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ORIGINAL PAPER

Frequency and predictors of blood transfusion and splenectomy in pediatric hereditary spherocytosis – a single-center retrospective analysis

Aleksandra Osińska[1], Marta Druszcz[1], Maksymilian Seweryn[1], Natalia Czarnecka[1], Aleksandra Kozińska[1], Dawid Grela[1], Monika Lejman[2], Małgorzata Mitura-Lesiuk[3], Joanna Zawitkowska[3]

[1]Student Scientific Society, Department of Pediatric Hematology, Oncology, and Transplantology, Medical University of Lublin, Lublin, Poland
[2]Independent Laboratory of Genetics Diagnostics, Medical University of Lublin, Lublin, Poland
[3]Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland

ABSTRACT

Introduction: Hereditary spherocytosis (HS) is the most common hereditary hemolytic anemia among children in Europe. It is characterized by membrane protein defects leading to spherocyte formation and increased hemolysis. Hereditary spherocytosis can present with a wide spectrum of clinical severity, from asymptomatic cases to severe anemia requiring multiple interventions. The aim of the study was to evaluate the frequency and predictors of blood transfusions and splenectomy in children with HS, considering factors such as sex, age at diagnosis, family history, and laboratory parameters.

Material and methods: A retrospective analysis was conducted on 37 pediatric patients with HS treated in 2019–2024 at the Children's University Hospital in Lublin. Data on sex, age at diagnosis, family history, clinical symptoms, laboratory findings, and treatment were collected. Statistical analysis was performed with a significance level of $p < 0.05$.

Results: Transfusions were required more frequently in boys (64.7%) than in girls (40%). Splenectomy was performed in 27% of patients, more often in boys. A positive family history was associated with a higher need for transfusions (up to 7 episodes), more frequent anemia, and earlier diagnosis. Low hemoglobin levels (< 8 g/dl) strongly predicted transfusion need. No significant correlation between reticulocyte count and transfusions was observed. Early diagnosis (within the first year of life) was linked to a more severe clinical course and increased splenectomy rate.

Conclusions: Positive family history, low hemoglobin at diagnosis, and early age at presentation appear to be linked with a more severe disease course. Male sex showed a trend toward more severe disease, though this finding should be interpreted with caution. Because of the limited sample size and retrospective nature of the study, the findings should be regarded as descriptive and primarily intended to generate hypotheses. Larger multicenter studies are required to confirm these trends.

KEY WORDS:

hereditary spherocytosis, hemolytic anemia, blood transfusions, splenectomy.

ADDRESS FOR CORRESPONDENCE:

Joanna Zawitkowska, Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland, e-mail: jzawitkowska1971@gmail.com

INTRODUCTION

Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia in individuals of Northern European ancestry, with an estimated prevalence of 1 in 2000 to 1 in 5000 live births [1, 2]. It is caused by defects in red blood cell membrane proteins, most commonly encoded by ANK1, SPTB, SPTA1, SLC4A1, and EPB42. These mutations disrupt the structural integrity of the red cell membrane and cytoskeleton, resulting in the formation of osmotically fragile spherocytes that are prematurely removed by the spleen [3–5].

The clinical severity of HS varies widely. Some patients remain asymptomatic, while others develop anemia, jaundice, splenomegaly, or gallstones. In more severe cases, infants may present with neonatal hyperbilirubinemia, and older children may experience aplastic crises following viral infections [1, 6]. Diagnosis relies on a combination of clinical findings, family history, and laboratory parameters such as elevated mean corpuscular hemoglobin concentration and the presence of spherocytes on peripheral smear. Confirmatory tests include the eosin-5'-maleimide (EMA) binding test, osmotic fragility testing, and increasingly, next-generation sequencing (NGS) panels targeting genes associated with HS [4, 5, 7].

Treatment decisions are guided by disease severity. Most of the patients should receive folic acid supplementation to support erythropoiesis. Transfusions are administered during hemolytic episodes, aplastic crises, or in cases of symptomatic anemia. In moderate to severe HS, splenectomy is considered to reduce hemolysis and transfusion dependency. The decision to perform surgery must take into account the patient's age, infection risk, and long-term outcomes [8–10].

Partial splenectomy has emerged as an alternative approach, aiming to reduce hemolysis while preserving some splenic immune function. Advances in genetic testing have also enhanced diagnostic accuracy and may help predict clinical course and response to treatment in affected individuals [5, 7, 9].

The aim of this study was to assess the frequency of blood transfusions and splenectomy in children with HS and to analyze how factors such as sex, age at diagnosis, family history, and clinical presentation influence the course and severity of the disease.

MATERIAL AND METHODS

This retrospective observational study included 37 pediatric patients with HS treated at the Department of Pediatric Hematology, Oncology, and Transplantology, Children's University Hospital in Lublin, in 2019–2024. The diagnosis was confirmed in all patients using the EMA binding test.

Data were extracted from medical records, including sex, age at diagnosis, positive family history of HS, clinical symptoms (anemia, jaundice, splenomegaly, cholelithiasis), number of blood transfusions, laboratory findings (hemoglobin level, reticulocyte count), and surgical interventions (splenectomy, cholecystectomy).

Patients were grouped by sex, age at diagnosis, and family history status. The frequency of transfusions and their correlation with clinical and laboratory parameters were assessed.

Descriptive statistics were used to summarize data. Non-parametric statistical tests were applied to compare categorical and numerical variables. A p-value < 0.05 was considered statistically significant.

RESULTS

SEX-RELATED DIFFERENCES IN CLINICAL FEATURES AND TREATMENT

Of the 37 patients, 20 were girls (54.1%) and 17 were boys (45.9%). Anemia occurred in 13 girls (65%) and 16 boys (94.1%) (p = 0.089), suggesting a trend toward more severe disease in males but not statistically significant. Jaundice was observed in 14 girls (70%) and 15 boys (88.2%) (p = 0.273, ns). Transfusion was required in 8 girls (40%) and 11 boys (64.7%) (p = 0.196, ns), and splenectomy was performed in 4 girls (20%) and 6 boys (35.3%) (p = 0.456, ns). These results indicate sex-related differences in disease severity, though none reached statistical significance (Table 1).

AGE AT DIAGNOSIS AND SPLENECTOMY

Most patients (28/37; 75.7%) were diagnosed at the age of 1–3 years. Among patients undergoing splenectomy (10/37; 27%), 7/10 (70%) were diagnosed at 1 year and 8/10 (80%) between 1–3 years. Comparison of age groups

TABLE 1. Comparison of clinical manifestations and treatment interventions between girls and boys with hereditary spherocytosis

Feature/ intervention	Girls (n = 20)	Boys (n = 17)	p-value	95% CI (girls)	95% CI (boys)
Anemia, n (%)	13 (65)	16/ (94.1)	0.048	0.43–0.82	0.73–0.99
Jaundice, n (%)	14 (70)	15 (88.2)	0.246	0.48–0.85	0.66–0.97
Transfusion, n (%)	8 (40)	11 (64.7)	0.191	0.22–0.61	0.41–0.83
Splenectomy, n (%)	4 (20)	6 (35.3)	0.460	0.08–0.42	0.17–0.59

TABLE 2. Distribution of patients according to age at diagnosis and corresponding splenectomy rates

Age at diagnosis	Total patients ($N = 37$)	Patients undergoing splenectomy ($n = 10$)	*p*-value	95% CI (total)	95% CI (splenectomy)
1 year, *n*/*n* (%)	7/26 (70.3)	7/26 (26.9)	1.000	0.14–0.46	0.10–0.57
1–3 years, *n*/*n* (%)	8/28 (75.7)	8/28 (28.6)	1.000	0.15–0.47	0.06–0.55
> 3 years, *n*/*n* (%)	2/9 (24.3)	2/9 (22.2)	1.000	0.06–0.55	0.15–0.47

TABLE 3. Transfusion requirements among patients with and without a family history of hereditary spherocytosis, highlighting the impact of familial predisposition

Family history of HS	Total patients	No transfusion	≥ 1 transfusion	Percentage of without transfusion (%)	*p*-value	95% CI (no transfusion)	95% CI (≥ 1 transfusion)
Positive, $n = 19$ (%)	19/37 (51.4)	7/19 (36.8)	12/19 (63.2)	36.8	0.103	0.41–0.81	0.41–0.81
Negative, $n = 18$ (%)	18/37 (48.6)	12/18 (66.7)	6/18 (33.3)	66.7	0.103	0.16–0.56	0.16–0.56

HS – hereditary spherocytosis

TABLE 4. Frequency of surgeries and severe infections among patients with and without a family history of hereditary spherocytosis

Outcome/intervention	Positive family history ($n = 19$)	Negative family history ($n = 18$)	*p*-value	95% CI (positive)	95% CI (negative)
Splenectomy or cholecystectomy, *n*/*n* (%)	4/19 (21.1)	6/18 (33.3)	0.476	0.09–0.43	0.16–0.56
Severe infections, *n*/*n* (%)	3/19 (15.8)	4/18 (22.2)	0.693	0.06–0.38	0.09–0.45
Transfusion in severe infection, *n*/*n* (%)	3/3 (100)	2/4 (50)	0.429	0.44–1.00	0.15–0.85
Hemolytic crises*, *n*/*n* (%)	5/19 (26.3)	0/18 (0)	0.046	0.12–0.49	0.00–0.18
Aplastic crises**, *n*/*n* (%)	5/19 (26.3)	0/18 (0)	0.046	0.12–0.49	0.00–0.18

** Hemolytic crisis – acute worsening of anemia with jaundice and reticulocytosis*
*** Aplastic crisis – severe anemia due to parvovirus B19 with reticulocytopenia*

with the rest of the cohort showed no statistically significant association with splenectomy ($p = 0.846$ for 1 year, $p = 0.781$ for 1–3 years, $p = 0.912$ for > 3 years) (Table 2).

TRANSFUSION REQUIREMENTS BY FAMILY HISTORY

Positive family history was noted in 19/37 patients (51.4%). Among them, 7/19 (36.8%) did not require transfusions, while 12/19 (63.2%) received at least one. Among patients without a family history (18/37; 48.6%), 12/18 (66.7%) avoided transfusion, and 6/18 (33.3%) required at least one. Children with a family history received up to 7 transfusions vs. a maximum of 2 in children without a family history. The difference in transfusion requirement between familial and non-familial groups was not statistically significant ($p = 0.103$) (Table 3).

SURGICAL INTERVENTIONS AND SEVERE INFECTIONS BY FAMILY HISTORY

Comparison of the frequency of surgeries (splenectomy or cholecystectomy) and severe infection-related events between patients with and without a family history was made, suggesting differences in management strategies and susceptibility to complications.

Children without a family history (48.6%) were more likely to undergo splenectomy or cholecystectomy (33.3% vs. 21.1%, $p = 0.482$, ns) and were more frequently hospitalized for severe infections (22.2% vs. 15.8%, $p = 0.673$, ns). Among children with severe infections (7/37; 18.9%), 5/7 (71.4%) required transfusion. All hemolytic and aplastic crises occurred in children with a family history, with statistically significant differences for both events ($p = 0.025$ for hemolytic, $p = 0.025$ for aplastic) (Table 4).

DEFINITIONS

Hemolytic crisis – acute worsening of anemia with jaundice and reticulocytosis.

Aplastic crisis – severe anemia most commonly by parvovirus B19 with reticulocytopenia.

TRANSFUSION REQUIREMENTS BY HEMOGLOBIN LEVEL AT DIAGNOSIS

Hemoglobin data were available for 20 patients. Among patients with Hb < 8 g/dl (8/20; 40%), 6/8 (75%) required

TABLE 5. Association between the hemoglobin level at diagnosis and subsequent transfusion requirements

Hemoglobin level	Total patients ($N = 20$)	No transfusion	≥ 1 transfusion	Percentage of patients without transfusion	*p*-value	95% CI (no transfusion)	95% CI (≥ 1 transfusion)
< 8 g/dl, *n*/*n* (%)	8/20 (40)	2/8 (25)	6/8 (75)	25	0.170	0.41–0.93	0.41–0.93
≥ 8 g/dl, *n*/*n* (%)	12/20 (60)	8/12 (66.7)	4/12 (33.3)	66.7	0.170	0.14–0.61	0.14–0.61

at least one transfusion. Among patients with Hb ≥ 8 g/dl (12/20; 60%), 4/12 (33.3%) required at least one transfusion. Lower Hb at diagnosis was significantly associated with higher transfusion dependency ($p = 0.047$) (Table 5).

DISCUSSION

In the analyzed group, boys more frequently required transfusions (64.7%) and splenectomy (35.3%) compared to girls (40% and 20%, respectively). The percentage of patients who needed at least one transfusion was comparable to previous studies. For example, Cheng *et al.* (Chinese children), who analyzed 64 children, found that about 12% underwent splenectomy and up to 66% required at least one blood transfusion. This percentage likely increases with age [5]. Similar trends have been reported in recent pediatric cohorts from Turkey and Germany [11, 12].

In 2022, Ang and Lam (Singaporean children) reported similar findings, with 19% undergoing splenectomy and 67% requiring transfusions [6]. Conversely, Sanli-Celik *et al*. (Turkish children) and Kiliç *et al*. (Turkish children) reported higher splenectomy rates (52% and 45%, respectively), probably due to longer follow-up or different surgical qualification standards [7, 8]. Regional protocols and institutional preferences have a significant impact on splenectomy thresholds and timing, according to a recent meta-analysis [13].

A positive family history and low hemoglobin levels at diagnosis were associated with a more severe clinical course, including more frequent anemia and transfusions. Only 34.6% of children with a positive family history did not require transfusion, whereas in the group without such a history, this proportion was nearly twice as high (63.6%). The maximum number of transfusions in the familial group was seven, consistent with Cheng *et al.*, who showed that more severe disease and greater transfusion needs were linked to ANK1 and SPTB mutations [5]. These associations have been confirmed by recent genotypic analyses employing NGS panels [14, 15].

Ang and Lam also observed that children with a family history are diagnosed earlier, facilitating earlier intervention, although they did not find a correlation between the family history or sex and splenectomy risk [6]. Hemoglobin levels below 8 g/dl at diagnosis were linked to a higher likelihood of transfusion, which aligns with the literature emphasizing anemia severity as a key predictor of HS severity. In Ang and Lam's study children needing transfusions had a mean hemoglobin level of 4.8 g/dl compared to 8.5 g/dl in others [6]. Recent Asian and North American cohorts showed similar thresholds [16, 17].

No recent studies have shown that sex influences disease severity, suggesting that differences observed here may be due to chance or a small sample size. In both our analysis and cited studies, symptoms like splenomegaly, anemia, and jaundice were frequent (Cheng *et al.*: neonatal splenomegaly 77%, jaundice 86%) [5]. The frequency of transfusions between children with and without splenomegaly or jaundice did not significantly differ in either/any study. However, more recent evidence suggests that splenomegaly at diagnosis may influence long-term transfusion needs in more severe phenotypes [18].

Data from Sanli-Celik *et al.* study confirm that children diagnosed in the first year of life tend to have a more severe course [7], similar to Cheng *et al.* study, who found an association between earlier diagnosis and higher risk of intervention and severe HS [5]. These findings are further supported by newer prospective data showing increased complication rates and faster disease progression in early-diagnosed patients [19].

Although our findings are consistent with current knowledge and highlight the importance of early diagnosis, the severity of anemia, and familial predisposition in determining the likelihood of requiring treatment in advanced HS, it should be emphasized that the retrospective design and the relatively small sample size limit the statistical power and the generalizability of the results. Nevertheless, these observations provide a descriptive basis for future studies, and emerging tools for risk stratification and molecular profiling may further refine individualized management strategies [14, 20].

CONCLUSIONS

Hereditary spherocytosis in children shows varying severity influenced by sex, family history, and age at diagnosis. In our cohort, a positive family history, early diagnosis, and low hemoglobin levels at presentation were associated with more frequent transfusions and splenectomy. Male sex appeared to correlate with a more severe disease course, although this observation did not reach statistical significance and has not been consistently confirmed in other studies.

Given the small sample size and lack of statistically significant results, the findings should be interpreted with caution. They highlight trends rather than definitive

predictors. Future multicenter studies with larger patient groups and longer follow-up are necessary to confirm these associations and optimize individualized treatment strategies.

DISCLOSURES

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4. Conflicts of interest: None.

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