THE ROLE OF SPLENECTOMY IN THALASSEMIA MAJOR. AN UPDATE

LISA PECORARI - ANTONELLA SAVELLI - CHIARA DELLA CUNA - SILVIA FRACCHIA - CATERINA BORRNA-PIGNATTI
Clinica Pediatrica - Dipartimento di Medicina Clinica e Sperimentale - Università degli Studi di Ferrara (Direttore: Prof.ssa Caterina Borgna Pignatti)

SUMMARY
In the past, splenectomy was frequently performed in thalassemic patients because of hypersplenism. The new more intense transfusional regimens have decreased the need for splenectomy.

Key words: Splenectomy, thalassemia major, infection, thrombosis, antibiotic prophylaxis

Introduction
The treatment of thalassemia major has traditionally included:
1) transfusion of red blood cells
2) chelation
3) splenectomy.

This triad is now been disputed, as splenectomy, still necessary in some extreme cases especially in thalassemia intermedia, has been shown to be preventable with the appropriate transfusional therapy.

In addition splenectomy is now known to facilitate severe, sometimes lethal, infections and to increase the risk of thrombosis.

In the past, splenectomy was performed shortly after diagnosis because the spleen soon became very large and severe hypersplenism ensued.

Neutropenia, thrombocytopenia and mechanical encumbrance were not rare.

The introduction of regular transfusions has determined a decrease in extramedullary erythropoiesis and has also decreased the number of non functional red cells that needed to be destroyed in the splenic tissue.

Therefore splenomegaly tends to develop later and splenectomy can be postponed until the second decade of life or later. Unpublished data collected in Italy demonstrate that, for patients born after 1970, the probability of having been splenectomized at age 20 is decreased.

The commonly adopted criteria for splenectomy is a blood consumption greater than 50% above the mean requirement of the splenectomized population, i.e. more than 200-250 ml/kg/year of pure red cells, to maintain a pre-transfusion Hb around 9 g/dL. The response to splenectomy is variable from patient to patient, but it is usually satisfactory, and it is long-lasting.

Tests performed with Tc-99 sulfur colloid or Tc-99 RBC uptake have been used in the past, but their results are not reliable, and have therefore been abandoned by the majority of clinicians.

Risks associated with splenectomy

Infection
An increased susceptibility to infections with encapsulated bacteria, as a consequence of splenectomy, has been recognized for many years.
The spleen, in fact, is a major site of antibody production (in particular the splenic marginal zone).

Overwhelming postsplenectomy sepsis (OPSI) appears to be more frequent in thalassemia patients than in other non-immunodeficient patients splenectomized for different causes

The most frequently responsible bacteria are Streptococcus pneumoniae, Hemophilus influenzae, Neisseria meningitidis, E. coli, and Staphylococcus aureus. Klebsiella is a frequent causative pathogen especially in the Far East.

It has been demonstrated that iron overload further increases the pathogenicity of these bacteria, probably through an inhibitory effect of iron on the activity of interferon gamma. As a consequence, iron-loaded macrophages lose the ability to kill intracellular pathogens via the interferon-gamma-mediated pathways. Part of this loss of ability is related to the reduced formation of nitric oxide in the presence of iron

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Malaria and babesiosis can be particularly severe after splenectomy an observation of particular interest for patients of the developing countries

Young children and patients recently splenectomized are at the highest risk of severe infections.

The risk, however, although decreasing with the passing of years, never disappears. A study from Thailand reported the frequency of postsplenectomy sepsis to be 4%, but the mortality associated with it was 89%

All splenectomized patients should undergo prophylactic measures against infections. Guidelines for this purpose have been published by the British Committee of Standards in Haematology in 1996 and updated in 2002.

They include antibiotic prophylaxis with penicillin, amoxicillin or erythromycin for the first two years after surgery and for children until age 16 years, in addition to early antibiotic treatment for fever and malaise. Polysaccaridic antipneumococcal immunization should be given two weeks before the procedure, or whenever possible after it.

Re-immunisation of asplenic patients is currently recommended every 5 years. The addition of the seven valent conjugated antipneumococcal vaccine might have a role in protecting asplenic patients from infection. Immunization against Hemophilus influenzae and with the meningococcal serogroup C conjugated vaccine is also recommended. Patients should also undergo yearly vaccination against the influenza viruses.

**Thrombotic risk**

That thalassemia patients are at an increase of thrombotic complications has been known for many years and it has been recently confirmed by a very large study conducted in the Mediterranean area and Iran.

The study demonstrated that thromboembolic events occurred 1.65% of 8,860 thalassaemia patients with a predilection for splenectomized patients. Thromboembolism occurred 4.38 times more frequently in thalassemia intermedia than in thalassemia major, with more venous events occurring in the former and more arterial events occurring in the latter.

Certain haemostatic anomalies found in thalassemia patients suggest the existence of a chronic hypercoagulable state. Thalassaemic red blood cells, in fact, facilitate thrombin formation as a consequence of the altered asymmetry of the membrane phospholipids with enhanced exposure of phosphatidylerine

Splenectomy increases the hypercoagulability, by permitting the circulation of greater numbers of altered membranes, and by increasing the number of platelets. Thrombocytosis, in fact, develops in 75% of the splenectomized patients, and in 15% it reaches 1,000,000/mm3 or more, reaching a maximum between one week and 4 months after splenectomy.

The role of therapy with low-dose aspirin has not been defined. Pulmonary hypertension has been reported more frequently in splenectomized than in non-splenectomized patients. Recurrent lung thromboembolism could be partially responsible for it.

**Splenectomy and iron**

The role of splenectomy in worsening iron overload is uncertain. It is often suggested that the spleen could represent a safe reservoir for the transfused iron and that splenectomy would, therefore, favour a more massive accumulation of iron in the liver. However, the iron content of the spleen, at splenectomy, is low, amounting to no more than one fifth to one tenth of the liver iron content.

In addition, no difference has been observed, in terms of liver fibrosis, between splenectomized and non-splenectomized patients.

On the other hand, the levels of transferrin saturation, serum ferritin and desferrioxamine-induc-
enced urinary iron excretion were significantly higher in splenectomized than in non-splenectomized patients, indicating that the spleen could have a role in the regulation of iron metabolism\textsuperscript{(20)}.

Alternatives to surgical laparotomic splenectomy

The advantages of laparoscopic splenectomy, in terms of aesthetics and reduced hospital stay are not offset by costs\textsuperscript{(20)}. However, the size of the spleen in thalassemia major and intermedia is rarely small enough to allow such an approach. In addition, the risk of post-operative thrombosis of the portal vein seems to be increased after the laparoscopic approach.

Several alternatives have been proposed to surgical splenectomy. The procedure most often reported, and more successful, has been partial embolization of the splenic artery\textsuperscript{(21)}. Results have been long lasting\textsuperscript{(22, 23)}. Partial splenectomy and partial dearterialization of the spleen have been reported to have an immediate beneficial effect, but to be of short duration\textsuperscript{(23, 24, 25)}. It is hoped that preserving a residual portion of the spleen will prevent infections and thrombotic events, but the numbers reported so far are to small to confirm this hypothesis.

Conclusions

Splenectomy has in the past played a major role in the treatment of thalassemia, but increased awareness of its adverse effects have significantly decreased its use. When the surgical procedure is necessary measures must be taken in order to protect the patient from the risk of infection and thrombosis.

References


Request reprints from:
Dott.ssa CHIARA DELLA CUNA
Via Corridoni, 151
48022 Lugo (RV)
(Italy)