens >20 cm in size, which are considered to be giant-sized spleens and are really difficult to remove laparoscopically because of limitations in instrumentation and visualization [30]. Recent studies have shown that the treatment of symptomatic splenomegaly with splenectomy is safe and beneficial in patients with SCD [31]. SCA may combine, notably in infancy, with functional hyposplenism and splenomegaly. At birth, the spleen in SCA is morphologically and functionally normal. Progressive injury occurs when the hemoglobin switch initiates the multiple changes in the sickle RBC adherence and signaling properties [27]. Splenomegaly may be associated with an overactive spleen (hypersplenism), a condition that can develop because too many blood cells build up and are destroyed within the spleen. Hypersplenism can contribute to anemia in individuals with SCTh and can lead to low levels of the white blood cells and platelets; hence, the risk of infection increases [32].

Splenic Abscess

Splenic abscess is a very rare condition that affects patients with SCD and is associated with a high mortality rate [33]. About only 600 cases have been reported in the literature. These have occurred mostly in the tropics. The causes of splenic abscess include a direct extension from the infected contiguous organ, hematogenic spread from another site of the body (most commonly bacterial endocarditis), infection secondary to spleen trauma, and in the immuno-compromised [34]. Patients usually have non-specific symptoms that can make the diagnosis very difficult. Frequently the symptoms and signs include fever, abdominal pain, and upper left quadrant tenderness, splenomegaly, leukocytosis, and left lower chest clinical problems. Diagnosis can be made by performing either computed tomography or abdominal ultrasonography. There is currently no consensus regarding the cutoff for the percutaneous drainage of the abscess versus splenectomy. As a general rule, unilocular abscesses < 3 cm in size with thin liquid content can be safety drained under radiological guidance [33]. When abscess size is >10 cm or non-surgical treatment has failed, splenectomy has been shown to be a safe alternative to treat the condition [35].

Surgical Splenectomy Indications in SCD

Certain clinical situations warrant surgical splenectomy in SCD. First, patients with acute splenic syndrome usually undergo splenectomy if their condition can be managed conservatively and splenic rupture has occurred [14]. Second, in patients who survive an acute splenic syndrome attack, subsequent splenectomy is usually performed to avoid the potentially life-threatening complications of recurrence [25,26]. Third, patients with symptomatic splenomegaly due to SCD are candidates for splenectomy [31]. Fourth, patients with splenic abscess can undergo splenectomy [35]. Additionally, splenectomy is performed in patients with massive splenic infarction [31].

Splenectomy Prophylactic Measures

Asplenia predisposes patients with SCD to the risks of overwhelming and life-threatening infections. The potential sepsis in patients with SCD is caused by encapsulated organisms [36]. It is, therefore, necessary for patients with asplenia and SCD to follow a strict vaccination program to prevent such overwhelming sepsis. Table 1 presents a summary of the advised protocol to follow for optimal sepsis prevention. Vaccines are recommended for adults (>18 years) with asplenia/hyposplenism (who have not been immunized previously).

Pre-splenectomy vaccines prophylaxes for elective splenectomy at least 2 weeks (ideally 4-6 weeks) prior to surgery; further, pneumococcal, meningococcal, Haemophilus influenzae type b, influenza, and hepatitis vaccines can be administered [37-39]. In emergency vaccination plus antibiotic injection as amoxicillin, phenoxymethylpenicillin (Penicillin V). If the patient is penicillin-allergic: erythromycin or clarithromycin can be substituted.

Post-Splenectomy Antibiotic Prophylaxis

Patients should be provided with a supply of oral amoxicillin or clarithromycin if penicillin-allergic to be kept at home. If a patient does become clinically infected despite prophylactic antibiotics, he/

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Table 1: Vaccination protocol for patients with asplenia and sickle cell disease [41-43].

Vaccine	Timing	Dose	Route	Revaccination Schedule	Comments
Polyvalent pneumococcal vaccine	Administer at least 2 weeks prior to splenectomy if possible, or 2 weeks after splenectomy	0.5 mL	SC	After every 5 years	Immunity may decline rapidly in certain patient groups.
Tetravalent meningococcal polysaccharide vaccine		0.5 mL	SC	After every 5 years	Used in previously unvaccinated individuals
Haemophilus influenzae type b conjugate vaccine		0.5 mL	IM in the deltoid region	None	
Influenza vaccine	Administer as soon as practicable before or after splenectomy, to ensure seasonal protection	0.5 mL	IM in the deltoid region	Yearly	Administered preferably in October
Hepatitis B vaccine		1 mL	IM in the deltoid region	At 0, 1, and 6 months that provide optimal protection at the seventh month.	Administered because SCD could require blood transfusions

1-Malaria prophylaxis is indicated when a patient is travelling to a malaria-endemic area [44].
2-Immediate reporting after animal bites is indicated [45].

she should immediately start a therapeutic course of antibiotics and seek urgent medical attention, as hospital admission may be required [36]. Some guidelines advise prophylactic antibiotics for the first 3-5 years after splenectomy; however, data indicate that the risk of overwhelming post-splenectomy infection does not decline with time. Unfortunately, long-term antibiotic therapy is a risk factor for selection of resistant strains, and antibiotic efficacy may reduce by non-compliance. Thus, the decision of whether to administer prophylactic antibiotics or not depends largely on the patient and the physician's preference. The choice of antibiotics is also controversial. Penicillin would provide prophylaxis only against sensitive pneumococci, meningococci, and streptococci; however, it is suitable for adults at a dose of 500 mg daily or twice a day. Amoxicillin would be a preferred choice in children. In penicillin-allergic individuals, alternatives are either co-trimoxazole or a fluoroquinolone with Gram-positive activity such as moxifloxacin [40].

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