Initial Assessment of the Beneficial Effect of Partial Splenectomy in Hereditary Spherocytosis

By G. Tchernia, F. Gauthier, F. Mielot, J.P. Dommergues, J. Yvart, J.A. Chasis, and N. Mohandas

Clinical manifestations of hereditary spherocytosis (HS), the most common red blood cell (RBC) membrane disorder, can be abrogated or markedly reduced by splenectomy. However, concerns regarding risks from overwhelming infections after splenectomy have restricted its use, especially in children. This study was designed to determine if partial splenectomy can decrease the hemolytic rate while maintaining phagocytic function of the spleen. Partial splenectomy was performed in 11 children (age 2 to 13) with HS. The effect on hemolytic rate was assessed by comparing the presurgical and postsurgical values for hemoglobin, reticulocyte number, and RBC life span. The residual splenic phagocytic function was assessed using technetium 99m scans and by enumerating the percentage of pitted RBCs in circulation. There were no complications from the surgical procedure in any of the 11 individuals. Following partial splenectomy, hemoglobin increased on the average by 3 g/dL, reticulocyte count decreased by 300 X 10⁶/L, and RBC life span was substantially prolonged. Normal technetium uptake was noted in the splenic remnant and the percentage of pitted RBCs was in the normal range. Partial splenectomy is effective in decreasing the hemolytic rate while maintaining residual splenic phagocytic function of the spleen in HS. We conclude that the use of this procedure as treatment for RBC membrane disorders warrants consideration, especially in infants under 5 years of age who need frequent transfusions.

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EREDITARY SPHEROCYTOSIS (HS) is the most common of the red blood cell (RBC) membrane disorders. While recent biochemical and molecular biologic studies have shown that this RBC phenotype is a consequence of defects in a number of different membrane skeletal proteins, the clinical expression of the disease appears to be related solely to the extent of cell surface area loss. The particular anatomical and cellular features of the spleen, including percolating microcirculation, high blood flow, and abundance of macrophages, make it an ideal organ for sequestering undeformable, spherocytic RBCs. Splenic sequestration of RBCs is indeed the primary determinant of the decreased survival of RBCs in this disorder and splenectomy has been shown to abrogate or markedly decrease hemolysis. However, the spleen, in addition to its role as a surveyor of functional RBCs, also plays an important role as a first-line defender against some blood-borne infectious pathogens. Moreover, the spleen as a lymphoid organ has an important, although not fully defined, role in the humoral response: a part of the antigen presentation takes place in the marginal zone and during the first years of life the spleen appears to play a role in pre-B cell maturation. During the last few decades concern has been raised that overwhelming infections that occur subsequent to splenectomy are caused by the elimination of this line of immunologic defense.

Overwhelming postsplenectomy infections are primarily caused by Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae and are characterized by an abrupt onset and a rapid spread of infection. The occurrence of these life-threatening infections is most often seen in individuals in whom splenectomy is performed early in life, but has also been reported to occur in older individuals with a wide range of probabilities in the risk of occurrence. While these infections are most commonly seen in the 2- to 3-year period after surgery, in some instances they have been reported many years after surgery. In HS, the overall risk of overwhelming postsplenectomy infection has been estimated to be approximately 3% to 5%, with infants under 5 years of age having a fourfold higher rate of risk.

Because of the risk of postsplenectomy complications, more conservative procedures such as splenorraphies, partial splenectomy, and splenic tissue graft have recently been studied and advocated as an alternative to total splenectomy in treatment of splenic trauma, thalassemia, Gaucher's disease, and also before renal transplantation. However, the effectiveness of partial splenectomy in reducing the hemolytic rate in RBC disorders caused by membrane defects has not been evaluated. In the present study, we have assessed the effectiveness of partial splenectomy in decreasing the hemolytic rate while adequately sustaining the phagocytic function of the spleen in 11 children with HS. Our data suggests that partial splenectomy is indeed effective in achieving this objective. We suggest that this surgical procedure be considered for individuals with RBC membrane disorders, particularly young children with transfusion-dependent anemia, so as to obtain the benefits of increased hemoglobin levels without the risks of overwhelming postsplenectomy infections, or of transmission of viral diseases through transfusions.

MATERIALS AND METHODS

Subjects. The 11 individuals studied were children whose ages ranged from 2 to 13 years at the time of surgery. The diagnosis of HS was confirmed by osmotic gradient ektacytometry. Spherocytic phenotype was inherited through a dominant mode in 7 patients, through a recessive mode in 3 individuals (nos. 1, 6, 10), and in an unknown manner in an adopted child (no. 2). Splenomegaly and icterus were noted in all subjects before surgery. Seven patients were anemic, 5 of whom required transfusions on various occasions to...
manage their hemolytic disease, while 1 patient (no. 10) required regular transfusions. For the 4 other patients, the reason for splenectomy was gallstones and cholestasis (nos. 7, 11), or chronic fatigue with marked splenomegaly (nos. 1, 5). Partial splenectomy was proposed as a mode of treatment for these 11 children following extensive discussions with the parents and on receiving assurances that the children will be available for long-term follow-up. The reasons for 25Cr RBC survival studies and for technetium 99m spleen scans were explained to the parents who were also informed of the nature of the surgical procedure and of the potential need for a total splenectomy in the future. Informed consent was obtained in all of these cases. Before surgery, all of the children received pneumococcal vaccine. After surgery, the children were treated prophylactically with oral penicillin for at least 1 year.

Surgical technique. The objective of the surgical procedure was to remove approximately 80% of the splenic tissue while preserving the lower pole of the spleen (Fig 1). After complete mobilization of the short gastric vessels of the spleen, all branches of the main splenic vessels, except for the vascular pedicle arising from left gastroepiploic vessels, were ligated and divided close to the splenic hilum. This procedure created a large bluish ischemic zone precisely delineating the splenic tissue to be excised. Sectioning of parenchyma was achieved with thermocautery, a few millimeters on the ischemic side of the organ. In some of the patients, to prevent bleeding and torsion of vascular pedicles, the following measures were used singly or in combination: the remaining vascular pedicles were cross-clamped during sectioning, fibrin sealant was applied to the section, and the residual splenic tissue was fixed to the posterior abdominal wall.

RBC studies. To assess the decrease in hemolytic rate following partial splenectomy, we compared the values for hemoglobin and reticulocyte numbers in the years before surgery with the values obtained after surgery. Hemoglobin levels and reticulocyte counts were quantitated using standard procedures. To objectively assess changes in RBC life span after partial splenectomy, 25Cr RBC survival studies were performed before and a year or more after surgery. 31

Phagocytic function of the spleen. Two different experimental approaches were used to assess phagocytic function of the spleen. The first, an indirect approach, involved evaluating the number of pitted RBCs in circulation. This assay relies on the finding that a functional spleen is necessary to perform phagocytic remodeling of the RBC membrane during reticulocyte maturation as well as during cell aging. Absence of splenic function and lack of normal membrane remodeling is manifested by increased numbers of circulating RBCs characterized by the presence of surface vesicles or pits. Increased numbers of pitted RBCs have indeed been reported after total splenectomy, in sickle cell disease (SCD) as a consequence of functional asplenia, and after splenic irradiation. 15-35 Moreover, increasing numbers of pitted RBCs have been shown to be a reliable index for the risk of infection in children with SCD. 36 For this assay, RBCs were fixed using a 1% buffered-glutaraldehyde solution and the number of pitted RBCs was counted using an interference contrast-phase microscope with Nomarski optics. The percentage of RBCs having one or more pits was determined by counting a minimum of 1,000 RBCs. This assay was performed on blood samples from the 11 children who underwent partial splenectomy, as well as on blood samples from 20 healthy volunteers and from 13 individuals who underwent total splenectomy. A more direct assessment of the phagocytic function of the spleen was achieved by monitoring the splenic uptake of technetium 99m-labeled heat-damaged RBCs 37 before and 1 year after surgery.

RESULTS

Surgical procedure. Partial splenectomy was feasible and successful in all 11 patients. Three of the patients who had gallstones (nos. 7, 9, 11) also underwent biliary surgery (two cholecystectomies and one choledocotomy for extraction of a bile duct stone). In the eight cases without associated biliary surgery, the mean duration of surgery for partial splenectomy was 70 ± 20 minutes, as compared with 50 to 60 minutes for total splenectomy. Weights of the resected parenchyma are shown in Table 1.

Effect of partial splenectomy on hemolysis. The variation in hemoglobin and reticulocyte count in two of the patients before and after surgery is shown in Fig 2. It can be seen that the increase in hemoglobin values and the decrease in number of reticulocytes, on average, was approximately 300 × 10⁶/L. In calculating these values, we did not include data from patient 10 because repeated blood transfusions before surgery prevent us from establishing a true steady-

Fig 1. Surgical technique used for partial splenectomy. (A) Division of all vascular pedicles except the pedicles arising from left gastroepiploic vessels during surgery. (B) The remnant lower pole of the spleen after surgery.
Table 1. Mean Values of Hemoglobin and Reticulocytes in the 11 Patients Before and After Surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Surgery (yr)</th>
<th>No. of Transfusions Before Surgery</th>
<th>Weight of Spleen Removed (g)</th>
<th>Hb Value (g/dL)</th>
<th>Reticulocyte Value (10⁹/L)</th>
<th>Increase in RBC Life Span (t₁/₂ days)</th>
<th>Post-Surgery Years of Follow-Up</th>
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<tr>
<td>1</td>
<td>6</td>
<td>0</td>
<td>140</td>
<td>11.8 ± 1.6</td>
<td>13.8 ± 1.0</td>
<td>500 ± 100</td>
<td>150 ± 100</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>0</td>
<td>350</td>
<td>7.7 ± 0.3</td>
<td>12.1 ± 1.0</td>
<td>300 ± 50</td>
<td>300 ± 100</td>
</tr>
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<td>3</td>
<td>8</td>
<td>2</td>
<td>220</td>
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<td>16.2 ± 0.4</td>
<td>400 ± 300</td>
<td>300 ± 50</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>1</td>
<td>360</td>
<td>9.9 ± 1.6</td>
<td>12.8 ± 0.6</td>
<td>500 ± 100</td>
<td>150 ± 100</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>0</td>
<td>300</td>
<td>11.1 ± 0.7</td>
<td>12.4 ± 0.5</td>
<td>400 ± 50</td>
<td>150 ± 100</td>
</tr>
<tr>
<td>6</td>
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<td>12.7 ± 0.9</td>
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<td>600 ± 200</td>
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<td>1,150 ± 250</td>
<td>200 ± 50</td>
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<td>8</td>
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<td>395</td>
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<td>500 ± 50</td>
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<td>12.4 ± 0.7</td>
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<tr>
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<td>440</td>
<td>11.3 ± 1.1</td>
<td>13.6*</td>
<td>600 ± 200</td>
<td>150*</td>
</tr>
</tbody>
</table>

Abbreviations: ND, value not reported because of repeated transfusions.
* One test only.

state value for hematologic parameters. The observed increase in hemoglobin and decrease in reticulocyte numbers is a direct consequence of an increase in RBC life span after surgery (Fig 3). In all eight individuals, in whom RBC survival studies were performed before and after surgery, RBC life span was substantially prolonged. As shown in Fig 3, the t₁/₂ values for RBC survival before surgery ranged between 4 and 7 days, while after surgery they ranged from 9 to 15 days. The mean increase in t₁/₂ after partial splenectomy was calculated to be 7.3 ± 1.1 days. During a follow-up period that ranged from 1 to 6 years, none of the patients required blood transfusions to maintain adequate hemoglobin levels except for two brothers (nos. 8, 9). These two individuals, who had required transfusions before surgery, were each transfused on one occasion 29 and 36 months after surgery during primary infection by parvovirus B19. After this episode a total splenectomy was performed on one of these individuals at a different institution on family request.

**Phagocytic function of the spleen.** The percentage of pitted RBCs, an indirect measure of splenic phagocytic function, was evaluated in patients who underwent partial splenectomy (Fig 4). The percentage of pitted RBCs was less than 2% in all the patients, a value similar to that observed in normal subjects with a fully functional spleen. In four patients, the percentage of pitted RBCs was sequentially evaluated during a 3- to 6-year follow-up and the counts remained low and unchanged during this time. In contrast, in 11 of 13 patients who underwent total splenectomy, the percentage...
of pitted RBCs was much higher, ranging from 5% to 30% (Fig 4).

Spleen scans performed on patient no. 1 before and 12 and 54 months after surgery showed persistent normal uptake of heat-damaged RBCs and no evidence of the growth of the remnant spleen (Fig 5). Spleen scans in eight other patients also showed normal uptake of technetium 99m-labeled heat-damaged RBCs 1 year after surgery, confirming the persistence of phagocytic function in the residual spleen. These findings enabled us to rationalize the discontinuation of oral prophylactic penicillin in all the patients 1 to 2 years after surgery. However, the parents were strongly advised to begin antibiotic treatment immediately if the children began to experience "flu-like" infections of even benign appearance.

**Improvement in quality of life.** Quality of life improved in 9 of 11 patients after partial splenectomy. This was reflected by improved participation in sporting activities, improved sleeping pattern in 8 cases, and an increase in the slope of growth curves in 2 children (nos. 1, 10) in whom a plateau had been observed before partial splenectomy.

**DISCUSSION**

Total splenectomy has proven to be extremely effective in reducing the hemolytic rate in individuals with RBC membrane defects and is a logical treatment modality for inherited RBC disorders such as HS, elliptocytosis, and pyropoikilocytosis. By eliminating the need for regular blood transfusions in severe cases, this surgical procedure also removes the associated risks of blood-related viral infections and iron over-load. Moreover, it also has an important impact on the quality of life. Most patients with HS who underwent splenectomy as adolescents or young adults report that even in the absence of profound anemia in years before surgery, a dramatic improvement in their physical and professional abilities followed surgery. Chronic compensated hemolysis, despite regular folic acid supplementation, can lead in our experience to chronic fatigue related to mild anemia and also hypothetically to the overproduction of monokines by splenic macrophages, whose numbers have been shown to be increased in individuals with chronic hemolysis. However, as the spleen plays a unique role in the clearance of particulate antigens including pathogenic bacteria from the peripheral blood and is also a key lymphoid organ in early childhood, the decision to perform splenectomy is a difficult one and the potential life-threatening risk from overwhelming postsplenectomy infections has raised concerns regarding the use of splenectomy. As there are no extensive studies that have evaluated the risk of infections in individuals after oral penicillin prophylaxis and regular vaccinations systematically instituted after total splenectomy, it is difficult at present to assess the exact magnitude of this risk. However, it should be noted that a few reports do suggest occurrence of infections in such individuals. Moreover, it is difficult to expect individuals to adhere to life-long compliance for oral penicillin prophylaxis, especially during adolescence or early adulthood. Thus, when taking care of patients with RBC membrane defects the physician is confronted with two uncomfortable situations: (1) in infants with transfusion-dependent anemia, in whom risk for episodes of postsplenectomy infections are high, one has to weigh the relative importance of two potential risks, that of total splenectomy versus that of transfusion-induced viral diseases; (2) in older children or adults needing no or infrequent trans-
fusions the need for splenectomy to counteract symptoms such as chronic fatigue, gallstones, and persistent splenomegaly is debatable. In these instances, a conservative strategy of partial splenectomy appears to be a valuable alternative. This surgical approach is feasible because of the unique anatomic features of this organ. Intrasplenic distribution of branches of splenic pedicles have been extensively studied and it has been documented that branches of both splenic artery and splenic vein enter splenic parenchyma in a digitiform pattern with intraparenchymatous anastomotic vessels being rare. Thus, the spleen is divided into a variable number of almost independent vascular territories whose general orientation is perpendicular to cranio-caudal axis of the organ. These anatomic features enable the safe surgical removal of large sections of the spleen while allowing the remnant organ to be functionally competent.

To our knowledge, the benefits of partial splenectomy as a treatment modality for hemolytic diseases has not previously been systematically evaluated. The following issues need to be considered in studying this approach: (1) the amount of splenic parenchyma that needs to be removed to effectively reduce RBC destruction; (2) the minimal amount of residual parenchyma necessary for maintaining adequate phagocytic function; and (3) the growth rate of the splenic remnant. Previous studies in rats have shown that these animals could survive intravenous (IV) injection of Streptococcus pneumoniae as long as 25% to 50% of the normal splenic tissue was present. The effect of partial versus total splenectomy on the immune response has not been assessed. However, it is likely that contact between antigens and lymphoid cells as well as maturation of pre-B cells can proceed in the remnant. We chose to preserve approximately 20% of the enlarged spleen, so as to decrease as much as possible the sequestration of RBCs while counterbalancing the need for an adequate amount of remnant spleen to preserve its phagocytic function. Postoperative ultrasonogram and scintigraphy...
showed that indeed the remnant spleen was approximately 25% to 35% of the normal splenic tissue. While there is not sufficient data to objectively predict the growth rate of remnant spleen, studies on accessory spleens found after failure of total splenectomy for thrombocytopenia suggest that splenic tissue growth is probably slow.\(^7\) This is consistent with the finding that in our patients the hemoglobin value and the percentage of pitted RBCs appeared to be stable over time and that in one of them no growth in the remnant spleen could be observed at 4 years after surgery. However, a much longer follow-up is needed to be certain that the observed beneficial effects will be long lasting. The potential need for a second surgical procedure as well as other complications such as parvovirus B19 erythroleukemia or gallstone generation in these individuals undergoing partial splenectomy need also to be considered in future evaluations of this procedure.

In summary, we have shown that partial splenectomy in HS is effective in decreasing the hemolytic rate while maintaining residual splenic phagocytic function. While the reduction in hemolytic rate is not as extensive as that observed after total splenectomy, it is of sufficient magnitude to provide clinical benefit. Most importantly, it appears that splenic phagocytic function appears to be retained and thus this procedure in the long run may abrogate the incidence of overwhelming infection. While many issues such as potential clinical consequences of the growth of remnant spleen remain unanswered, we conclude that partial splenectomy can be proposed as treatment for RBC membrane disorders. Its use in infants with transfusion-dependent hemolytic anemia caused by RBC membrane defects deserves a special consideration. At an age when the infectious susceptibility related to the loss of splenic function is enhanced by immunologic immaturity, partial splenectomy could be the answer to the dilemma for surgery. It can lead to a discontinuation of transfusions while sparing the clearance process and the immune maturation.

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