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Original Research

Clinical Characteristics and Treatment Outcome of Hereditary Spherocytosis: A Single Center's Experience

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Abstract

Objectives: The objective of the study is to present the demographic characteristics, clinical and laboratory features and outcome of our patients with hereditary spherocytosis (HS).

Methods: Demographic, clinical, and laboratory data; complications; and splenectomy results were analyzed retrospectively. The severity of the disease was scaled according to Eber's criteria.

Results: Sixty-nine patients (42 boys, 27 girls, median age: 3 years) were eligible. Sixty-eight percent of the patients had a history of neonatal jaundice. The complaints at admission were jaundice (71%), fatigue (27.5%), fainting (4.3%), and pallor (4.3%). The median follow-up duration was 8.5 years. According to Eber's criteria, three (4.3%), 57 (82.6%), and nine (13.1%) patients had mild, moderate, and severe diseases, respectively. Thirty-six patients (52.1%) had a splenectomy. Following splenectomy, we observed a significant rise in hemoglobin levels and a decline in indirect bilirubin levels. Post-operative thrombocytosis was common, with a tendency to fall and stabilize after 1 month. There were no thromboembolic complications.

Conclusion: In spite of the high rate of consanguinity, familial history of HS, and neonatal jaundice in our study group, the majority of the HS patients were identified relatively late, about 3 years. This finding shows that HS might be insufficiently acknowledged by primary care. Splenectomy, in selected cases, may reduce the need for transfusions. Post-splenectomy transient thrombocytosis is common and has a benign course.

Keywords: Hemolytic anemia, hereditary spherocytosis, splenectomy

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Hereditary spherocytosis (HS) is the most frequent form of non-immune hemolytic anemia in children. The signs and symptoms might appear at any age, which include anemia of various severity, jaundice, splenomegaly, as well as asymptomatic cholelithiasis. The underlying pathology involves a congenital membrane protein defect in which erythrocytes are transformed into the shape of spherocytes, leading to increased susceptibility to hemolysis. Seventy-five percent of the cases show autosomal dominant inheritance, whereas 25% of the patients have no family history.[1,2]

The laboratory findings of the disease include compensated

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hemolytic anemia, and in some cases, the hemoglobin value might decrease to 2–3 g/dL; increased indirect bilirubin levels due to hemolysis; decreased mean corpuscular volume (MC0V); increased mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width; and reticulocytosis.[2] Spherocytes, microspherocytes, and hyperchromia are seen in peripheral blood smears. Red cell osmotic fragility is increased, occasionally only demonstrated after incubation of a blood sample at 37°C for 24 h.[1]

In this study, we presented the demographic, clinical, and laboratory features and the outcome of the HS patients followed in our clinic.

Methods

This study is a single-centered retrospective case series conducted in our pediatric hematology clinics. Patients diagnosed with HS between 2000 and 2021 were eligible. Our study was conducted in accordance with the Declaration of Helsinki. According to the ethical standards of Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee, retrospective case studies using already existing collections of data or records are exempt from ethical review.

Data regarding gender, age at diagnosis, consanguinity, parental history of HS and/or splenectomy or cholecystectomy, neonatal phototherapy, or exchange transfusion were collected from patient files. The complaints and the physical examination findings at the initial diagnosis were assessed. Among laboratory tests, hemoglobin, MCV, MCHC, reticulocyte, indirect bilirubin values at the time of diagnosis, peripheral blood smear findings, and osmotic fragility test findings were recorded. None of the patients had genetic or molecular analysis or a sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) or eosin-5′-maleimide (EMA) binding test for HS. Patients were separated into three groups (mild, moderate, and severe) according to the severity of illnesses based on Eber's criteria.[3] The frequency of transfusions, need for splenectomy, age, time of splenectomy, and outcome after the surgery were also recorded. Independence from transfusion and correction of anemia were accepted as treatment responses.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Inc., released in 2006, SPSS for Windows, Version 15.0 Chicago, SPSS Inc. Descriptive statistics–numbers and percentages for categorical variables and mean and standard deviation for numerical variables–were submitted. Hemoglobin, MCHC, platelet, and indirect bilirubin values before and after surgery were compared using the related samples t-test. Categorical variables in mild, moderate, and severe HS groups were compared using the chi-square test, and continuous variables in each group were compared using the one-way ANOVA test. A p-value less than 0.05 was accepted as statistically significant.

Results

Sixty-nine patients (42 boys, 27 girls) with a median age of 3 years (range: 18 days–16 years) were included. Twenty-nine percent of the cases' parents had a consanguineous marriage, whereas 60.8% of the cases had a familial history of HS (42 splenectomies plus 19 cholecystectomies in the family). The median follow-up was 7.4 years (range: 3.5 months–21 years).

Icterus (71%), fatigue (27.5%), syncope (4.3%), and pallor (4.3%) were the most common admission complaints. Forty-five patients (67.1%) had early-onset or pathologic jaundice during the neonatal period, whereas three of them required exchange transfusions. Six patients had a history of receiving a red blood cell transfusion for neonatal anemia. Physical examination revealed pallor, jaundice, hepatomegaly, and splenomegaly in 43%, 42%, 65.6%, and 77.6% of the patients, respectively.

The mean hemoglobin level at admission was 8.3±2.1 g/dL (range: 5.1–15.3 g/dL). The mean MCV value was 83.1±9.7 fl, the mean MCHC value was 34.9±1.6 g/L and the median reticulocyte percentage, total bilirubin value, and indirect bilirubin value were 6.69±3.96%, 6,3 mg/dL, and 1.77 mg/dL, respectively. In the peripheral blood smear, all patients had typical spherocytosis morphology. In the osmotic fragility test (incubated), the median percentage of hemolysis was found to be 25% at a 0.9% NaCl concentration. According to modified Eber's criteria,[3] three (4.3%), 57 (82.6%), and nine (13.1%) patients had mild, moderate, and severe diseases, respectively (Table 1).

At a median follow-up of 7.4 years, 24 patients (34%) never needed a transfusion; 31 (44%) had transfusion requirements during infection periods; and 14 (20%) patients were transfused on a regular basis. Abdominal ultrasonography revealed gallstones or biliary sludge in 17 patients (25%), who had symptoms or a family history of cholecystectomy. In these cases, the average age at the time gallstones or sludge were discovered was 11.2±3 years. Thirty-six (52.1%) patients had a splenectomy since there was an increased need for transfusion in 7 (8.3%) patients, 17 (55.6%) had frequent hemolytic crises, and 12 (36.1%) had a splenectomy for comorbidities such as hypersplenism and growth failure. One of our patients developed a Wilms tumor during the follow-up, and she has been in remission for 2 years.

The average age for splenectomy was 9.9±3.8 years (me-

Table 1. Clinical and laboratory results of the patients according to the EBER's criteria

	Mild spherocytosis (n=3)	Moderate spherocytosis (n=57)	Severe spherocytosis (n=9)	p
Gender, n (%)				
Female	3 (100)	21 (36.8)	3 (33.3)	0.085
Male	0	36 (63.2)	6 (66.7)	
Median age at diagnosis (years)	7,88	4,82	3,76	0.425
Family history of HS, n (%)				0.172
1st°	3 (100)	28 (49.1)	4 (44.4)	
2nd°	0	3 (5.3)	3 (33.3)	
3rd°	0	1 (1.8)	0	
No	0	25 (43.9)	2(22.2)	
Consanguineous marriage				0.447
Yes	0	18 (31.6)	2 (22.2)	
No	3 (100)	39 (68.4)	7 (77.8)	
Mean age of splenectomy (years)	13.3±0.58	9.4±3.5	3.69±0.6	0.336
Hemoglobin (g/dL)	12.90±2.16	8.55±2.35	7.07±1.90	N/A
Reticulocytes (%)	4,77	5.27±3.16	10.61±5.32	N/A
Bilirubin (mg/dL)	1.64±1.14	2,4	4.12±2.85	N/A
Splenectomy (n)	2 (66.7)	30 (52.6)	4 (44.4)	N/A
Needed transfusion at least once (n)	0	36 (63.1)	8 (88.8)	N/A

HS: Hereditary spherocytosis; N/A: Not applicable.

dian 9.6, range: 6–17.4 years). All patients were vaccinated against encapsulated bacteria before the operation. There were no perioperative complications. The average time from diagnosis to splenectomy was 3.5±2.2 (median 3.48) years. There was no correlation between gender, the median age at diagnosis, and the mean age for splenectomy. Although statistically insignificant, the median age at diagnosis was lower in patients with moderate and severe HS. Sixteen patients had a concomitant splenectomy and cholecystectomy due to bile sludge and gallstones.

The laboratory outcomes of the patients were evaluated before and 2 months after the splenectomy. A significant increase in hemoglobin and platelet levels ($p<0.01$) and a significant decline in indirect bilirubin levels ($p<0.01$) were achieved. Eighty-eight percent of the patients benefited from splenectomy, i.e., they became transfusion-independent. The MCHC levels did not differ significantly ($p=0.053$) after the operation (Table 2).

After the splenectomy, the platelet counts reached their maximum value in the 1st week and decreased and stabilized after the 1st month in our patients. Acetylsalicylic acid treatment was initiated for 13 (36.1%) patients (Fig. 1).

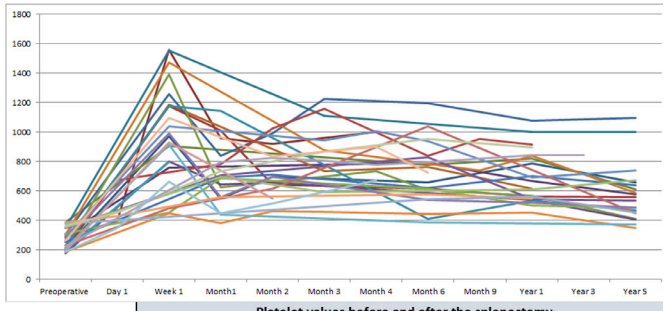
Discussion

Depending on the severity of the disease, the clinical manifestations of HS range from an asymptomatic state to severe anemia and hyperbilirubinemia in the neonatal period and life-threatening hemolytic or aplastic crises in later ages. Pathogenesis involves a defect in membrane proteins that provide cytoskeleton stability. Spectrin deficiency is the most frequent defect in HS patients in our country. Unfortunately, we were not able to test the defective membrane proteins or mutation analyses of our patients.[4] In our study, all patients were diagnosed with the osmotic

Table 2. Evaluation of laboratory results of patients who underwent splenectomy (n=36)

	Before splenectomy	After splenectomy (Post-operative 2nd month)	p
Hemoglobin (g/dL)	10.17±1.96	12.51±2.7	<0.01
Platelets (10^9/L)	284588±93292	696117±228412	<0.01
Indirect bilirubin (mg/dL)	3.42±1.86	1.05±1.04	<0.01
MCHC (g/L)	35±1.6	34.5±1.91	0.053

MCHC: mean corpuscular hemoglobin concentration.



	Platelet values before and after the splenectomy			
	Preoperative	First day	First week	First month
Mean±SD (/mm^3)	269±68	460±113	1001±332	697±197
Median (range)(/mm^3)	264(177-387)	441 (346-673)	981 (449-1557)	692 (383-1142)

Figure 1. The course of platelet levels before and after the splenectomy. Each curve represents a patient's platelet level. The platelet counts reached their maximum value in the 1st week and decreased and stabilized after the 1st month in our patients.

fragility test because it is cheaper, easily accessible, and applicable.

Although the disease is usually diagnosed during childhood and young adulthood, it can be diagnosed at a later age depending on the severity of clinical findings like hemolysis.[1] The median age of our patients at the time of diagnosis was 3 years. In similar studies conducted in our country, the mean age at diagnosis was found to be between 2 and 5.4 years.[5,6] Our study is also similar to other studies in our country in terms of early diagnosis age. However, given the fact that most of our patients had a history of neonatal hyperbilirubinemia and consanguineous parents, as well as a family history of HS, one might anticipate an earlier recognition age for HS.

Approximately 75% of HS cases display an autosomal dominant pattern of inheritance without gender pre-dilection. The rest of the HS cases are due to an autosomal recessive pattern of inheritance and de novo mutations.[1,7] However, in our study, the male gender was seen with a frequency of more than 60%. In the study of Oliveira et al.,[7] family history was also found at a rate of 57%. In our study, 60.8% of the patients had a family history, which is similar to other studies conducted in our country.[5,6] Thirty-four patients (49.2%) without consanguineous parents had a family history of HS in our cohort, which supports the autosomal dominant inheritance of the disease in such cases.

HS is diagnosed on clinical grounds based on family history, physical examination, and laboratory findings. The clinical spectrum ranges from asymptomatic status to pallor, jaundice, and even heart failure due to severe hemolytic anemia.[1] The most common types of presentation in our patients were pallor, jaundice, and fatigue.

Tao et al.[8] reported that an MCHC level higher than 334.9 g/l can be used as a screening test for diagnosing HS, with a sensitivity and specificity of 82.1% and 94%, respectively. The mean MCHC value of our HS patients is similar to the proposed threshold value.

The percentages of moderate and severe HS cases according to Eber's criteria in the literature are 54–72 and 7–24%, respectively, which is similar to the severity distribution of our cases.

The main complications of HS are aplastic, hemolytic, and megaloblastic crises, severe neonatal hemolysis, cholecystitis, and cholelithiasis. Hemolytic crises are the most common, usually triggered by viral diseases, and usually occur during childhood.[9] In our study, hemolytic crises were the most frequent complication.

Splenectomy is an important treatment method to prevent hemolytic crises.[10] It is recommended in patients with severe HS, growth retardation, structural bone changes, and extramedullary hematopoiesis.[11] In our study, 52.1% of our patients underwent a splenectomy. Age at the time of splenectomy ranges from 5 to 12 years,[12] similar to the age of splenectomy in our study. After splenectomy, an improvement in terms of laboratory and clinical findings was observed in nearly all patients (Table 2). The slight decrease in the MCHC value was not statistically significant. The MCHC test, the proposed screening test for the disease, did not change after the splenectomy, despite the improvement in the clinical findings of the patients.

Reactive thrombocytosis is a well-known result of splenectomy.[13] In our case series, platelet counts returned to near-normal values 1 month after the surgery. Only a few patients needed prophylactic aspirin against thrombotic events, which none of our patients experienced. Thus, early and aggressive antiaggregant administration might be unnecessary in these patients.

The most remarkable feature of our study is the follow-up of patients for as long as 21 years in a single center. Patients who needed splenectomy continued to be followed up after the surgery, which was also precious for their prognosis. Our study was a single-centered retrospective study with genetic or molecular analysis, and the SDS-PAGE or EMA binding test could not be used as a diagnostic method but can be shown as an improvement in the study.

Conclusion

Although our patients had high frequencies of consanguineous marriage, a familial history of HS, and neonatal jaundice, the majority of them were diagnosed relatively late, around 3 years. This finding might point to poor awareness about HS in primary care. The most common complications are hemolytic crises and cholelithiasis. Splenectomy, in carefully chosen cases, may provide a significant increase

in hemoglobin and a decline in transfusion requirements. Post-splenectomy reactive thrombocytosis is common but transient, and it does not impose a significant risk for thromboembolic events.

Disclosures

Ethics Committee Approval: According to the ethical standarts of Sisli Hamidiye Etfal Institutional Ethical Committee, retrospective case studies using already existing collection of data and/or records are extempt from ethical review.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Z.Y.Y.; Design – D.B.G.; Supervision – Z.Y.Y.; Materials – Z.Y.Y.; Data collection &/ or processing – S.S.C.; Analysis and/or interpretation – S.S.C.; Literature search – S.S.C.; Writing – D.B.G., S.S.C.; Critical review – Z.Y.Y., D.B.G.

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