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Hereditary spherocytosis: Retrospective evaluation of 65 children

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Hereditary spherocytosis (HS) is a common cause of congenital hemolytic anemia in Caucasians and it could be diagnosed at any age. The aim of this study is to examine the demographic characteristics, clinical features and laboratory findings of children with HS and their complications observed during follow up. Sixty-five patients, with hereditary spherocytosis between January 2008 and September 2013, were enrolled into this retrospective study. The age of patients at the time of diagnosis varied between 15 days and 17 years. The median age of patients at diagnosis was 48 months (IQR 2-78). The female/male ratio was 1.1. Forty-seven patients (72.3%) had a family history of HS. The patients were classified according to laboratory findings: 13 of them (20%) were diagnosed as mild HS, 36 (55.4%) as moderate HS and of 16 (24.6%) as severe HS. During follow-up, nine patients (13.8%) experienced an aplastic crisis. Megaloblastic crisis was not observed in any patient. Twenty patients (30.8%) had cholelithiasis. Splenectomy was performed in 20% of patients and the mean age for splenectomy was 8.3 years. Complications such as sepsis or thrombosis were not detected after splenectomy. Hereditary spherocytosis should be kept in mind in patients with anemia, jaundice and splenomegaly and the family history must be questioned. The most common complication was gallstone; even patients without severe hemolysis should be followed intermittently by abdominal ultrasonography in order to control the development of gallstone.

Key words: spherocytosis, child, anemia, and hemolysis.

Hereditary spherocytosis (HS) is a common cause of congenital hemolytic anemia in Caucasians. The estimated prevalence rate is 1/2,000 in Northern Europe. It is characterized by spherocytes that result from the defects of the erythrocyte structural membrane proteins mostly spectrin or ankyrin; the absence of band 3 and protein 4.2 is observed as well.[1-3]

Hereditary spherocytosis is usually inherited in an autosomal dominant pattern but 25% of the patients have sporadic or autosomal recessive inheritance.[2,4] The symptoms of the disease could emerge in any period of life from birth to older age, and the clinical picture may vary from being asymptomatic to severe hemolysis. Some patients (20-30%) have compensated hemolysis without any symptoms in which production and destruction process of erythrocytes is in balance that causes difficulty for diagnosis. In 5-10% of the patients, transfusion dependent severe anemia is observed.[4-6]

In this study, the demographic characteristics, clinical features, laboratory findings and complications of pediatric HS patients were retrospectively evaluated.

Material and Methods

The files of 65 children, who were followed with HS at University of Health Sciences, Ankara Child Health and Diseases Hematology

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Oncology Training and Research Hospital between January 2008 and September 2013, were evaluated retrospectively.

The gender of the patients, age at diagnosis, and consanguinity between parents, family history, phototherapy and neonatal erythrocyte transfusion histories were recorded. Their symptoms and physical examination findings at first admission were assessed. Complete blood count, peripheral smear, reticulocyte count, and direct- indirect Coombs' test, incubated osmotic fragility test (OFT) and abdominal ultrasonography (US) findings were recorded. During the follow-up, transfusion needs, folic acid prophylaxis and splenectomy history were also recorded.

Patients were classified into three groups according to their hemoglobin (Hb), bilirubin and reticulocyte values, as mild, moderate and severe.[2]

Mild HS: The cases who had Hb between 11.5 and 15.0 g/dl, reticulocyte value between 3.0 and 5.9 % and total bilirubin value <2.0 mg/dl

Moderate HS: Patients that had Hb between 8.0 and 11.4 g/dl, reticulocyte value between 6.0 and 9.9 % and total bilirubin value between 2.0 and 2.5 mg/dl

Severe HS: The cases who had Hb value between 6.0 and 7.9 g/dl, reticulocyte value 10% and over and total bilirubin value >2.5 mg/dl

Hemoglobin, mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) ratios were calculated and the relationship between disease severity were examined.

Statistical analyses were performed using the Statistical Package for Social Science (SPSS), Version 18.0 (SPSS, Inc., Chicago, IL). Mean, median, interquartile range (IQR) and standard deviations were calculated for numerical parameters. In order to investigate the association between mean Hb, reticulocytes (RET), Hb/MCHC, Hb/RDW and HS classification one-way ANOVA test was performed in all groups. Student t-test was used to compare two groups. A $p<0.05$ was accepted as statistically significant differences. The research was reviewed and approved by Institutional Review Board (2013-158) and informed consent was obtained from the patients involved in this study.

Results

Of sixty-five patients, 34 patients were girl (52.3%); the female/male ratio was 1.1. The age of patients at the time of diagnosis varied between 15 days and 17 years. The median age of patients at diagnosis was 48 months (IQR 2-78) and the median age of mild HS patients, moderate HS and severe HS at diagnosis was 60 months (IQR 29-121), 48 months (IQR 2.75-94.5) and 3 months (IQR 1-24), respectively.

Though 32 patients (49.2%) had a history of phototherapy, no exchange transfusion history was noted in any patient. Thirteen patients (20%) were diagnosed during neonatal period and ten of them (76.9%) had positive family history for HS. The diagnosis for three patients who had non-immune hemolytic anemia without family was confirmed with repeated OFT 3-4 months later; and monitored regularly for hematologic status. Of these 13 patients, six patients (46.2%) were classified as moderate HS and seven patients (53.8%) were classified as severe HS. Twelve patients (18.5%) had a history of erythrocyte transfusion during neonatal period.

Family history of HS was present in 47 patients (72.3%) and 45 of them (95.7%) had HS in the first-degree relatives. The complaints and the physical examination findings at the first admission were presented at Table I. The laboratory values of patients at the admission were as follows: mean Hb 8.9±2.30 g/dl (range 3 to 15.1); mean erythrocyte volume (MCV) 81.1±7.81 fL (range 66 to 114); mean corpuscular hemoglobin concentration (MCHC) 35.6±1.36 g/dl (range 31 to 38.2); red cell distribution width (RDW) 21.4±4.67% (range 15 to 33,3), lactate dehydrogenase (LDH) 738±326 U/L (range 374 to 1,900), reticulocytes (RET) 10,52±6,5% (range 0,5 to 33) and total bilirubin (TB) 4,12±3,7 mg/dl (range 0,61 to 16,68).

Coombs' test was performed at diagnosis in 58 to 65 patients for differential diagnosis of autoimmune hemolytic anemia and all results were negative. Seven patients, in whom Coombs' test was not performed, had positive family history of HS. Incubated OFT was increased in all patients, however spherocytes was observed 83.1% of our patients' blood smear. Ninety-one percent of patients whom spherocytes were not seen in blood smear

Table I. The Clinical Features of the Patients.

Clinical Features	N	(%)
Complaints at presentation		
Jaundice	48	73.8
Weakness	20	30.8
Family history of disease	19	29.2
Abdominal swelling	1	1.5
Physical examination finding		
Icterus	54	83.1
Splenomegaly	46	70.8
Pallor	34	52.3
Hepatomegaly	26	40.0

had family history of HS. In forty-eight patients (73.8%) splenomegaly was detected by abdominal US.

The patients were classified according to laboratory findings. Thirteen patients (20%) were defined as mild HS, 36 patients (55.4%) as moderate HS and 16 patients (24.6%) as severe HS. The mean Hb, MCHC, reticulocyte; total bilirubin values of the patients according to classification were presented in Table II.

The Hb/MCHC ratio value was 0.30±0.066 in mild HS patients, 0.24±0.053 in moderate HS patients and 0.21±0.050 in severe HS patients. A significant difference was found between mild HS patients and moderate/severe HS patients in terms of Hb/MCHC ratio rates ($p=0.006$ and $p=0.001$, respectively). However, no significant difference was identified between moderate HS patients and severe HS patients ($p>0.05$). In all our patients, RDW value was 15% and over and mean RDW value was 21.4±4.67%. The Hb/RDW ratio was 0.58±0.19 in mild HS patients, 0.43±0.12 in moderate HS patients and 0.35±0.15 in severe HS patients. A significant relationship was found between mild HS patients and moderate/severe HS patients in terms of Hb/RDW ratio rates ($p=0.009$ and $p=0.001$, respectively). However, no significant difference was found between moderate HS patients and severe HS patients ($p>0.05$).

During the follow-up, nine patients (13.8%) experienced aplastic crisis. Among seven patients (77.8%), who had an aplastic crisis, parvovirus B19 IgM was positive. In two patients, no etiologic agents were identified. All patients had used prophylactic folic acid; and megaloblastic crisis was not observed in any patients.

Cholelithiasis was detected in 20 patients (30.8%). It was detected in 13 patients at first admission; and seven patients developed gallstone during follow-up period. Though cholelithiasis was detected at diagnosis in 13 patients, we did not know the exact time of its occurrence. We analyze the age of seven patients who developed gallstone at follow-up period and found that the mean age was 11.01±3.94 years. Of twenty patients who had cholelithiasis, six patients (30%) were in mild HS group, 10 patients (50%) in the moderate HS group and 4 patients (20%) in the severe HS group. There was no significant difference between the groups regarding the development of gallstone ($p>0.05$). Similarly, no significant relationship was found between the cholelithiasis and transfusion frequency ($p>0.05$).

Thirty-nine patients (60%) had a history of erythrocyte transfusion, at least once. Four of these patients (10.3%) were in the mild HS group, 19 patients (48.7%) in the moderate HS group and 16 patients (41%) in the severe HS group. The median age for the first erythrocyte transfusion was 24 months (IQR 1-72). There was no significant difference between the disease severity and erythrocyte transfusion needs ($p>0.05$).

Thirteen patients (20%) underwent splenectomy and 12 patients (18.5%) underwent cholecystectomy. Nine of 13 patients (69.2%) who underwent splenectomy were classified as severe HS and four (30.8%) patients who were classified as moderate HS, splenectomized for hypersplenism (3) and growth failure (1). In seven patients, splenectomy and cholecystectomy

were performed simultaneously. The median age for splenectomy was 8.3 (IQR 6-12.5 years). The youngest age for splenectomy was 5 years old. In eleven of thirteen patients, laparoscopic splenectomy were performed; and in two patients laparotomic splenectomy were executed. All patients were vaccinated against encapsulated bacteria before splenectomy and penicillin prophylaxis was administered to all patients after splenectomy. No complications such as sepsis or thrombosis were seen after splenectomy. The median follow-up period for the patients underwent splenectomy was 33 months (IQR 9.5-56.5).

Discussion

Hereditary spherocytosis is characterized by decreased surface area to volume ratio in erythrocytes as a result of heterogeneous alterations in various genes that encode for proteins involved in vertical associations that tie the membrane skeleton to the lipid bilayer.[2,7] It was demonstrated that there were differences among countries in terms of defective erythrocyte membrane protein.[2,8] Although evaluation of defective membrane proteins and their genes could not be performed in our patients, isolated spectrin defect has been reported with a high frequency in our country.[9]

In general, HS has autosomal dominant inheritance and the disease is observed in both genders equally.[1] Seventy-two percent of our patients had a family history of the disease and 95.7% of them the disease was observed in the first-degree relatives. Hereditary spherocytosis is diagnosed frequently in childhood and early adulthood, as well as it could be diagnosed at any age.[2] In our study, the age at diagnosis was ranging from 15 days to 17 years; and 20% were diagnosed during neonatal period. Patients with severe HS were diagnosed at an earlier age. The triad of anemia, splenomegaly and jaundice wass not present in most neonates with HS. If a neonate had a family history and/or elevated MCHC, MCHC/MCV ratio >0.36, after ABO hemolytic disease is ruled out, it is likely to have HS. When the diagnosis is unclear, eosin-5-maleimide binding test (EMA) or incubated OFT can be helpful. Neonatal red blood cells show altered response to osmotic stream due to decreased membrane surface area. However, incubated OFT was succesfully used for the diagnosis of neonatal HS.[10]

Clinical presentation of HS varies from being asymptomatic to paleness and icterus resulting from severe hemolysis, even heart failure related to severe anemia.[2-4] In most of HS patients, the enlarged spleen is observed. Splenomegaly is noted in 50% of infants, 75 to 95% of older children and adults.[2] In our study, the spleen was palpable in 70.8% of patients and the median size of spleen was 3 cm (IQR 2-4 cm).

Hereditary spherocytosis was classified as mild, moderate and severe according to Hb, bilirubin and reticulocyte values.[1,2] Frequency of transfusion could be added to the classification, as well[1]. Pinto et al.[11] reported 468 children with HS; 72% of them were classified as moderate HS and 7% of them as severe HS. In a series of 63 Brazilian patients, 54% was classified as moderate and 20% were severe.[12] In our study, 20% of the patients were classified as mild HS, 55.4% of patients as moderate HS and 24.6% of patients as severe HS. Infections may exacerbate the severity of anemia. Patients should be classified when clinically stable thus the severity of HS may not be overestimated.[1,12]

The most significant finding in HS is the appearance of spherocytes in peripheral blood

Table II. Laboratory Findings According To Hereditary Spherocytosis Classification.

	Groups		
Laboratory findings	Mild	Moderate	Severe
Hemoglobin (g/dl)	11.07±2.41	8.86±1.94	7.55±1.78
MCHC (g/dl)	36.12±0.77	35.74±1.23	35.11±1.83
Reticulocyte (%)	5.94±2.83	11.3±5.56	12.37±8.85
Total bilirubin (mg/dl)	2.59±1.6	3.94±3.51	5.78±5.01

MCHC: mean corpuscular hemoglobin concentration.

smear. However, in 20-25% of the cases the blood smear is completely normal or a few spherocytes can be seen.[1,2] Spherocytes was not observed 16.9% of our patients' smear and also 28% of patients did not have family history of HS. The reticulocyte count is increased related to chronic hemolysis; MCHC is higher than 35 g/dl in 50-75% of the patients which correlated with the decrease in erythrocyte volume.[4] In a study, which compares MCHC and RDW values of 112 patients with HS and 112 healthy children, it was detected that MCHC and RDW values were higher in patients with HS. Nevertheless, it was demonstrated that higher MCHC value (>35.4 g/dl) increased the probability of HS by 14 fold and the higher RDW value (>14%) raised the possibility of HS by 28 fold. It was reported that MCHC and RDW values could be used as a screening test.[13] In all our patients, RDW value was 15% and higher. Rocha et al.[5] demonstrated that the ratio of Hb/MCHC and Hb/RDW was decreased in the cases with HS and this decrease was related to clinical classification. In our study, a significant difference was detected between mild HS and moderate or severe HS, regarding both Hb/MCHC and Hb/RDW ratio and disease classification. However, any significant differences could not be identified between moderate and severe HS patients. Adding clinical parameters such as splenectomy needs and transfusion frequency would be useful to classify the disease severity.

The most frequently observed complication is cholelithiasis in HS. The incidence of bilirubin gallstone was reported as 21-63 %.1-4 In our study, cholelithiasis was detected in 30.8 % of the patients. No correlation was detected between the disease classification, transfusion frequency and the development of gallstone. Even in mild disease, regular ultrasonographic examination should be performed in order to detect gallstone. Aplastic crisis, which results from the suppression of bone marrow by viral infections mostly parvovirus B19, are generally less common complication in HS.[1,14] In our study aplastic crisis were seen 13.8% of patients; most of them were associated with parvovirus B19 infection.

It is known that splenectomy, removing the main site of red cell destruction, decreases hemolysis and reduces anemia by extending the life of the erythrocytes.[1] Splenectomy indications are defined as severe HS, growth failure, bone changes and transfusion dependence.[2,4] In our study 20% of patients underwent splenectomy. Pincez et al.[15] recommended subtotal splenectomy in children under the age of 6 years with severe anemia and/or transfusion requirement, and they noted that it alleviates the transfusion rate and increases the Hb to a level compatible with normal growth and activity. Cholecystectomy is indicated only for symptomatic gallstones and concomitant splenectomy is controversial. Due to changes in bile salt metabolism that is believed a predisposing factor for colon carcinoma, some surgeons prefer simple cholecystostomy, in which gallstone is removed but gallbladder is left.[16,17] In our study gallstone was detected in 30.8% of patients and 12 symptomatic patients underwent cholecystectomy.

The incidence of HS is not known in Turkey. Most of the reports from our country were case presentations, and only a few studies about the diagnosis, clinics and follow-up of children with HS were found in the literature. The limitations of our study are its retrospective design and exclusion of some of our patients due to missing data.

In conclusion, HS was a benign disease and anemia, jaundice and hepato/splenomegaly were the most common clinical features. Frequently observed complication was cholelithiasis; even patients without severe hemolysis should be followed intermittently by abdominal US in order to control the development of gallstone. The diagnosis of HS is straightforward based on a combination of the clinical and laboratory findings such as spherocytes on peripheral smear, increased MCHC values and osmotic fragility tests. Clinical parameters such as splenectomy and transfusion requirement and laboratory findings such as Hb/MCHC and Hb/RDW ratios might be helpful for classifying the clinical severity.

REFERENCES

1. Lux SE. Disorders of the red cell membrane. In: Orkin SH, Nathan DG, Gingsburg D, Look TA, Fisher DE, Lux SE (eds). Nathan and Oski's Hematology of Infancy and Childhood (8th ed). Philadelphia: WB Saunders, 2015; 515-548.

2. Bolton-Maggs PH, Langer JC, Iolascon A, Tittensor P, King MJ. Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update. Br J Haematol 2012; 156: 37-49.

3. Eber S, Lux SE. Hereditary spherocytosis--defects in proteins that connect the membrane skeleton to the lipid bilayer. Semin Hematol 2004; 41: 118-141.

4. Segel GB. Hereditary spherocytosis. In: Behrman RE, Kliegman RM, Jenson HB (eds). Nelson Textbook Pediatrics (18th ed). Philadelphia: WB Saunders, 2007: 2020-2023.

5. Rocha S, Costa E, Rocha-Pereira P, et al. Complementary markers for the clinical severity classification of hereditary spherocytosis in unsplenectomized patients. Blood Cells Mol Dis 2011; 46: 166-170.

6. Gallagher PG. Red cell membrane disorders. Hematology Am Soc Hematol Educ Program 2005: 13-18.

7. Miraglia del Giudice E, Iolascon A, Pinto L, Nobili B, Perrotta S. Erythrocyte membrane protein alterations underlying clinical heterogeneity in hereditary spherocytosis. Br J Haematol 1994; 88: 52-55.

8. Yawata Y, Kanzaki A, Yawata A, Doerfler W, Ozcan R, Eber SW. Characteristic features of the genotype and phenotype of hereditary spherocytosis in the Japanese population. Int J Hematol 2000; 71: 118-135.

9. Ayhan AC, Yildiz I, Yüzbaşıoğlu S, et al. Erythrocyte membrane protein defects in hereditary spherocytosis patients in Turkish population. Hematology 2012; 17: 232-236.

10. Christensen RD, Yaish HM, Gallagher PG. A pediatrician's practical guide to diagnosing and treating hereditary spherocytosis in neonates. Pediatrics 2015; 135: 1107-1114.

11. Pinto L, Iolascon A, Miraglia del Giudice E, Materese MR, Nobili B, Perrotta S. The Italian survey on hereditary spherocytosis. Int J Pediatr Hematol Oncol 1995; 2: 43-47.

12. Oliveira MC, Fernandes RA, Rodrigues CL, Ribeira DA, Giovanardi MF, Viana M. Clinical course of 63 children with hereditary spherocytosis: A retrospective study. Rev Bras Hematol Hemoter 2012; 34: 9-13.

13. Michaels LA, Cohen AR, Zhao H, Raphael RI, Manno CS. Screening for hereditary spherocytosis by use of automated erythrocyte indexes. J Pediatr 1997; 957-960.

14. Brown KE. Haematological consequences of parvovirus B19 infection. Baillieres Best Pract Res Clin Haematol 2000; 13: 245-259.

15. Pincez T, Guitton C, Gauthier F, et al. Long-term follow-up of subtotal splenectomy for hereditary spherocytosis: a single-center study. Blood 2016; 127: 1616-1618.

16. Das A, Bansal D, Das R, Trehan A, Marwaha RK. Hereditary spherocytosis in children: Profile and post-splenectomy outcome. Indian Pediatr 2014; 51: 139-141.

17. Tracy ET, Rice HE. Partial splenectomy for hereditary spherocytosis. Pediatr Clin North Am 2008; 55: 503-519.