Surgical management of hereditary spherocytosis

Current strategies

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BACKGROUND: *Hereditary spherocytosis is a benign hematologic disease, which needs surgical treatment when medical therapy fails. Currently, the surgical strategies consist mainly in total or partial splenectomy, which can be performed either in open or in laparoscopic fashion. In this study, we analyzed our series of splenectomies for hereditary spherocytosis and we discuss about the surgical management, reviewing the Literature.*
MATERIAL AND METHODS: *Twenty-seven patients (mean age 16.5 years, range 8 – 30 years) affected by hereditary spherocytosis were retrospectively evaluated. Indication to surgery was based on hemolysis severity. Thirteen patients were submitted to laparoscopic splenectomy and 14 to open splenectomy, after preventive specific vaccinations. Cholecystectomy for associated cholelithiasis was performed during the same operation in 4 laparoscopic patients and in 6 open patients.*
RESULTS: *Main reasons for performing splenectomy were anemia unresponsive to iron supplementation in 7 patients (42%), splenomegaly in 6 patients (37%), and jaundice in 4 cases (21%). All the patients had a severe disease with hemoglobin level below 80 g/L, median reticulocytes count 6,5%, median value of indirect bilirubin concentration 2,0 mg/dL. Indications to splenectomy were increased need for red cell transfusions in 11 patients (66%) and symptoms related to cholelithiasis in 6 patients (34%).*
A post-operative early complication was observed after open splenectomy, consisting in a pancreatic fistula, which was treated conservatively. No post-operative complications were observed after laparoscopic splenectomy. Neither intra-operative complications nor conversions to open surgery were recorded during the laparoscopic approach. In a long-term follow-up, no infective complications were recorded.
CONCLUSIONS. *According to our results, total splenectomy is associated with good results and few complications. In our opinion, it remains the best therapeutic option in selected adult patients non-responder to the medical treatment.*

KEY WORDS: Hereditary spherocytosis, Laparoscopic splenectomy, Partial splenectomy

Introduction

Hereditary spherocytosis is one of the commonest hematologic diseases in Northern Europe and North America [1], while it is rare elsewhere. When medical therapy fails, surgical treatment is required. Over time, the surgical techniques have evolved and new ones have been introduced. Since its introduction in 1991, laparoscopic splenectomy has been increasingly performed worldwide. Few years later, partial splenectomy was also performed in laparoscopy. Despite evolving technologies in surgery and the developed new strategies in the overall management, several aspects of the surgical treatment of hereditary.

In this paper, we analyzed our experience in the surgical treatment of hereditary spherocytosis have to be clarified. A review of the literature on the subject has been reported.

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Materials and Methods

Twenty-seven patients operated on with splenectomy for hereditary spherocytosis from July 1982 to December 2016 in the Department of General Surgery at the University of Catania, were retrospectively evaluated. Thirteen patients were submitted to laparoscopic splenectomy, and fourteen patients to open splenectomy. Cholecystectomy was performed before splenectomy in 4 laparoscopic patients and in 6 open patients with associated cholelithiasis.

Hereditary spherocytosis was diagnosed based on clinical history, physical examination and laboratory tests. Complete blood count, blood smear, reticulocytes count, bilirubin concentration, osmotic fragility test and direct Coombs test were evaluated at the Hematologic Unit. Abdominal ultrasonography was performed to all patients in order to evaluate spleen size and associated cholelithiasis.

Patients were stratified pre-operatively based on the severity of the disease according to the hemoglobin level, and were classified into severe, moderate and mild disease.

At least thirteen days before the surgical procedure, all the patients received immunization for Haemophilus influentiae, Streptococcus pneumoniae and Meningococcus.

Antibiotic prophylaxis was accomplished with a single-dose pre-operative administration and was continued for at least 2 months after surgery.

Laparoscopic and open splenectomies were accomplished in the traditional fashion using the techniques we have reported elsewhere [2-5]. In our series, composed by patients operated in an age where immunocompetency was probably acquired, complete total splenectomy has been performed in each case.

Results

Median age at the diagnosis was 16,5 years (range 8 – 30 years). Male to female ratio was 0,8 (12/15).

Main reasons for referral to our Institution were anemia unresponsive to iron supplementation in 7 patients (42%), splenomegaly in 6 patients (37%), and jaundice in 4 cases (21%).

All the patients had a severe disease with hemoglobin level below 80 g/L, with a peripheral blood smear showing spherocytic red cells. The median reticulocytes count was 6,5%. Indirect bilirubin concentration ranged from 1,5 to 3 mg/dL, with a median value of 2,0 mg/dL. A positive red cell osmotic fragility test was recorded in all the patients. Neither signs / symptoms of hypersplenism nor other hereditary hemolytic anemia were recorded in all patients.

TABLE I - *Clinical data of patients with hereditary spherocytosis*

N° of patients	27
Gender	
Male	12 patients (%)
Female	15 patients (%)
Median age at diagnosis	16.5 years (range 8-30 years)
Severity classification of the disease	
Mild (Hb>110-120 g/L)	0
Moderate (80<Hb<110-120 g/L)	0
Severe (Hb<80 g/L)	27 patients
Mean spleen size	18 cm (range 10-22 cm)
Associated laparoscopic cholecystectomy	4 patients in laparoscopy 6 patients in open
Mean operative time	50 min (range 40-75 min in laparoscopy) 50 min (range 50-75 min in open)
Conversion rate	0%
Mean hospital stay	3.5 days (range 3-7 days) in laparoscopy 10 days (range 8-13 days) in open
Complications	1 pancreatic fistula after open splenectomy 0 in laparoscopic splenectomy

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Indications to splenectomy were increased need of red cell transfusions in 11 patients (66%) and symptoms related to cholelithiasis in 6 patients (34%).
The spleen size ranged from 10 – 22 cm (mean 18 cm) at ultrasound examination.
Splenectomy was performed in 14 patients through the open approach, and in 13 patients by means of the laparoscopic approach. Cholecystectomy was associated to the removal of the spleen in 4 patients through laparoscopic technique, and 6 by open approach.
Mean operative time was 50 minutes for both laparoscopic and open splenectomies (range 40 – 75 minutes for laparoscopic surgery; range 50 – 75 minutes for open approach).
A post-operative complication was observed in one case after open splenectomy, consisting in a pancreatic fistula, treated conservatively. No post-operative complications were observed after laparoscopic splenectomy.
Neither intra-operative complications nor conversions to open surgery were recorded during the laparoscopic approach. The mean amount of operative bleeding was 50 ml (range 0 - 150 ml) and no blood transfusions were administered during surgery. No peri-operative mortality was recorded.
Mean hospital stay was 10 days (range 8 - 13 days) for open splenectomies; 3,5 days (range 3 – 7 days) for the laparoscopic group.
Patients' data are showed in Table I.
Post-operative hematologic surveillance showed a persistent correction of anemia without need of post-operative blood transfusions, one year after surgery.
All the splenectomised patients were subjected to thromboprophylaxis for at least 3 weeks. Neither portal vein thrombosis nor thrombo-embolic disorders were observed in the follow-up period after surgery.
No case of post-operative severe infections or sepsis was recorded in a long-term follow-up, lasting up to 5 years.

Discussion

Hereditary spherocytosis is the commonest inherited hemolytic anemia in Northern Europe [1,6] and North America [1]. It is due to deficiency or dysfunction of erythrocyte cytoskeletal proteins: the red blood cell cannot maintain its shape, deformability and elasticity, resulting in a shorter lifespan [7], since the spleen destroys the altered red blood cells.
Treatment strategies depend on classification of hereditary spherocytosis. It is based on anemia's degree and is defined as asymptomatic (normal levels of hemoglobin and reticulocytes), mild (12 ≤ hemoglobin ≤ 15 g/dl and 3% ≤ reticulocytes ≤ 6%), moderate (8 ≤ hemoglobin ≤ 12 g/dl and reticulocytes > 6%) and severe (6 ≤ hemoglobin ≤ 8 g/dl and reticulocytes > 10%) [8]. Seventy per cent of patients have moderate hereditary spherocytosis, 20% mild hereditary spherocytosis and 3 – 5% a severe form of hereditary spherocytosis [7,9,10]. The age of diagnosis ranges from 5 to 21 years [7] and is often made in childhood. The diagnosis is based on clinical features and laboratoristic findings.
Generally, the treatment of HS involves a medical care, a surgical treatment, and management of post-splenectomy complications, which are described in the guidelines for the diagnosis and management of hereditary spherocytosis published in 2011 [11]. Medical therapy with folate supplementation is suggested only in case of moderate hereditary spherocytosis, because of their low levels of chronic hemolysis, especially for those who have not undergone splenectomy and during pregnancy. Aplastic crises occasionally can cause severe anemia especially in the first few years of life, when spherocytes destruction is not balanced by new red blood cell (RBC) production. In these cases, blood transfusions are needed. The use of erythropoietin can help in reducing or avoiding blood transfusion.
According to the Guidelines, splenectomy is indicated in children with severe hereditary spherocytosis, suggested in patients with moderate disease and should probably not be performed in those with mild disease [11]. Patients should be considered for splenectomy based on their symptoms and complications, after failure of medical therapy [7,11-13] or if symptoms become worse [16]. Clinical indications and timing for splenectomy are still a matter of debate. Splenectomy is recognized to be of benefit in reducing the symptoms of hereditary spherocytosis due to hemolysis, leading to an increase in red cell life span [11,14], in reducing the need for transfusions [15] and in compensating the growth failure or skeletal changes due to the increased erythropoiesis [16].
Splenectomy should be performed in patients after acquisition of immunocompetency. For this reason, guidelines recommend the surgical removal of the spleen after the age of 6 years [14], when the risk of sepsis is lower than younger patients [1]. Before the age of 6 years, splenectomy is only recommended in case of transfusion – dependence and should not be performed before the age of 3 years.
In case of associated cholelithiasis, cholecystectomy can be accomplished together with splenectomy in mini-invasive fashion. Cholecystectomy is perfomed when cholelithiasis becomes symptomatic [7,14]. If gallbladder stones are an incidental finding and remain asymptomatic, cholecystectomy remains controversial [14]. In absence of gallbladder stones, splenectomy alone is sufficient, since it drastically decreases the incidence of cholelithiasis [11].
Results after splenectomy in HS and comparison between laparoscopic and open approach have been reported by some Authors. Rice et al. in a review from the Literature reported that the post-operative hemoglobin concentration increased from 10,1 ± 1,8 g/dL to 12,8 ± 16 g/dL 52 weeks after laparoscopic splenectomy [15].
Sapucahy et al. compared two homogeneous groups of

patients respectively subdue to laparoscopic and open splenectomy for hematologic diseases, among them hereditary spherocytosis. They found that the laparoscopic procedure permitted a more effective recovery of hematocrit values in the laparoscopic group (P = 0.033), whereas no differences were observed in platelet counts. Within the follow-up period of 2 years, hematologic recurrences were uncommon in both groups (4/30 vs. 3/28). Four conversions to open surgery were required (13.3%), two of these for persistent hemorrhage, and two for adherences. The most frequent intraoperative complication in both groups was bleeding, with comparable numbers of patients who required blood transfusions (12/30 vs. 7/28). Serious early complications in laparoscopic group were represented by 1 episode of bleeding that required re-operation and 1 death on the 2nd postoperative day due to myocardial infarction. In open group, 3 re-operations were necessary, 1 due to bleeding with hemorrhagic shock, another connected to a subphrenic abscess, and the third one because of abdominal dehiscence. Significant late complications in a laparoscopic patient included 1 wound abscess that was drained, and 3 incisional hernias after conventional surgery [17].

From above reported data from the Literature, laparoscopic technique seems to be more advantageous than the open procedure. Our experience confirms these data. In our opinion, the laparoscopic approach could allow a better-magnified vision of the surgical field, reducing the risk of iatrogenic lesions of the surrounding structure such as pancreatic tail.

In our series, positive response to total splenectomy was observed in all the patients after one year of follow-up. Post-operative complications consist mainly of post-operative bleeding, subphrenic abscess, pancreatic fistula, portal vein thrombosis, thrombocytosis and systemic infections including sepsis (overwhelming post-splenectomy infection –OPSI).

OPSI is a fearful and life-threatening complications following splenectomy [18,19], since the poorly opsonized bacteria, such as the encapsulated species, can be cleared only by the spleen [20]. Its incidence is approximately 1% to 5% of splenectomised patients [18]. Patients should be vaccinated against these bacteria, as suggested by the guidelines [21,22], and should be informed about. The risk of sepsis is lifelong and is not completely eliminated by vaccinations and post-operative antibiotic prophylaxis [22].

In order to reduce OPSI, in alternative to total splenectomy some Authors have suggested to perfom partial splenectomy [1,11]. The rationale is that leaving the upper pole or the lower pole of the spleen may allow maintaining a residual parenchyma [18,23,24] with a valid immunologic function [25]. Indications to partial splenectomy remain to be defined, but up to now, it is strongly recommended in case of children younger than 6 years who need splenectomy, suffering from moderate and symptomatic hereditary spherocytosis, with or without splenomegaly [1,26]. In other cases, total splenectomy is required.

Partial splenectomy can be also performed laparoscopically [18,26,27], which is associated to many advantages either for the patient or for the surgeon.

Uranues et al. [27] performed the first laparoscopic partial splenectomy in 1994.

Partial splenectomy leads to a sustained decrease in hemolytic rate [1,16,25,26,28,29] with persistent increase of hemoglobin levels [25,29,30] and decrease in reticulocyte count [25,26,28], but less than after total splenectomy [26]. The need of blood transfusions decreases [25,28] in the early post-operative period for most patients.

Seims et al. [26] reported a series of 87 hereditary spherocytosis children, 71 of them were submitted to laparoscopic total splenectomy and 16 to laparoscopic partial splenectomy. Reticulocytes and hemoglobin levels improved after both operations, although laparoscopic partial splenectomy had lower preoperative and post-operative hemoglobin level. Partial splenectomy was less effective in decreasing the reticulocyte count, due to a residual hemolytic activity. No child required blood transfusion in the early post-operative period. Three children out of 16 in the partial splenectomy group required transfusions years after the operation. Therefore, laparoscopic partial splenectomy decreases hemolysis, but laparoscopic total splenectomy is more effective. None case of OPSI was recorded.

In order to compare the effectiveness of total splenectomy and partial splenectomy in pediatric hereditary spherocytosis, Guizzetti et al. [30] performed a systematic review and meta-analysis. They found in 14 observational studies that total splenectomy is more effective than partial splenectomy in increasing hemoglobin level (3.6 g/dl versus 2.2 g/dl) and in reducing reticulocytes' number (12.5% versus 6.5%) after one year. Partial splenectomy results were stable for at least 6 years. There were no case of OPSI. Regrowth of the splenic remnant was lowest at younger age and severe disease. The incidence of second look (total splenectomy) was 5% and the length of hospital stay was comparable between partial splenectomy and total splenectomy groups.

Other Authors have reported their experience with partial splenectomy [27,28]. In their experience, a consistent group of operated patients required a further surgical treatment with complete removal of the remaining spleen. After partial splenectomy, regrowth of the splenic remnant (whose incidence ranges from 0% to 11% [11,18,23], could explain this occurrence.

Nowadays, it is reasonable to perform a partial splenectomy for hereditary spherocytosis symptomatic patients younger than 6 years, since the risk of infection is higher in this range of age [1].

In alternative to total splenectomy, with the same rationale of partial splenectomy of reducing OPSI, in 1973 Maddison [31] introduced partial splenic embolization [32] for the treatment of hypersplenism. This procedure was

soon after abandoned for about 10 years, because of the high incidence of complications, such as fever, upper abdominal pain and leukocytosis, which are common in the first week after the procedure [33,34]. In the eighties, the role of partial splenic embolization was revised and partial splenic embolization was reintroduced as a therapeutic option for hematologic and non-hematologic pathologies, but the advantage of avoiding a surgical intervention is often nullified by the post-partial splenic embolization morbidity. Partial splenic embolization can be suggested to adult and infant patients without splenomegaly and with an increased risk of perioperative complications.

In conclusion, surgical treatment of hereditary spherocytosis is indicated in selected patients not-responding to medical therapy. Total splenectomy remains the standard surgical treatment, when reduction of spleen tissue is required. Partial splenectomy and splenic artery embolization should be reserved to patients at high risk of post-operative infections. The laparoscopic approach for the removal of the spleen should be preferred to the open splenectomy, if an experienced laparoscopic team is available.

Riassunto

La sferocitosi ereditaria è una malattia ematologica benigna, che necessita di un trattamento chirurgico quando la terapia medica fallisce. Attualmente, le strategie chirurgiche consistono principalmente nella splenectomia totale o parziale, che può essere eseguita sia in open che in laparoscopia. In questo studio, abbiamo analizzato la nostra serie di splenectomie per sferocitosi ereditaria e discutiamo sulla gestione chirurgica, riportando i dati della letteratura.

Materiale e Metodi: Ventisette pazienti (età media 16,5 anni, range 8 - 30 anni) affetti da sferocitosi ereditaria sono stati valutati retrospettivamente. L'indicazione al trattamento chirurgico si basa sulla gravità dell'emolisi. Tredici pazienti sono stati sottoposti a splenectomia laparoscopica e 14 a splenectomia open. La colecistectomia per colelitiasi associata, è stata eseguita durante l'intervento chirurgico di splenectomia in 4 pazienti laparoscopici e in 6 pazienti open.

Risultati: Le principali indicazioni all'esecuzione della splenectomia erano l'anemia che non rispondeva alla supplementazione di ferro in 7 pazienti (42%), la splenomegalia in 6 pazienti (37%) e l'ittero in 4 casi (21%). Tutti i pazienti avevano una malattia grave con livelli di emoglobina inferiori a 80 g / L, la conta mediana dei reticolociti era del 6,5%, il valore mediano della concentrazione di bilirubina indiretta era di 2,0 mg / dL. Le indicazioni alla splenectomia sono state l'aumento della necessità di emotrasfusioni in 11 pazienti (66%) e i sintomi correlati alla colelitiasi in 6 pazienti (34%).

Una precoce complicanza postoperatoria è stata osservata dopo splenectomia open, consistente in una fistola pancreatica, trattata in modo conservativo. Non sono state osservate complicanze post-operatorie dopo splenectomia laparoscopica. Durante l'approccio laparoscopico non sono state registrate né complicanze intra-operatorie né conversioni in chirurgia open. In un follow-up a lungo termine, non sono state registrate complicanze infettive. Conclusioni. Secondo i nostri risultati, la splenectomia totale è associata a buoni risultati e poche complicanze. A nostro avviso, rimane la migliore opzione terapeutica in pazienti adulti selezionati che non rispondono al trattamento medico.

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