RESEARCH BRIEF

Hereditary Spherocytosis in Children: Profile and Post-splenectomy Outcome

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Objective: To describe profile of 82 children with hereditary spherocytosis diagnosed over a period of 27 years (1985-2011) from a single center. **Methods:** Retrospective analyses of case records. **Results:** The mean (SD) age at diagnosis was 6.7 (2.8) years; 7 (8.5%) were diagnosed in infancy. Pallor (100%), icterus (67%), undocumented fever (28%), splenomegaly (96%) and hepatomegaly (73%) were the most frequent findings. Cholelithiasis was observed in 26%. Twenty-six (32%) underwent splenectomy and were followed for a median duration of 4.5 years. Two (7.7%) children developed post-splenectomy sepsis. **Conclusion:** Anemia, hepato-splenomegaly and jaundice are commonest clinical features of hereditary spherocytosis. Post-splenectomy sepsis is uncommon.

Keywords: *Gallstones, Hemolytic anemia, Osmotic fragility.*

Hereditary spherocytosis (HS) is a hemolytic membranopathy characterized by anemia, jaundice and splenomegaly [1]. The commonest cause of inherited hemolysis in the West [2,3], it is reported less frequently from Southeast-Asia [4-6]. The objectives of present study were: a) to report the clinical and investigational profile of HS in children, and b) to record complications, including cholelithiasis and post-splenectomy sepsis (PSS).

METHODS

Case files of patients with HS, enrolled in the pediatric-hematology-clinic of the institution over 27 years (1985-2011) were retrieved. Patients enrolled during the study period (July 2010 to June 2011) were included prospectively. Diagnostic criteria were: (*a*) age ≤15 years at diagnosis, (*b*) presence of anemia, splenomegaly and jaundice (all three not necessary to be present simultaneously), (*c*) spherocytosis on the peripheral smear, (*d*) positive osmotic-fragility-test (OFT) [7], and (*e*) negative direct-antiglobulin-test. In the institute, incubated OFT has replaced conventional OFT as the first line test since 2008. The eosin-5'-maleimide flow-cytometry test [1] was unavailable during the study period. The information compiled included: demographic data, clinical presentation, presence of an affected family-member (by history or screening with OFT), inheritance-pattern by pedigree-analysis, and history of neonatal jaundice (NNJ) or red-cell transfusion(s). Severity of disease was based on hemoglobin, bilirubin and reticulocyte count at presentation (***Table* I**) [8]. Complications, including growth failure and cholelithiasis were recorded. Ultrasonography of abdomen, if not done in the preceding year, was requested. WHO-criteria were utilized to assess growth-failure [9]. Additional information, including age at splenectomy, immunization, penicillin prophylaxis and PSS, was noted. PSS was defined as an episode of illness with a positive blood culture, or an episode of illness requiring hospitalization and treatment with antibiotics, where no other cause was apparent. The study was approved by institutional ethics committee and consent was obtained from parents/ guardians for prospective investigations.

Chi-squared and Fischer's tests were used to analyze categorical variables. Pearson and Spearman correlations were utilized for parametric and nonparametric data,

TABLE I CLASSIFICATION OF DISEASE SEVERITY*

Parameters	*Mild*	*Moderate*	*Moderately severe*	*Severe*
Hemoglobin (g/dL)	11-15	8 - 12	6-8	<6
Reticulocyte (%)	3-8	≥ 8	≥10	≥10
Bilirubin (mg/dL)	1-2	≥ 2	>2-3	>3

******The most deranged value was considered for classification*

respectively. Multinomial logistic regression model was used to evaluate relationship between the disease severity and selected variables.

RESULTS

Ninety children were enrolled; 8 were excluded in view of incomplete records. Clinico-investigational profile of 82 patients (male:female 2:1) with HS was examined. Prospective follow-up was possible in 62 (76%) patients, including 19 (73%) with splenectomy. All these patients were asymptomatic. Forty-two (51%) had severe disease; 18 (22%) moderately-severe, 16 (20%) moderate and 6 (7%) had a mild disease. The mean (SD) age at diagnosis was 6.7 (2.8) years (range: 1 month–15 years); 7 (8.5%) were diagnosed in infancy. The median symptom-diagnosis interval was 2 years (range: 4 days–15 years). Severity of disease was not related to age (P=0.35) or gender (P=0.32). History of neonatal jaundice was present in 25 (30.5%); one had required an exchange transfusion. These children had a lower mean (SD) age at diagnosis as compared to those without NNJ [5.1 (3.6) years *vs*. 7.5 (3.7) years; P=0.007]. At least one family member was affected in 29 (35%) patients. Suggestive history was elicited in 19; further 10 were diagnosed by screening. Patients with a family history neither presented at an early age (P=0.16) nor had a more severe disease (P=0.79). Forty-five (55%) patients had received a blood transfusion prior to reporting to our institution; 17 (38%) and 12 (27%) patients had received 2 and more than 2 transfusions, respectively. History of receiving a blood transfusion did not correlate with disease severity (P=0.31).

Pallor (6.8%), jaundice (51%) and fever (2.8%) were the predominant symptoms whereas most frequent clinical signs were: pallor (100%), splenomegaly (96%), hepatomegaly (73%), icterus (67%) and hemolytic facies (2.8%). Mild splenomegaly (<3 cm) was observed in 28/79 (35%), while 31/79 (39%) had moderate and 20/79 (25%) had massive splenomegaly. Sixteen (80%) patients with massive splenomegaly had a severe disease (P=0.008). Laboratory parameters of the included children are presented in ***Table* II**.

Ultrasonography records were available in 62 (76%) patients; 16 (26%) had gallstones, with a mean (SD) age of detection of 8.5 (2.7) years (range: 2.3-14 years). Cholelithiasis was asymptomatic in majority, and detected on screening ultrasound. A single patient underwent cholecystectomy for recurrent cholangitis along with splenectomy for transfusion dependence. Underweight patients were more likely to have a severe or moderately-severe disease (P=0.056) and a lower mean (SD) hemoglobin [6.8 (2.5) g/dL *vs*. 8.1 (2.1) g/dL; P=0.037] as compared to children with normal weight. Stunting was more common in older (>7.5 years) patients (P=0.006), and in those with a severe disease (P=0.008). No episode of aplastic crisis was recorded.

All the patients received oral folate. Twenty-six (32%) patients with severe HS and transfusion-dependence underwent splenectomy at a mean (SD) age of 7.9 (3.7) years (range 2-14 years). They were followed up for a median duration of 4.5 years (range: 4 months–19 years). Twenty-five (96%) had received pneumococcal vaccine, while 9 (35%) were immunized against *Haemophilus-influenzae*-b (Hib). Following splenectomy, patients were prescribed prophylactic oral penicillin for a minimum duration of 5 years. Two children developed PSS, one 5 years following splenectomy; both had received pneumococcal and Hib vaccines (overall incidence: 0.68 episodes in 1000 patient years).

DISCUSSION

The children with HS in our series typically presented with pallor, jaundice and undocumented fever. A family history was elicited in merely one-third. Majority had

TABLE II LABORATORY PARAMETERS AT DIAGNOSIS IN CHILDREN WITH HEREDITARY SPHEROCYTOSIS

Parameters	*N**	*Mean (SD)*	*Range*
Hemoglobin (g/dL)	82	7.6 (2.4)	2.8 - 12.5
Reticulocyte count (%)	70	12.6 (10.3)	1 - 50
Total bilirubin (mg%)	39	3.6 (2.1)	0.8 - 8.4
Platelet count (10^3/L)	79	290 (130)	31 - 640
Mean corpuscular volume (fL)	14	81.6 (7.4)	70.1 - 93.9
Mean corpuscular hemoglobin (pg)	14	26.8 (2.5)	20.5 - 29.7
Mean corpuscular hemoglobin concentration (%)	13	31.9 (2.6)	28 - 36
Red cell distribution width (%)	10	23.4 (4.7)	18 - 32
Plasma hemoglobin (g/dL)	11	20.9 (16.4)	0 - 60

**Number of patients in whom data were available.*

WHAT THIS STUDY ADDS?

- A prolonged symptom-diagnosis interval and lack of correlation of disease-severity with history of receiving blood transfusion(s), indicates sub-optimal awareness of hereditary spherocytosis.
- The size of the spleen is an indicator of disease severity in hereditary spherocytosis.
- Post-splenectomy sepsis is not common if vaccination and prophylactic antibiotic guidelines are followed.

severe disease. Size of the spleen correlated with the disease severity. Earliest age at detection of cholelithiasis was 2.3 years. Growth failure was frequent in older children and those with severe HS.

Frequency of receiving blood transfusion(s) in 55% of patients was similar to previous Indian data [6] but higher than that in the West [10]. Relatively prolonged symptom-diagnosis interval and lack of correlation of disease severity with prior transfusions indicated sub optimal awareness regarding diagnosis and management. Predominance of severe disease (51%), as compared to the West (3-5%) is likely a referral bias as well as an indication that milder phenotype is being over looked [3]. Rarity of family history in comparison to the West (75%) was similar to previous Indian studies [Mumbai (16.6%), Delhi (28.6%), index-study (35%)] [2-4,6]. Fever, otherwise infrequent [1-3,8], was a presenting complaint in 65.5% of cases reported by Mehta, *et al.* [4]. A plausible explanation for the prevalence of undocumented fever (28%), described as 'warm to touch', could be hyperdynamic circulation secondary to anemia. Significance of a large spleen in HS has been debated. Bolton-Maggs, *et al.* opined splenomegaly to have little clinical significance beyond aiding diagnosis [2]. In contrast, our study proves an association between splenic size and disease-severity, as postulated previously by Perrotta, *et al.* [3]. Severe disease likely results in increased hemolysis and consequently, enlarged size of spleen. The incidence of PSS in our study (0.68 per 1000 patient-years) was similar to that reported in the West (0.69 per 1000 patient-years) [11]. The limitations of the study include predominantly retrospective data and limited number of splenectomized patients.

In conclusion, anemia, hepato-splenomegaly and jaundice are the typical clinical features of HS. A lack of family history is common in India. Regular monitoring for growth failure and cholelithiasis is warranted. PSS is uncommon, though can occur several years following splenectomy and necessitates vigilance.

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