Natural History of Hereditary Spherocytosis Among Egyptian Pediatric Patients

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Abstract

Objective: This study aimed to better characterize short term and long term natural history of hereditary spherocytosis (HS) in Egyptian pediatric patients.

Design and Methods: A retrospective record review was performed on 40 children with HS. Demographics, age at diagnosis, presenting features, history of complications, hospitalizations and medications were reviewed. Transfusion, neonatal and family history and spleen status were reviewed. All laboratory data at diagnosis and thereafter were revised.

Results: Five (12.5%) cases were mild, 22 (55%) were moderate and 13 (32.5%) of our patients were severe HS. Nine (22.5%) cases presented during the first year of life. Patients presented with intermittent jaundice in 34 (85%), pallor in 36 (90%), dark colored urine in 8 (20%) and abdominal distention in 10 (25%). The commonest sign was splenomegaly (87.5%), hepatomegaly 18 (45%), cholelithiasis in 3 (7.5%). Blood transfusion at the time of diagnosis was needed in 25 (62.5%) patients. At presentation, the hemoglobin ranged from 3.0-11.0g/dl, reticulocytosis was present in all cases. Spherocytes were seen in 82.5% and Osmotic fragility test (OFT) was positive in 50%. AGLT was performed for 29 cases and was positive in 89.5%. HbF level was seen in 10 cases. Ten (25%) cases were splenectomized and 9/10 required no blood transfusion thereafter and all had no reported complications after splenectomy.

Conclusions: Hereditary spherocytosis is not a rare disease in Egypt with its natural history nearly similar to that reported worldwide. However, severe HS was found to be more common among our cases. Gall stones and hypersplenism are the commonest complications. Splenectomy was the most effective and safe line of management of severe cases.

Key Words: Hereditary spherocytosis – Natural history – Children – Egypt.

Introduction

HEREDITARY spherocytosis (HS) is the most common hemolytic anemia due to a red cell membrane defect. It derives from alterations of the following genes: ANK1, EPB3, ELB42, SPTA1 and SPTB. The osmotically fragile spherocytes are selectively trapped in the spleen and destroyed. Increased red blood cell destruction causes the main clinical signs of HS [1].

The hallmarks of HS are anemia, reticulocytosis, jaundice, splenomegaly, spherocytes in the peripheral blood smear, increased erythrocyte osmotic fragility and family history of this disease [2,3,4]. Most affected individuals have mild or only moderate haemolysis. There is usually a family history and a typical clinical and laboratory picture so that the diagnosis is often easily made without additional laboratory tests [2].

Atypical cases may require measurement of erythrocyte membrane proteins to clarify the nature of the membrane disorder and in the absence of a family history, occasionally molecular genetic analysis will help to determine whether inheritance is recessive or non-dominant [2].

Proper diagnosis and classification of HS patients according to the clinical severity is one of the most important aspects in clinical management of HS, especially in children when a decision about the benefits of splenectomy has to be made and the knowledge of the clinical outcome of the disease might be important as well [5].

In our study we aimed to better characterize the short term and long term natural history of hereditary spherocytosis (HS) including diagnosis, complications, and indications for and response to splenectomy in pediatric patients.

Patients and Methods

This is a retrospective study of the medical records of 40 patients, with a mean age 6.6 ± 4.8 yrs (range 0.5 to 18 yrs, median 5 yrs). All cases
were diagnosed as hereditary spherocytosis based on the clinical history, physical examination and the results of laboratory tests: Complete blood count, blood smear examination, reticulocyte count, bilirubin concentration, red blood cell osmotic fragility tests, and negative direct antiglobulin test [2].

The study was carried out at the Pediatric Hematology Clinic, New Children’s Hospital, Cairo University. The study protocol was approved by our Investigational Review Board (IRB) and was conducted in accordance with the University bylaws for human research.

Review of the previous and current medical records and patient interview were performed for medical history assessment. Data collected included demographic data, age at diagnosis, presenting symptoms, transfusion history including. history of related complications, hospitalizations and medications were reviewed. Past history of neonatal jaundice necessitating intervention and family history of similar conditions, hydrops fetalis or still births and spleen status were reviewed.

All laboratory investigations including laboratory data at diagnosis: Complete blood picture (CBC), osmotic fragility test (OF), acidified glycerol lysis test (AGLT) and hemoglobin electrophoresis. All laboratory records thereafter were revised. The recruited cases were classified as presenting mild, moderate or severe HS, according to the criteria described in the Guidelines for the diagnosis and clinical management of Hereditary Spherocytosis [2].

Statistical analysis: Continuous variables were presented as mean ± standard error (SE), range, median and interquartile range whereas categorical variables were analyzed as percentages. SigmaStat program; version 3.5 (Systat Software, Inc., USA) was used for Data management and analysis.

Results

In this study, 40 patients were included; 25 (62.5%) males and 15 (37.5%) females (M/F=1.7). Nine (22.5%) cases presented and diagnosed during the first year of life with mean age at diagnosis 3.4±1.0 yrs (range: 0.2-11, median 2.5yrs). In accordance with the Guidelines by Bolton-Maggs et al. [2] and considering the clinical/family history of the patients, we classified 5 (12.5%), 22 (55%) and 13 (32.5%) of our patients as presenting mild, moderate HS or severe HS, respectively. Patients commonly presented with intermittent jaundice in 34 (85%), pallor in 36 (90%), dark colored urine in 8 (20%) cases and abdominal distension in 10 (25%). The commonest sign was splenomegaly which was evident in 35 (87.5%), hepatomegaly 18 (45%), cholelithiasis in 3 (7.5%), one case aged 4 years undergone cholecystectomy before diagnosis. Positive consanguinity was seen in 10 (25%) patients and similar condition in the family was present in 30 (75%). Blood transfusion at the time of diagnosis was needed in 25 (62.5%) patients. The patient’s data are illustrated in Table (1).

At presentation, the hemoglobin ranged from 3.0-11.0g/dl with a mean of 6.8g/dl (±0.4) with Spherocytes seen in 33 (82.5%) cases. Reticulocytosis was evident in all cases and conjugated hyperbilirubinemia was seen in 33 (82.5%) cases. Osmotic fragility test (OF) on fresh blood was positive in 20 (50%) patients. AGLT was performed for 29 cases and was positive in 26 (89.5%). HbF level was detectable in 10 cases ranging from 1 to 7.1% with a mean of 3.6%, two of these had associated beta thalassaemia trait (Table 2).

All patients were maintained on folic acid, vitamin D and calcium supplementation. Two (5%) cases needed addition of an iron chelator. Ten patients (25%) underwent splenectomy. The main indication of splenectomy was frequent transfusion in 8 cases and secondary hypersplenism in 2 cases. Nine patients did not require any blood transfusion.
post-splenectomy and all had no reported complications. Among the 30 patients treated conservatively 12 (40%) patients had persisting pallor and 8 (27%) had transfusion requirement.

Table (2): Laboratory data at presentation (n=40).

<table>
<thead>
<tr>
<th>Variables</th>
<th>The studied cases</th>
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<tbody>
<tr>
<td>Hematologic parameters:</td>
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<tr>
<td>• Hemoglobin level (g/dl):</td>
<td>Mean±S.E. (Range)</td>
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<tr>
<td></td>
<td>6.8±0.4 (3-11)</td>
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<tr>
<td>• Spherocytes (n, %)</td>
<td>Median (IQR)</td>
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<td></td>
<td>7 (-)</td>
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<tr>
<td>Markers of hemolysis:</td>
<td></td>
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<tr>
<td>• Reticulocytosis (n, %)</td>
<td>40 (100%)</td>
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<tr>
<td>• Unconjugated hyperbilirubinemia</td>
<td>33 (82.5%)</td>
</tr>
<tr>
<td>Fetal hemoglobin (%) (n=13):</td>
<td></td>
</tr>
<tr>
<td>• Mean±S.E. (Range)</td>
<td>3.6±0.6 (1.0-7.1)</td>
</tr>
<tr>
<td>• Median (IQR)</td>
<td>3.5 ( )</td>
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<tr>
<td>Positive Osmotic fragility test (n, %):</td>
<td>20 (50%)</td>
</tr>
<tr>
<td>Positive AGLT (n, %):</td>
<td>26/29 (89.5%)</td>
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</table>

**Discussion**

HS is a heterogeneous group of disorders with regard to clinical severity, protein defects and mode of inheritance [2]. It is reported worldwide and is the most common inherited anemia in individuals of northern European ancestry [4]. It has also been reported in Japanese populations [6]. Although the disease arises in all racial and ethnic groups [4] its incidence has not been widely surveyed in some areas, including Egypt, nor have its exact clinical, molecular and inheritance patterns been widely investigated.

We studied 40 patients with an established diagnosis of HS and we found that both genders were affected. However, among our cases there was a male sex predominance with M/F=1.7. Two studies have been carried out on the Egyptian patients and one of these studies [7] reported that X-linked mode of inheritance may run in certain families where the disease is transmitted from the mother to her sons and not daughters. Previous studies reported that HS genes have all been assigned to several autosomal chromosomes including 1, 8, 14, and 17 and X-linked mode was not reported in HS, which has equal sex distribution [8,9,10].

HS may present at any age, although typically in childhood and adolescence and its clinical severity is variable [4]. Mean age of the studied cases was 6.6±4.8 yrs (range: 0.5 to 18 yrs, median 5 yrs). Nine (22.5%) cases presented and diagnosed during the first year of life with mean age at diagnosis 3.4±1.0 yrs (range: 0.2-11, median 2.5yrs). this was in line with previous studies [2,7,11,12].

In accordance with the Guidelines by Bolton-Maggs et al. [2] we classified 5 (12.5%), 22 (55%) and 13 (32.5%) of our patients as presenting mild, moderate HS or severe HS, respectively. This in agreement with many previous authors reported the typical type of moderate severity as the most common clinical type of HS patients [2,7,13]. We have a higher prevalence of severe cases than that reported in the literature and this may be explained by being a tertiary referral hospital.

Among our cases, pallor was the most frequent sign (90%) followed by splenomegaly (87.5%) and jaundice (85%) this was in accordance with previous studies that reported that anemia and splenomegaly were the most frequent complaints in children [11,12,14,15].

Thirty-six (90%) of our cases had history of neonatal jaundice but intervention was needed by phototherapy in 12 cases and exchange transfusion in 2, this in agreement with previous studies reporting that HS often presents as jaundice in the first few days of life [7,16,17].

Chronic haemolysis leads to the formation of bilirubinate gallstones, which are the most common complication of hereditary spherocytosis. Among our cases, cholelithiasis was evident in 3 (7.5%) and one case aged 4 years underwent cholecystectomy before diagnosis. This was in agreement with previous studies reporting that gallstones are noted in at least 5% of children less than 10 years of age [7,14,18].

The laboratory hallmarks of HS are the presence of spherocytes in a blood smear and/or the demonstration of increased red cell fragility. It is worth noting that about 10% of HS cases had very few or no detectable spherocytes, and this may account for HS being misdiagnosed in some patients [11]. Among our cases (82.5%) had spherocytes in their blood smear this was in agreement with [12] who reported spherocytes in 88.6% of cases.

Red cell fragility tests are known to have different sensitivities [2]. They have a poor sensitivity because about 20% of mild cases of hereditary spherocytosis are missed [19]. They are unreliable in patients with small numbers of spherocytes, including those who have recently received a blood transfusion [20].
Among our cases, fresh OF test was positive in 50% while AGLT was positive in 89.5% of cases. Our results confirmed that the sensitivity of these tests varies greatly and this was in accordance with what was reported by previous authors [11,21]. We also demonstrated that, among the traditional screening tests for HS, the acidified glycerol lysis test had the highest sensitivity and this agrees with previous studies [11,22].

Previously, splenectomy was considered “routine” in HS patients. However, the increased risk of infections, the emergence of penicillin-resistant pneumococci, and growing recognition of increased risk of cardiovascular disease, particularly thrombosis and pulmonary hypertension, have led to reevaluation of the role of splenectomy in HS [23,24].

In this study, ten patients (25%) underwent splenectomy. The main indications of splenectomy were frequent transfusion in 8 cases and secondary hypersplenism in 2 cases. Nine patients did not require any blood transfusion post-splenectomy and all had no reported complications taking into consideration that none of them underwent revaluation of cardiovascular problems. Among the 30 patients treated conservatively 12 (40%) patients had persisting pallor and 8 (27%) had transfusion requirement.

Conclusions: Hereditary spherocytosis is not a rare disease in Egypt with its natural history nearly similar to that reported worldwide. However, severe HS was found to be more common among our cases. Gall stones and hypersplenism are the commonest complications among our children. Splenectomy is the most effective and safe line of management of severe cases. We recommend close follow-up of splenectomized cases for early detection of post-splenectomy cardiovascular problems.

References
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