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Correlation of Genetic Mutation With Outcomes in Children With Hereditary Spherocytosis Undergoing Partial Splenectomy: A Multicentre Study

Joshua K. Ramjist [a, b, *], Tamara Dubljevic [a, b], Eveline Lapidus-Krol [a], Rachael F. Grace [c], Matthew M. Heeney [c], Morohuntodun O. Oni [c], Alison Towerman [d], Andrew Davidoff [e], Clifford Takemoto [e], Rebeccah L. Brown [f], Joseph Brungardt [f], Makenzie Beaman [g], Henry E. Rice [g], Shari Nichols [h], Payam Saadai [h], Manuel Carcao [i, j], Jacob C. Langer [a, b]

[a] Division of General & Thoracic Surgery, The Hospital for Sick Children, Toronto, ON, Canada
[b] Department of Surgery, The University of Toronto, Toronto, ON, Canada
[c] Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA, USA
[d] Division of Hematology & Oncology, St. Louis Children's Hospital, St. Louis, MO, USA
[e] Department of Surgery, and Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN, USA
[f] Department of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[g] Division of Pediatric General Surgery, Duke University School of Medicine, Durham, NC, USA
[h] Department of Surgery, UC Davis Medical Center, Sacramento, CA, USA
[i] Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada
[j] Department of Pediatrics, The University of Toronto, Toronto, ON, Canada

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ABSTRACT

Purpose: Hereditary Spherocytosis (HS) is a common genetic hematological disorder causing a life-long hemolytic anemia, with sequela of hemolysis. Children with severe HS commonly undergo partial or total splenectomy (PS, TS); PS confers the theoretical advantage of maintaining splenic immune function, but may be associated with regrowth, ongoing hemolysis, and need for completion splenectomy. HS can be caused by 5 different pathogenic gene variants. A rare and severe form is caused by homozygous/compound heterozygous mutations in the SPTA1 gene, coding for alpha spectrin. We hypothesized this form of HS is associated with worse outcomes following PS.

Methods: Following REB approval, a retrospective chart review of children with HS undergoing PS between 2000 and 2023 was conducted across 7 sites in the USA and Canada. Pre- and post-operative hematological values and need for completion splenectomy were analyzed. $P < 0.05$ was significant.

Results: Of 51 eligible patients, 10 had SPTA and 41 had non-SPTA1 HS. The SPTA1 group underwent PS at a younger age to non-SPTA1 (5.1 vs 9.6 yr, $p = 0.003$), and had lower pre-operative hemoglobin (86.2 vs 98.8 g/L, $p = 0.04$). There were no differences between groups regarding peri-operative surgical or hematological outcomes. The SPTA1 group required completion splenectomy at a higher rate than the non-SPTA1 group (70.0 % vs 24.4 %, $p = 0.01$).

Conclusion: Children with SPTA1 HS are more likely to require completion splenectomy following PS than children with other HS-causing mutations. These results support the role of genetic testing to permit an evidence-based individualized approach to patient selection for partial vs. total splenectomy.

Level of evidence: III.

1. Introduction

Splenectomy is commonly used to treat anemia, jaundice, lethargy, and symptoms of splenomegaly in children with hereditary spherocytosis (HS). Because of the potential risks of post-splenectomy sepsis and thrombosis, partial splenectomy (PS) has

* Corresponding author. Division of General and Thoracic Surgery, The Hospital for Sick Children 555 University Avenue, Toronto, ON M5G 1X8, Canada.
E-mail address: Joshua.ramjist@sickkids.ca (J.K. Ramjist).

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been proposed as an alternative to total splenectomy for HS patients. Multiple studies have suggested that partial splenectomy provides excellent relief of anemia and other symptoms, but that it may not be as effective in some patients, particularly over longer-term follow-up. Furthermore, a small subset of patients (approximately 15–20 %) who undergo PS will ultimately require a completion splenectomy [1].

There is a significant degree of heterogeneity in disease severity among children with HS. This is expected as HS is caused by genetic mutations that affect one or more of 5 different proteins (Ankyrin (ANK1), alpha (SPTA1) and beta (SPTB) spectrin, band 3 (SCL4A1) and protein 4.2 (EPB42)) that are part of the red cell membrane. Our group has previously documented that genetic mutation is correlated with severity of HS [2], but there have not been any large studies investigating whether response to partial splenectomy is influenced by genetic mutation [3].

The primary objective of this study was to determine in a large cohort of patients whether outcomes from partial splenectomy are influenced by type of genetic mutation.

2. Methods

Research Ethics Board approval was obtained at each institution.

2.1. Data sources

A retrospective chart review was performed at seven institutions in the United States of America and Canada. Clinical data were anonymized and compiled using REDCap (Research Electronic Data Capture). Pre-operative data collected included indication for splenectomy, transfusion requirements, size of spleen on ultrasound, history of gallstones/cholecystectomy, and age at partial splenectomy. Pre-operative hematological data included baseline hemoglobin, platelets, reticulocyte count, and bilirubin. Perioperative data included surgical approach/findings and early post-operative complications. The need for transfusion, weight of resected spleen, length of hospital stay, and readmission rate were also collected. Because the percentage of spleen resected was often not documented in the operative note, we estimated the extent of the partial splenectomy using the ratio of weight of resected spleen (gm)/preoperative splenic size (cm). Finally, post-operative data collected included change in hematologic parameters – hemoglobin, platelets, reticulocyte count and bilirubin. Also collected were the recurrence of preoperative symptoms, incidence of post-splenectomy sepsis or thrombosis, and rate of later completion splenectomy.

2.2. Study participants

Patients with HS who underwent partial splenectomy between 2000 and 2023 with at least 20 months of follow-up time were identified. Patients who underwent a total splenectomy or were incorrectly coded were excluded. Patients with inadequate follow-up time were also excluded.

2.3. Genetic analysis

If not previously obtained for clinical purposes, mutational analysis of five genes was performed (ANK1, SPTA1, SPTB, SCL4A1, and EPB42), by Prevention Genetics (Madison, Wisconsin) after obtaining consent from participants and/or their guardians.

2.4. Outcomes

The primary outcome was the rate of completion splenectomy by genotype. The indication for completion splenectomy was at the discretion of the primary hematology or surgical team. The main secondary outcomes were changes in hematological parameters and recurrence of symptoms by genotype.

2.5. Statistical analysis

Chi square tests were performed for binary variables, while two-tailed T-Tests were utilized for normally distributed nonparametric data, and Mann-Whitney-U tests were performed for non-normally distributed continuous data. Analysis of variance was used to determine if there were any correlations between type of genetic mutation and perioperative and late postoperative outcomes. A $p < 0.05$ was considered statistically significant. Results were analysed with IBM SPSS Statistics version 29.0.1.0.

3. Results

A total of 88 eligible patients were identified, however only 51 of these met the inclusion criteria. Of these, 10 had an SPTA1 type HS and 41 had non-SPTA1 (Ankyrin (ANK1), beta spectrin (SPTB), band 3 (SCL4A1)) HS. Table 1 describes the pre, intra, and post-operative characteristics of the patients. The indication for splenectomy included need for transfusions in 14 patients, lethargy/decreased exercise tolerance in 27 patients, jaundice in 33 patients, abdominal discomfort for 16 patients and splenomegaly/trauma concern for 33 patients; of note, multiple indications were provided for the same patient. The SPTA1 group had a high proportion of patients with transfusion as an indication for PS (60 % vs 19.5 %, $p = 0.018$) compared to the non-SPTA1 group. The SPTA1 group underwent PS at a younger age than the non-SPTA1 group (5.1 vs 9.6 years, $p = 0.003$). The percentage of patients ever transfused was 100 % in the SPTA1 group and 66 % in the non-SPTA1 group ($p = 0.045$). Despite the SPTA1 group undergoing splenectomy at a younger age, the median number of lifetime transfusions pre-splenectomy was higher at 7 (IQR 16) for the SPTA1 group and 2 (IQR 5) for the non-SPTA1 group ($p = 0.021$). There was no difference in family history of HS between the SPTA1 and non-SPTA1 groups.

Intra-operative and early post-operative surgical outcomes were similar for patients in both groups. Patients in both cohorts typically underwent a laparoscopic splenectomy. There was no difference in history of gallstones, previous cholecystectomy, or concomitant cholecystectomy between the two groups. Extent of partial splenectomy, as estimated by weight of resected spleen/preoperative splenic size was similar between the two groups. The need for transfusion intraoperatively or within 24 h post-operation was observed in 10 % of the SPTA 1 group and 22 % of the non-SPTA1 group ($p = 0.664$). The median hospital length of stay was 6 days for the SPTA1 group and 5 days for the non-SPTA1 group ($p = 0.657$). Post-operative complications were reported in 40 % of the SPTA1 group and 54 % of the non-SPTA1 group ($p = 0.496$). The complications reported were minor and consisted mainly of fever and pleural effusion, with no patients undergoing repeat operation in the early postoperative period.

Table 2 presents the hematological changes pre- and post-operatively between the SPTA1 and non SPTA1 cohorts. Both cohorts showed a significant increase in hemoglobin levels post-operatively, from 86.2 g/L (SD 11.9) to 110.93 g/L (SD 22.2) in the SPTA1 group and from 98.8 g/L (SD 19) to 130.66 g/L (SD 18) in the non-SPTA1 group, the difference between pre and post-operative hemoglobin was statistically significant within each group ($p = 0.005$). Platelet counts rose from 275.6 (SD 64.2) to 477.1 (SD 196.7) in the SPTA1 group and from 263.7 (SD 74.5) to 459.2 (SD 144.6) in the non-SPTA1 group, though the difference post-operatively was not statistically significant ($p = 0.747$). Reticulocyte counts decreased from 11.8 % (SD 4.5) to 5.8 % (SD 12.03) in the

Table 1
Demographic information.

	SPTA1 N = 10	Non-SPTA1 N = 41	*p*
Pre-operative			
Age (years) [mean (STD)]	5.1 (3.24)	9.6 (4.29)	0.003
Family history of hereditary spherocytosis (%)	60	68.3	0.714
Ever transfused (%)	100	66	0.045
Pre-operative (number of lifetime transfusions pre-splenectomy) [median (IQR)]	7 (16)	2 (5)	0.021
History of cholecystectomy (%)	10	15	1.000
History of gallstones (%)	30	66	0.070
Intra-operative			
Laparoscopic approach (%)	80	90	0.511
Concomitant cholecystectomy (%)	20	46	0.167
Weight of spleen resected/size of spleen at baseline [median, IQR]	10.18 (12.34)	16.52 (22.25)	0.220
Intraoperative complications (%)	0	5	1.000
Post-operative			
Need for intraoperative transfusion -or within 24 h postoperatively (%)	10	22	0.664
Hospital length of stay (d) [median]	6 (3)	5 (4)	0.657
Time to full diet (d) [median]	4 (3)	4 (2)	0.933
Any postoperative complication[a] (%)	40	54	0.496
Follow-up (years) [mean, STD]	7.02 (2.8)	6.52 (4.02)	0.713

[a] No post splenectomy sepsis in either group.

Table 2
Hematological changes.

	SPTA1		Non-SPTA1		*p*
	Pre-op (Mean, SD)	Post-op (Mean, SD)	Pre-op (Mean, SD)	Post-op (Mean, SD)	
Hemoglobin (g/L)	86.2 (11.9)	110.93 (22.2)	98.8 (19)	130.66 (18)	0.005
Platelets	275.6 (64.2)	477.1 (196.7)	263.7 (74.5)	459.2 (144.6)	0.747
Reticulocyte count (%)	11.8 (4.5)	5.8 (12.03)[a]	16.9 (7.2)	6.5 (7.7)[a]	0.877
Total bilirubin	45.73 (56.3)	34.5 (55.8)[a]	61.56 (56)	28 (35)[a]	0.214

SD=Standard deviation.
[a] Reported in Median (IQR) due to non-normal distribution.

SPTA1 group and from 16.9 % (SD 7.2) to 6.5 % (SD 7.7) in the non-SPTA1 group, with no significant difference between the groups post-operatively (p = 0.877). Total bilirubin levels declined from 45.73 μmol/L (SD 56.3) to 34.5 μmol/L (SD 55.8) in the SPTA1 group and from 61.56 μmol/L (SD 56) to 28 μmol/L (SD 35) in the non-SPTA1 group, also without a significant post-operative difference between the groups (p = 0.214).

Table 3 illustrates the genetic subtypes of HS patients who have undergone partial splenectomy and if they required a completion splenectomy, categorized by the causative gene responsible for HS. The table includes data for four genetic mutation subtypes: ANK1, SPTB, SLC4A1, and SPTA1. Among patients who underwent completion splenectomy, 7 had the SPTA1 mutation, 6 had the ANK1 mutation, 4 had the SPTB mutation and none had the SCL4A1 mutation. In contrast, among those who did not undergo completion splenectomy, 3 had the SPTA1 mutation, 18 had the ANK1 mutation, 12 had the SPTB mutation and 1 had the SLC4A1 mutation. It is noteworthy that some patients also exhibited additional non-pathogenic variants in genes associated with HS, thus the causative gene was used for primary categorization. There was no difference in completion splenectomy for patients with ANK1 and SPTB subtypes of HS.

Table 3
Genetic Subtypes of Hereditary Spherocytosis Patients Undergoing Completion Splenectomy (grouped according to causative gene responsible for HS).

		Genetic Mutation Subtype[a]			
		ANK1	SPTB	SLC4A1	SPTA1
Completion splenectomy	Yes	6	4	0	7
	No	18	12	1	3

P = 0.01 for SPTA1 vs non-SPTA1 genetic mutation subtypes.
[a] Note that some patients showed additional non-pathogenic variants in genes involved in HS.

The mean follow-up period was 7.02 years (SD 2.8) for the SPTA1 group and 6.52 years (SD 4.02) for the non-SPTA1 group (p = 0.713). No patients in either cohort had an episode of post-splenectomy sepsis during the follow-up period. One patient had splenic vein thrombosis immediately post-operatively and was subsequently found to have a protein C deficiency. Figure 1 displays the proportion of patients who required completion splenectomy. The SPTA1 group required completion splenectomy at a significantly higher rate than the non-SPTA1 group (70.0 % vs 24.4 %, p = 0.01). The median time from PS to completion splenectomy in the SPTA1 group was 3.5 years compared to 5.3 years in the non-SPTA1 cohort (p = 0.728).

4. Discussion

Our study confirms that patients with SPTA1 genetic mutations have a more severe clinical manifestation of HS compared to non-SPTA1 patients. SPTA1 patients underwent PS at a younger age, had a higher percentage requiring transfusion and a greater median number of lifetime transfusions before splenectomy. Most importantly, 70 % of the SPTA1 group required completion splenectomy compared to 24.4 % in the non-SPTA1 group. These findings underline the important role of genetic testing in the management of patients with hereditary hemolytic anemias. Currently, genetic testing is funded by the Ministry of Health for the respective provinces.

Our findings align with previous research, in that we again demonstrate the ability of PS to improve post-operative

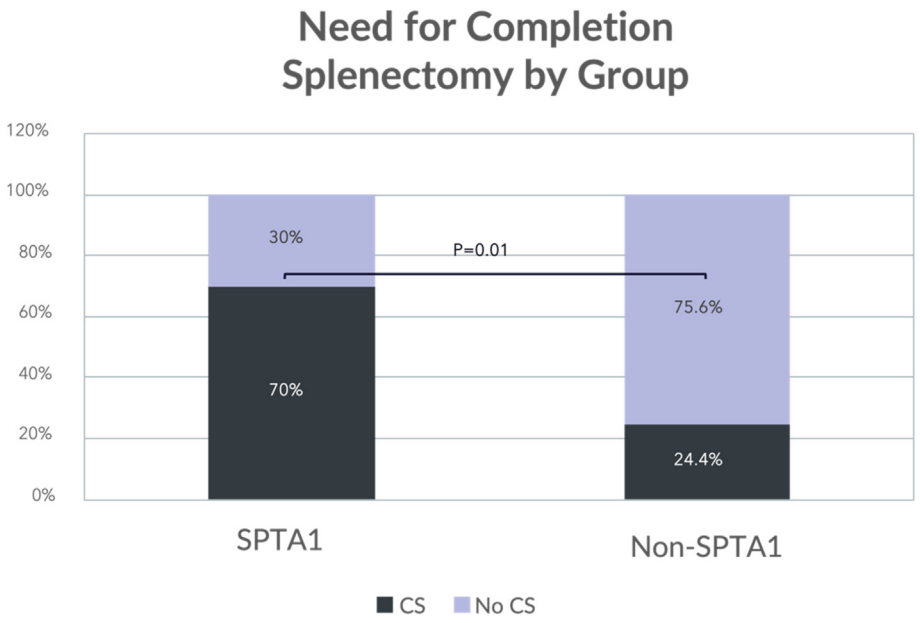

Fig. 1. Proportion requiring completion Splenectomy.
CS – completion splenectomy.

hemoglobin levels in patients with HS [4]. Additionally, our findings support the increased disease severity associated with SPTA1 mutations [5]. This correlation underscores the role of genetic factors in influencing disease progression. Furthermore, our data reinforce the clinical practice of earlier splenectomy in patients with SPTA1 mutations [2,6], secondary to splenomegaly and increased transfusion requirements. Notably, earlier studies evaluating the efficacy of total versus partial splenectomy may not have adequately considered genetic variability among patients [7]. By factoring in genetic differences, our study offers a more individualized understanding of PS outcomes in SPTA1 patients. Based on our findings, clinicians need to recognize that most patients with SPTA1 form of HS if they undergo a PS are likely to undergo a completion splenectomy at some point in future. Despite this, there may be a role for PS even in these patients if it is a way of delaying a total splenectomy in very young patients.

The strengths of this study include its multicenter design, capturing patients across North America. Both cohorts had a mean follow-up of 6–7 years which provides adequate time for splenic regrowth and to assess for need for completion splenectomy. However, there are limitations to this study. While the majority within the SPTA1 group required completion splenectomy, it was not 100 %. This may also be the result of inherent phenotypic variability of SPTA1 due to different types of mutations (recessive SPTA1 with alpha^{LEPRA} vs. biallelic null or intronic mutations [8]), or it may be that some of the children may ultimately require completion splenectomy at a later time. The phenotypic variability may also account for some patients with non-SPTA1 genetic subtypes having severe disease requiring completion splenectomy. Although not statistically significant, a lower proportion of patients in the SPTA1 cohort underwent cholecystectomy; this is likely due to the younger age of PS in this cohort and not having enough time to form gallstones prior to operative intervention. There may also be variability in the volume and viability of residual spleen after PS, depending on the surgical technique used. While there is a lack of standardization in how the procedure is done, our estimate of extent of PS was consistent for all patients irrespective of their genetic status. The multicenter nature of this review allows for generalizable results that can be applied across a mix of practice patterns [9].

Our findings suggest that pre-operative discussions for patients with SPTA1 should consider the benefits of an upfront total splenectomy, particularly in patients age 5 years and older. Although these patients often develop splenomegaly at a younger age, the increased risk of overwhelming post-splenectomy infection (OPSI) in younger patients necessitates a balanced approach [10]. Clinicians should manage expectations, emphasizing the high likelihood of needing a completion splenectomy later in life, ideally when the child is less susceptible to infection. We did not specifically evaluate the complications associated with completion splenectomy or the optimal follow-up surveillance into adulthood for these patients. These remain areas for future study.

In conclusion, the results of our study highlight that a higher proportion of patients with the SPTA1 mutation required a completion splenectomy. Post-operative outcomes demonstrated significant improvement in hemoglobin levels, indicating the clinical benefit of surgical intervention. These findings underscore the importance of genetic testing and careful pre-operative planning and patient counseling, as well as the need for ongoing monitoring to optimize patient outcomes and manage expectations.

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