REVIEW ARTICLE

Functional hyposplenism

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Abstract
Functional hyposplenism is a condition accompanying many diseases such as sickle cell disease, celiac disease, alcoholic liver disease, hepatic cirrhosis, lymphomas and autoimmune disorders. It is characterised mostly by defective immune responses against infectious agents, especially encapsulated organisms, since the spleen is thought to play an important role in the production and maturation of B-memory lymphocytes and other substances like opsonins, both of which are considered crucial elements of the immune system for fighting infections. It is also associated with thrombocytosis, which might lead to thromboembolic events.
Functional hyposplenism is diagnosed by the presence of Howell-Jolly bodies and pitted erythrocytes in the peripheral blood smear, and by nuclear imaging modalities such as spleen scintigraphy with the use of Technetium-99m and/or spleen scintigraphy with the use of heat-damaged Technetium-99m labeled erythrocytes.
Severe infections accompanying functional hyposplenism can lead to the overwhelming post infection syndrome, which can often be fatal.
Identifying patients with functional hyposplenism is important because simple measures such as vaccination against common infective microorganisms (e.g. *Streptococcus pneumonia, Neisseria meningitides* and *Haemophilous influenzae*) and antibiotic therapy when needed are considered beneficial in diminishing the frequency and gravity of the infections accompanying the syndrome. Hippokratia 2014; 18 (1): 7-11.

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Introduction

The integrity and proper function of the spleen are considered important for the protection against infectious diseases in the adult. The reduction of splenic function encountered in various pathological conditions is called functional hyposplenism (FH). FH is a term first used a few decades ago (1969) when Pearson et al, in the USA[1] identified some children suffering from sickle cell disease, who presented with the same clinical course as in splenectomised patients, despite the fact that their spleen had not yet been removed (their spleen was in fact enlarged due to their illness).

FH can be accompanied, to a various extend, by all pathological findings encountered in splenectomised patients. In fact, FH can lead to a series of clinical manifestations which are described under the term of post-splenectomy syndrome. This includes, among others, an increased incidence of infections caused by encapsulated microorganisms. These infections are often serious and life-threatening and they can lead to the 'overwhelming post-splenectomy infection syndrome' (OPSI). Peripheral blood thrombocytosis can also exist and might lead to increased risk of thromboembolic events, especially during the first weeks after the establishment of FH[2].

Removal of non-functional or destroyed erythrocytes from the circulation is often defective in FH. This defective function can be detected by observation of peripheral blood smear under an optical microscope which reveals the presence of many pathological erythrocyte inclusions and particles. The most important of them are called Howell-Jolly bodies[3] (basophilic nuclear remnants). Characteristic pits[4] in the surface of erythrocytes can also be found in the blood of patients with FH.

Principles of anatomy and physiology of the spleen

The spleen consists of three types of tissue: white pulp, marginal zone and red pulp. The white pulp is composed primarily of lymphatic tissue creating structures called germinal centers. Germinal centers contain lymphocytes (activated B-lymphocytes among others), macrophages and dentritic cells and are situated in direct contact with splenic arterioles, branches of the splenic artery. Another important region of the white pulp is the periarteriolar lymphatic sheath, which consists of nodules containing

mostly B lymphocytes. The marginal zone surrounds the white pulp and consists of blood vessels, macrophages and specialized B cells.

The red pulp is composed of vascular sinusoids separated by cords of tissue (cords of Billroth), containing specialized macrophages and forming a sponge-like region that functions as a filter for blood elements. Erythrocyte flow decreases as they pass through this area and conditions favoring their damage and removal from the circulation are created[5].

Erythrocyte removal from the circulation is one of the most important functions of the spleen. This is achieved through either phagocytosis or a process called 'pitting', during which inclusions of erythrocyte cytoplasm or parts of their surface membrane are removed, while their integrity remains intact.

The spleen is considered indispensable for the maturation and maintenance in circulation of IgM memory B-lymphocytes (elements of humoral immunity), which are crucial for immunity against encapsulated microorganisms. Cellular immunity (mediated through T-lymphocytes and complement) is initially ineffective against this type of microorganisms, as it is triggered by protein particles of the cell membrane hidden by the presence of the polysaccharide capsule.

The spleen is also an important site of production of opsonins (like tuftsin and properdin) which are protein particles derived by enzymatic fragmentation of immunoglobulin G molecules (produced by B-lymphocytes). Opsonised microorganisms are easily recognized and removed by macrophages. Significantly important low levels of both B-memory lymphocytes and opsonins have been found in patients with FH in various studies[6,7].

The spleen is the main site of storage of circulating platelels - about 30% of platelels are sequestrated in the splenic tissue.

Definition and causes of functional hyposplenism

FH is an acquired disorder caused by several hematological and immunological diseases and characterized by impairment of splenic function. The most common conditions associated with FH are sickle-cell anemia, alcoholic liver disease, celiac disease, bone marrow transplantation and inflammatory bowel disease[8]. A list of the most important causes of FH is shown in Table 1.

Pathophysiology of functional hyposplenism

The exact mechanisms due to which FH develops, in the conditions mentioned above, are still not completely clarified. In sickle cell anemia, which is considered as a template of the conditions associated with FH, spleen is initially enlarged due to excessive red cell entrapment. Spleen atrophy and degeneration is noted in advanced disease. This atrophy is called autosplenectomy and is probably consequent to multiple acute episodes of entrapment of massive red cell volumes in the splenic tissue, followed by splenic infarctions[1].

Table 1: Main causes of functional hyposplenism.

Hematologic- neoplastic disorders: sickle cell disease, bone marrow transplantation, acute leukemias, non-Hodgkin's lymphoma , advanced breast cancer
Hepatic disorders: alcoholic liver disease, chronic active hepatitis, liver cirrhosis and portal hypertension, primary biliary cirrhosis
Autoimmune Disorders: systemic lupus erythematosus, antiphpspholipid syndrome, vasculitis, rheumatoid arthritis, Hashimoto's thyroiditis
Gastrointestinal diseases: celiac disease, Crohn's disease, ulcerative colitis, Whipple's disease
Infectious Diseases: acquired immunodeficiency syndrome
Circulatory Disorders: splenic/celiac artery thrombosis, splenic vein thrombosis
Miscellaneous: amyloidosis, sarcoidosis, primary pulmonary hypertension, total parenteral nutrition, splenic irradiation, high dose corticosteroid administration

FH accompanying celiac disease and inflammatory bowel disease is thought to be caused by excessive loss of lymphocytes through the inflamed enteric mucosa, leading to spleen's reticuloendothelial atrophy. Reticuloendothelial block due to circulating immune complexes could also be one of the major mechanisms implied. This could also be valid in the case of hyposplenism accompanying autoimmune disorders.

In most hematologic and neoplastic disorders FH is probably due to splenic tissue infiltration by tumor cells or due to vascular occlusion.

In hepatic disorders, hyposplenism might be caused by disruption of normal hepatic microcirculation due to portal hypertension. Direct toxic effect of alcohol is implied in all disorders caused by acute or chronic alcohol consumption.

Clinical manifestations of functional hyposplenism

OPSI is a septic syndrome encountered in splenectomised patients, characterised by the following features[9-11]: a) massive bacteremia caused by encapsulated microorganisms, b) no obvious primary source of infection, c) short, non-specific prodromal phase, d) septic shock accompanied by disseminated intravascular coagulopathy, e) mortality rates of 50-70%, f) death may ensue in a short period of time (24-48 hours) and g) concomitant bilateral adrenal hemorrhage (Waterhouse-Friedrichsen syndrome). The microorganisms most commonly responsible for OPSI are *Streptococcus pneumoniae*, *Neisseria*

meningitides, *Haemophilous influenzae* type B and less frequently, *Klebsiella pneumoniae*, *Salmonella typhi*, and others. OPSI is encountered in patients with FH too, though its frequence is difficult to estimate.

Hematological abnormalities such as leukocytosis (lymphocytosis and/or monocytosis) and mild thrombocytosis are common in patients with FH[12], and an increased risk of thrombotic events could be a logical consequence, even though this fact has not yet been confirmed by all studies. It must be noted that many conditions that can cause FH, are accompanied themselves by augmented incidence of thrombosis.

Epidemiological features of OPSI-FH

According to various studies, the risk of OPSI is 50% higher in splenectomised patients compared to healthy individuals[13]. Even though the risk of OPSI for patients with FH has not been estimated yet, there is an undoubtedly strong correlation between FH and OPSI. Features such as underlying disease, age, microorganism involved and immune-compromise are considered important for determining the frequency and severity of OPSI in different patients.

In fact, the prevalence, the severity of FH and the frequency of OPSI vary among different conditions[4]. Sickle cell disease, for example, is accompanied with severe hyposplenism in almost 100% of cases, and OPSI is encountered more frequently. The prevalence of FH is about 37-100% in alcoholic liver disease, 33-76% in celiac disease, 47% in Whipple's disease and 40% in bone marrow transplantation, whereas in some other cases the frequency of hyposplenism is relatively low (e.g. around 7% in systemic lupus erythematosus). Age is an important factor, and subjects younger than 16 years old are considered to be at higher risk of OPSI[14] due to their immune system immaturity. Regarding the microorganism involved, certain serotypes of *Streptococcus pneumoniae,* which is the most common microbe involved in OPSI, are associated with worse outcome and more fatal events[15].

Diagnosing functional hyposplenism

Patients suffering from one of the conditions mentioned above and presenting with smaller than normal spleen dimensions in any imaging modality and peripheral blood thrombocytosis (except for patients with liver cirrhosis and portal hypertension which are accompanied by splenomegaly and thrombocytopenia), are all candidates of presenting with FH. Diagnosis is based on either microscopic observation and quantification of morphological abnormalities of red blood cells in peripheral blood smear, or on radioisotope imaging modalities. The basic methods are:

A. Presence of Howell-Jolly bodies in peripheral blood smear

Howell-Jolly bodies are erythrocyte nuclear remnants which cannot be easily eliminated by the cells due to FH. They are identified with the use of a normal optical microscope, and appear as spots obtaining a purple (basophilic) color through hematoxylin and eosin staining, easily distinguished by the otherwise eosinophilic erythrocyte. Their presence is highly suggestive of FH. The sensitivity of Howell-Jolly bodies' detection in diagnosing FH is low, especially in mild hyposplenism.

B: '*Pitted' erythrocytes quantification*

It is considered as the gold standard method for diagnosing FH. Pits are characteristic depressions on erythrocyte surface in blood smear through the use of special equipment (Nomarski optics) applied to the optical microscope. Despite the fact that this equipment is not always available to use, even initial stages of FH are discovered. A percentage of 4% or more of pitted erythrocytes among a sample of at least 2000 in total, is considered diagnostic of FH[10,16]. Another advantage of this method is the ability to rate FH in various degrees (mild, moderate, severe) in respect to the percentage of pitted erythrocytes.

C: *Spleen scintigraphy with the use of Technetium-99m*

Liver-Spleen scintigraphy with the use of Technetium-99m sulfur colloid was the imaging modality more often used in past for diagnosing FH. Lower than expected spleen uptake of Technetium-99m sulfur colloid is suggestive of FH. A variation of this method is measurement of the *uptake rate* of the above radioisotope, which is a dynamic (non static) image with a percentage of 96% of sensitivity and 97% of specificity if performed correctly[17]. Spleen scintigraphy with the use of heat-damaged Technetium-99m labeled erythrocytes is performed lately and is considered advantageous in determining splenic function. This method can be also combined with single photon emission computed tomography in order to calculate the *splenic functional volume,* which is obtained by dividing the percentage of splenic uptake of the labeled erythrocytes with the total splenic volume (measured by computed tomography). Splenic functional volume is measured in % uptake/cm^3 [18]. The above radioisotope methods, however, have the disadvantage of being more invasive and time-consuming for the patient.

Newer methods of determining the immunological function of the spleen, such as the immune response upon vaccination or the evaluation of specific B-cell subsets, are being used in the present. According to certain studies, there is a significant positive correlation between functional splenic volume and percentage of IgM^+CD27^+ cells in hyposplenic patients[18].

Guidelines for prevention of serious infections in patients with functional hyposplenism

Prevention of serious infections and OPSI in patients with FH is achieved mostly through vaccine and antibiotic prophylaxis. Various guidelines exist, suggesting, among others, immunization against *Streptococcus pneumoniae* (which is the most common cause of serious infections in hyposplenic patients), *Haemophilous influenzae* type B,

Neisseria meningitides and immunization with the annual influenza vaccine, combined with antibiotic prophylaxis for a period of time depending from the underlying disease and the age at which hyposplenism first appeared. A selection from the guidelines proposed by the Doncaster and Bassetlaw Hospitals (in year 2011)[19], for management of asplenic patients, is shown in Table 2. These guidelines, however, recommend lifelong antibiotic prophylaxis and have been characterized as "conservative" by many authors. This recommendation is based on the fact that OPSI syndrome has been observed even 10-30 years after splenectomy[20], and this is thought to be also valid in case of Functional Hyposplenism. According to others (Australasian Society for Infectious Diseases)[21], antibiotics should be only given for two years after diagnosing FH, as the risk of OPSI has not proved to be the same in all diseases. Antibiotic prophylaxis is not routinely suggested for all patients with FH. Local microorganism resistance should be taken in consideration, before choosing the type of antibiotic therapy.

Immunization of hyposplenic patients has been included in the Canadian Immunization Guide (2006) and includes vaccination against *Streptococcus pneumoniae*, *Neisseria meningitides* and *Haemophilous influenzae* type B[22].

Guidelines also include other preventive measures such as prophylaxis against malaria in case of traveling to endemic countries, as hyposplenic patients are thought to be particularly susceptible to this infection.

It is important to educate the patient and their family, emphasizing on the necessity of seeking immediate medical help in case symptoms such as high fever, malaise and shivering develop. It should be also advised to the patient to keep a supply of penicillin or amoxicillin ready to use in the same occasion.

Guidelines for hyposplenic children differ because of the immaturity of their immune system. Antibiotic prophylaxis should be used routinely until the age of two, regardless of the underlying condition. The 7-valent pneumococcal conjugate vaccine should be used instead of the 23-valent polysaccharide vaccine, because of the ability of its protein "carrier" to induce immediate and more intense immune response[23]. A new 13-valent pneumococcal conjugate vaccine was approved for use in children in 2010 and, according to the ACIP (United States Advisory Committee on Immunization Practices) it is recommended for use in individuals older than 19 years of age with FH, with concomitant use of the 23-polyvalent pneumococcal vaccine[24].

According to several studies the percentage of serious infections in hyposplenic patients after immunization with the pneumococcal vaccine has been significantly reduced[25]. This could justify the pneumococcal vaccine administration to all hyposplenic patients in everyday clinical practice. Annual measurements of antibody levels should be performed, and revaccination should be undertaken if these levels are low.

Conclusions

Functional hyposplenism is described in this article and guidelines about the treatment of hyposplenic patients are given. They consist mostly of preventive measures against possible serious complications, even though their efficacy has not been proven by clinical studies yet.

Immunization of patients at risk seems to be the most effective measure and vaccination against *pneumococcus* should probably be applied to all hyposplenic subjects. Identifying the patients at risk is also of crucial importance with the aim to educate these patients and their families about possible risks and measures to be taken if necessary.

Conflict of interest

Authors report no conflict of interest.

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Table 2: Guidelines for management of asplenia/hyposplenia in adults.

Antibiotic Prophylaxis	1: All patients, regardless of underlying condition, should be on life long antibiotic prophylaxis. This should be either Penicillin V or Amoxycillin, with a preference for Penicilline V. Adult doses: Penicillin V 500 mg bid. Amoxycillin 500 mg od. 2: For penicillin allergic patients Erythromycin 250mg bid should be used.
Immunization	1: All splenectomised patients and those with functional hyposplenism should receive the 23-polyvalent pneumococcal vaccine; the Haemophilus influenza type B conjugate vaccine and the meningococcal C conjugate vaccine as soon as possible. 2: Patients undergoing elective splenectomy should receive the above vaccines at least two weeks before surgery. 3: All adults should receive an annual influenza immunization.

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