Araştırma Makalesi
Research Article

Evaluation of adult patients with hereditary spherocytosis

HEREDİTER SFEROSİTOZLU ERİŞKİN HASTALARIN DEĞERLENDİRİLMESİ

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ABSTRACT

Intruduction: Hereditary spherocytosis (HS) is frequently diagnosed in the pediatric period. Therefore, studies on HS have often been conducted among pediatric patients, and there is no clear data on the disease in adulthood. Our aim was to reveal the follow-up findings of patients with adult HS and their geographic distribution in Turkey.

Materials and Methods: The sample comprised 172 subjects with a HS diagnosis. Data collection commenced retrospectively in February 2004 and was completed by September 2020.

Results: A total of 172 patients, 106 of whom were splenectomized and 66 of whom were non-splenectomized, were included in the study. Mean age of the entire group was 22.7 years. At the time of diagnosis, mean age of the entire group was 12.4 years; for splenectomized and non-splenectomized patients, it was 9.9 years and 16.6 years, respectively (p=0.000). At the time of diagnosis, anemia was more common in the splenectomized group (65.1%) than the non-splenectomized group (45.5%) (p=0.011). Thromboembolic event was not experienced in any patient after splenectomy. None of the patients in the splenectomized group was transfusion-dependent in their last visit, but in the non-splenectomized group, 6 patients (9.1%) were still transfusion-dependent (p=0.003).

Conclusion: Anemia was more common finding at the time of diagnosis and the age at diagnosis was lower in the splenectomized patients. Transfusion-dependency had completely disappeared in splenectomized patients. HS was more frequently seen in the Black Sea, northern Central Anatolia, and northern Marmara regions than in other regions in Turkey.

Keywords: Spherocytosis, splenectomy, adult, hemolytic anemia

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ÖZ

Amaç: Herediter sferositoz (HS) sıklıkla pediatrik dönemde tanısı konulan bir hastalıktır. HS ile ilgili çalışmalar ve yayınlar genellikle çocuk yaş grubu hastalarda yapılmıştır. Erişkin hastalar hakkında literatürde yeteri kadar veri bulunmamaktadır. Bu çalışmada erişkin HS'li hastaların izlem bulguları ve coğrafik konumlarına göre Türkiye'deki coğrafi dağılımlarını ortaya koymak amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya HS tanılı 172 erişkin olgu dahil edildi. Şubat 2004 ile Eylül 2020 tarihleri arasında merkezlerimize HS tanısıyla başvurmuş veya merkezlerimizde tanısı konmuş hastaların klinik ve laboratuvar verileri retrospektif olarak kayıt edilmiştir.

Bulgular: Geçmişte splenektomi olmuş 106, olmamış 66 hasta olmak üzere toplam 172 hasta çalışmaya dahil edildi. Tüm çalışma grubunun ortalama yaşı 22,7 yıl idi. Tüm grubun ortalama tanı yaşı 12,4 yıl iken Splenektoni olan grubun 9,9 yıl, olmayan grubun 16,6 yıl olarak gözlendi (p=0,000). Tanı anında anemi varlığı splenektomili grupta (%65,1), splenektomisiz gruba (%45,5) göre daha yaygındı (p=0,011). Splenektomi sonrası hiçbir hastada tromboembolik olay gözlenmedi. Splenektomili gruptaki hastaların hiçbiri son kontrollerinde transfüzyona bağımlı değildi, ancak splenektomi yapılmayan grupta 6 hasta (%9,1) hala transfüzyona bağımlıydı (p=0,003).

Sonuç: Splenektomili hastalarda tanı anında anemi en sık rastlanan bulguydu, ayrıca tanı yaşı bu grupta daha düşüktü. Splenektomili hastalarda transfüzyon bağımlılığı tamamen ortadan kalkmıştı. Hastalığın Karadeniz, Kuzey İç Anadolu ve Kuzey Marmara bölgelerinde Türkiye'nin diğer bölgelerine göre daha sık gözlendiği saptandı.

Anahtar Kelimeler: Sferositoz, splenektomi, yetişkin, hemolitik anemi

Hereditary spherocytosis (HS), although a rare disease, is the most common cause of hemolytic anemia due to a defect of the erythrocyte membrane. The disease was first described by Oskar Minkowsky in the early 1900s (1).

The disease is caused by mutations in genes encoding the structural proteins supporting the erythrocyte membrane. These changes impair the ability of the erythrocytes to change their shape according to the diameter of the vessel through which they pass, making them fragile. Spherocytic erythrocytes are destroyed mainly in the spleen, and thus clinical signs and symptoms of the disease occur due to hemolysis.

Genetic transmission is autosomal dominant in 70% of patients, autosomal recessive in 15%, and the remaining 15% are due to new mutations (2). HS can appear at a ratio of 1: 200 to 1: 5000 in all ethnicities, with more prevalence in White populations in Northern Europe and North America (3). There is no data about the prevalence of the disease in our country.

General characteristics of patients are presence of family history, history of neonatal jaundice or photopheresis due to jaundice and exchange transfusion, splenomegaly, and indirect bilirubin increase due to hemolysis. Although most of the patients are diagnosed in infancy or childhood, the mild form of the disease especially can also be diagnosed in adulthood (4).

Previous literature that examined demographic and clinical data on HS were generally conducted on a pediatric population. That is why we set out to examine adult HS patients and compare the clinical and laboratory parameters of patients with or without splenectomy.

MATERIALS AND METHODS

One hundred seventy-two patients with HS who applied to our clinics between the dates of February 2004 and September 2020 for army recruitment examination were included. The study was conducted at hematology clinics. The data of these patients were evaluated retrospectively during their army recruitment examination. Outcome measures included in the analysis were clinical and laboratory factors associated with the disease and geographical dispersion across the country of Turkey.

Most of the patients had previously been diagnosed at another centers. In patients admitted to our clinic with the findings of hemolytic anemia, HS was diagnosed based on the clinical history, physical examination, and the results of laboratory tests: complete blood count (CBC), blood smear examination (BSE), reticulocyte count, bilirubin concentration, red blood cell osmotic fragility (OF), and negative direct antiglobulin test. The diagnosis of patients who had previously been diagnosed with HS at another center were confirmed. Patients' historical information such as age at the time of diagnosis, hometown, disease findings at the time of diagnosis (anemia, splenomegaly, hyperbilirubinemia, gallstones), whether splenectomy or cholecystectomy was performed, indication for splenectomy (transfusion dependence, massive splenomegaly, splenic infarct or hemorrhage), and history of thrombosis after splenectomy were recorded. Splenic scintigraphy was performed for the presence of accessory spleen in patients who have undergone splenectomy, and abdominal ultrasound in those who did not have splenectomy was performed during the recruitment examination, and all of the results recorded. The study was approved by the local Institutional Review Board and Ethics Committee and was conducted in accordance with the Helsinki Declaration of 2013.

The study population was described using frequencies with associated percentages for qualitative data using mean, range, and standard deviation for quantitative data. The difference in blood levels in the two groups was compared using the independent sample T-Test. Cross-tables, Chi-Square tests, and Fishers' exact tests were used for categorical variables. A p-value ≤ 0.05 was considered statistically significant. The IBM SPSS System version 25 was used for all analyses.

RESULTS

Demographic Datas and Clinical Findings at Diagnosis

In our study, we included a total of 172 male patients, 106 of whom were splenectomized and 66 were non-splenectomized. Demographic data and clinical characteristics at diagnosis were presented at Table 1.

TABLE 1. Demographic Data And Clinical Characteristics at Diagnosis

Variables	All n:172	Splenectomized n:106	Non-splenectomized n:66	*p* value
Current age, mean (range), years	22.7 (18-50)	22.4 (18-50)	23.1 (19-41)	0.393
Age at diagnosis, mean (range), years	12.4 (0-40)	9.9 (0-31)	16.6 (2-40)	**0.000**
Clinical Characteristics at Diagnosis, n (%)				
Splenomegaly	166 (%96.5)	103 (%97.2)	63 (%95.5)	0.676
Hyperbilirubinemia	161 (%93.6)	100 (%94.3)	61 (%92.4)	0.751
Gallbladder Stone	54 (%31.4)	33 (%31.1)	21 (%31.8)	0.925
Anemia	99 (%57.6)	69 (%65.1)	30 (%45.5)	**0.011**

$p \leq 0.05$: statistically significant.

When we compare the clinical characteristics of the patients at the time of diagnosis, splenomegaly was seen in 103 patients (97.2%) in splenectomized patients and 63 patients (95.5%) in non-splenectomized patients.

Hyperbilirubinemia and gallbladder stone were also seen as similar between groups 94.3% and 31.1% vs 92.4% and 31.8%, respectively. Anemia was more common in the splenectomized group (69 patients, 65.1%) than the non-splenectomized group (30 patients, 45.5%) (p=0.011) (Table 1). The hometowns of the patients are shown in the map of Turkey (Figure 1).

Figure 1: Distribution of patients by geographical region/city.(Every dots belongs to one patient)

Laboratory Results

Red blood cell (RBC), hemoglobin (Hgb), and hematocrit (Hct) levels were 5.1x10⁶/μL, 15.4 g/dl, and 44.1% for the splenectomized group and 4.38 x10⁶/μL, 12.9 g/dl, and 36.6% for the non-splenectomized group (p=0.000), respectively. MCV, MCH, and MCHC were similar between groups; 87 fL, 30.5 pg, 35.1 g/dl, and 87.8 fL, 30.8 pg, and 35.6 g/dl, respectively. Mean platelet count was 468000/μL for the splenectomized group and 222000/μL for the non-splenectomized group (p=0.000). When we compare hemolysis markers; mean LDH, total & indirect bilirubin levels and absolute reticulocyte counts were 317 IU/L, 2.9 mg/dl, 2.4 mg/dl, and 101900/μL for the splenectomized group and 498 IU/L, 5 mg/dl, 4.5 mg/dl, and 219700/μL for the non-splenectomized group (p=0.000). Spherocyte ratio in peripheral blood was similar between groups and 55.8% and 54.3%, respectively (Table 2). OF was positive in 80% of patients in both groups.

TABLE 2. Laboratory Results of Patients.

Laboratory Results, absolute count ± standart deviation	All	Splenectomized	Non-splenectomized	*p* value
Hemogram				
Leukocyte, 10³/μL	10.2 ± 3.8	10.9 ± 3.9	9.1 ± 3.5	**0.004**
Neutrophil, 10³/μL	6.5 ± 3.5	7.1 ± 3.9	5.7 ± 2.5	0.115
RBC, 10⁶/μL	4.79 ± 0.95	5.1 ± 0.87	4.38 ± 0.89	**0.000**
Hgb, g/dl	14.4 ± 2.6	15.4 ± 2.2	12.9 ± 2,5	**0.000**
Hct, %	41 ± 7.6	44.1 ± 6.2	36.6 ± 7.3	**0.000**
MCV, fL	87.3 ± 8.7	86.9 ± 9.8	87.8 ± 6.9	0.618
MCH, pg	30.6 ± 2.7	30.5 ± 2.7	30.7 ± 2.7	0.657
MCHC, g/dl	35.2 ± 1.7	35 ± 1.5	35.5 ± 1.9	0.075
Platelet, 10³/μL	372 ± 169	468 ± 144	222 ± 60	**0.000**
Hemolysis Markers				
LDH, IU/L	405 ± 156	317 ± 96	498 ± 153	**0.000**
Total Bilirubine, mg/dl	3.92 ± 2.64	2.87 ± 2.52	5.02 ± 2.3	**0.000**
Indirect Bilirubine, mg/dl	3.46 ± 2.57	2.41 ± 2.4	4.52 ± 2.3	**0.000**
Reticulocyte, /μL	166,500 ± 121,100	101,900 ± 65,600	219,700 ± 131,100	**0.000**
Spherocyte ratio, %	55.1 ± 17.7	55.8 ± 18.3	54.2 ± 17.1	0.609

RBC: red blood cell, Hgb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, LDH: lactate dehydrogenase, $p \leq 0.05$: statistically significant.

Splenectomy Indications And Outcomes

Splenectomy was performed in 61.6% of all patients. Isolated splenectomy was performed in 61.3% of all splenectomized patients, while 38.7% of them also underwent cholecystectomy besides splenectomy. Isolated cholecystectomy was performed in 6.2% of the whole group. Intrahepatic choledocholithiasis was not observed in patients who underwent isolated cholecystectomy in the following period. The reasons for splenectomy were severe anemia in 29.2%, massive splenomegaly in 92.5%, and splenic hemorrhagic/infarct in 12.3% of the splenectomized patients. Thromboembolic event was not experienced in any patient after splenectomy. Only one patient had splenosis after splenectomy who was detected by splenic

scintigraphy. Mean spleen size of the non-splenectomized patients was 164 ± 26 mm. None of the patients in the splenectomized group were transfusion-dependent in their last visit, but in the non-splenectomized group, 6 patients (9.1%) were still transfusion-dependent (p=0.003).

DISCUSSION

HS is usually diagnosed in childhood and young adulthood, however, cases of patients diagnosed in their 80s' have been reported in the literature. The age of diagnosis is related to the severity of the disease and the awareness of clinicians (4). In our study group, earlier diagnosis of patients with more severe clinical findings and as a result of splenectomy also supports this clinical situation.

Olivera et al. reported anemia 63.5%, splenomegaly 69.8%, hyperbilirubinemia 38% at the time of diagnosis in their study including 63 pediatric patients with a median age of diagnosis 5.2 years (5). Although only adult patients were included in our study, anemia rates were found to be similar to the pediatric group. The reason for the higher rates of splenomegaly was thought to be related to the duration of the disease. In HS disease, the incidence of splenomegaly increases, correlating with increasing age (6).

Nowadays, splenectomy is recommended for patients with erythrocyte transfusion dependency and for those whose quality of life is impaired due to splenomegaly (7). Splenectomy was performed in 106 (61.6%) of our patients in the past. Güngör et al. reported the rate of splenectomy as 20% (8). Olivera et al. reported the rate of splenectomy as 34.9% (5). The other reason why the rate of splenectomy is higher than previous literatures is probably that most of our patients were diagnosed with HS in the 1980s' and early 1990s'. Splenectomy has been used as a routine practice in the management of HS in the past. The presence of massive splenomegaly was found to be the most common reason for splenectomy indication in our patients. Pincez et al. reported the indications for splenectomy were transfusion dependence or severe anemia in 39 HS patients and other symptoms (fatigue, gallstones, icterus) in 40 patients in their study including total 79 HS patients (9).

Cholecystectomy was also performed simultaneously with splenectomy in 38.7% of patients, and isolated cholecystectomy was performed in 6.2% of the whole group. There are doubts of the risk of intrahepatic choledocholithiasis when only cholecystectomy without splenectomy is performed in patients with HS (10). There were no signs or symptoms consistent with recurrence of intrahepatic choledocholithiasis in the follow-up of our patients who underwent isolated cholecystectomy. Ruparel et al. reported 5 HS patients who underwent cholecystectomy without splenectomy, and none of them experienced signs or symptoms consistent with gallstones over a median follow-up of 15.6 years (11).

When we compare the clinical characteristics of splenectomized and non-splenectomized patients at the time of diagnosis, hyperbilirubinemia and gallbladder stones were seen as similar between groups. Anemia was more common in the splenectomized group than the non-splenectomized group (p=0.011). Based on this data, we could say that patients who are anemic at the time of diagnosis have a higher risk of having a splenectomy in the future. Spherocyte ratio in peripheral smear was 55.1 ± 17.7% and OF test was 79.6% positive in all patients. We observed that our OF positivity rate was slightly higher than the literature. Cynober et al. reported positivity of OF in 37 (66%) of 55 HS patients, when they performed the incubation OF test in 18 OF negative patients, they obtained positive results in 10 more patients (12). If we had performed an incubated OF testing, we would have expected this rate to be even higher.

Spleen size was measured by ultrasonography in 60 of the non-splenectomized group (n: 66) patients, and splenomegaly was detected in 57 patients (95%) (mean splenic size: 164 ± 26 mm). Güngör et al. reported the incidence of splenomegaly as 73.8% in 65 pediatric HS patients (8). We know that spleen size increases with age in HS patients (6). Our high rate of splenomegaly is likely due to the adult age of our patients.

As expected, depending on the ongoing hemolysis in the spleen, hemolysis markers were significantly higher in the non-splenectomized group. In a study by Mariani et al., analysis of 21 patients evaluated before and after

splenectomy showed an increase of median hemoglobin levels (from 10.8 g/dL to 13.9 g/dL) and a decrease of reticulocyte count (from 337×10⁹/L to 51×10⁹/L), and unconjugated bilirubin (from 32.5 IU to 12 IU) were also reported (13). In our study, the median hemoglobin was found to be higher in the splenectomized group compared to the non-splenectomized group (15.4 vs 12.9 g/dL), while the reticulocyte (101,900//μL vs 219,700/μL) and unconjugated bilirubin (2.41 vs 4.52 mg/dl) levels were found to be lower, similar with the literature.

MCHC is a valuable parameter to show the presence of spherocytosis. Michaels et al. reported that an MCHC >35g/dl had 70% sensitivity and 86% specificity for the diagnosis of HS in their study, including 112 HS patients. In addition, the mean MCHC was lower in the splenectomy group compared to the non-splenectomy group (35.2 vs 35.6 g/dl, p: 0.04) (14). In our study, we found the mean MCHC value as 35.2 ± 1.7 g/dl in all participants of our study group. Mean MCHC was higher in the non-splenectomized group compared to the splenectomized group as expected due to the reduction of microcytic-hyperdense erythrocytes, however it was not statistically significant (35.5 g/dl vs 35 g/dl, p:0.075).

There is always the question regarding the risk of venous thromboembolism after splenectomy in HS patients. The available evidence suggested that the only individuals who have an increased risk of late thrombosis after splenectomy were those patients with myeloproliferative disorders or persisting anaemia with abnormal red blood cells. Furthermore, the risk of venous thrombosis is increased if splenectomy was performed for beta thalassemia intermedia and hereditary forms of stomatocytosis. In our study there was no history of thrombosis in cases of thrombocytosis due to splenectomy. Long-term thromboprophylaxis is not indicated in patients with splenectomy due to HS (4).

Total splenectomy was performed in all splenectomized patients; none of the patients underwent partial splenectomy. Accordingly, none of the patients in the splenectomized group was transfusion-dependent in their last visit. However, six patients (9.1%) were still transfusion-dependent in the non-splenectomized group. We recommended splenectomy to these patients due to transfusion dependence.

The regional distribution rate of hometowns of the patients according to geographical regions in Turkey were: Marmara 17%, Aegean 10%, the Black Sea 26%, Central Anatolia 24%, Mediterranean 10%, Southeastern Anatolia 3%, Eastern Anatolia 10%. HS was more frequently seen in the Black Sea, Northern Central Anatolia, and Northern Marmara than the other regions in Turkey. We have not encountered any publications in the literature regarding the distribution of HS disease in Turkey. We have therefore offered the first geographical distribution of HS in Turkey. It can be expected that HS is less frequently inherited as autosomal recessive and its frequency increases with consanguineous marriage. However, in regions where consanguineous marriage is more common, its frequency was low, and consanguineous marriage was not at all common in all patients' histories. Therefore, it is difficult to conduct a review that demonstrates the frequency of HS in certain regions in Turkey.

Clinical history, physical examination, and the results of laboratory tests; CBC, BSE, reticulocyte count, bilirubin concentration, OF, and direct antiglobulin tests were used for diagnosis of HS in our study. None of the criteria we used in the diagnosis has 100 percent sensitivity alone. Therefore, we diagnosed HS based on the combined availability of diagnostic criteria and excluding other possible diagnoses. We could not perform confirmatory and specialized tests with high sensitivity such as eosin-5'-maleimide binding, acidified glycerol lysis test and DNA sequencing in our centers. Patients with a family history of HS, typical clinical features and laboratory investigations (spherocytes, MCHC, increase in reticulocytes) do not require any additional tests for HS diagnosis according to the 2011 guidelines for HS diagnosis and management of the General Haematology Task Force of the British Committee for Standards in Haematology (4). In suspected or atypical cases, a screening confirmatory and specialized tests with high predictive value for HS is helpful. Therefore, we have no doubts about the accuracy of the diagnoses of the patients we included in our study. Several limitations of our study deserve to be mentioned. The main limitation of this study is its retrospective design. Since most of the

patients were diagnosed in another centers before our evaluation, we could not access the laboratory data of some patients at the time of diagnosis. Therefore, we could not evaluate the disease severity of some patients at diagnosis. Another limitation of our study was that all of our patients were male and in the young adult age group, due to the fact that all patients included in the study were recruited from the army recruitment examination.

In conclusion, anemia was more common at the time of diagnosis and the age at diagnosis was lower in the splenectomized patients. Any complications (thrombosis, infection) related to splenectomy were not observed in the following period after splenectomy. We observed that the transfusion-dependency had completely disappeared in splenectomized patients. Disease was frequently seen in the Black Sea, northern Central Anatolia and northern Marmara regions than other regions in the Turkey.

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