RESEARCH PAPER

Growth Failure in Hereditary Spherocytosis and the Effect of Splenectomy

ANIRBAN DAS, DEEPAK BANSAL, AMITA TREHAN AND *REENA DAS

*From Pediatric Hematology/Oncology unit, Department of Pediatrics and *Department of Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Correspondence to:
Dr Deepak Bansal, Professor, Hematology-Oncology unit, Department of Pediatrics, Advanced Pediatrics Center, PGIMER, Chandigarh, India.
deepakbansaldr@gmail.com
Received: August 07, 2016;
Initial review: November 05, 2016;
Accepted: February 23, 2017.

Objectives: To analyze growth-failure and improvement, if any, following splenectomy in children with hereditary spherocytosis. **Methods:** Data collection from case-records (*n*=82) over 27-years (1985-2011). **Results:** Prevalence of stunting was 26%; 32% were underweight. Stunted children were older in age (*P*=0.006) and presented late (*P*=0.003). Splenectomy (*n*=26) improved anemia (*P*<0.001). However, height-for-age did not improve at 1-year, or 4.5-years (median) following splenectomy (*P*=1.0). Number of underweight children did not reduce at 1- (*P*=0.21), or 4.5-years (*P*=0.21) following surgery. **Conclusion:** Growth-failure is frequent in children with hereditary spherocytosis in India. Splenectomy corrected the anemia but failed to improve the growth.

Key words: *Hemolytic anemia, Stunting, Underweight*

Published online: March 29, 2017. PII:S097475591600058

Hereditary spherocytosis (HS) is an inherited membranopathy, where hemolysis results in anemia, jaundice and splenomegaly. Typical complications include cholelithiasis, hemolytic episodes and aplastic crises [1,2]. Growth-failure is described in severe HS; however, prevalence is not well-documented [3,4]. Splenectomy is indicated for severe HS, and is often considered for moderate disease [2,3]. It is reported to alleviate growth-failure [5,6]. However, there is a paucity of studies to corroborate this viewpoint [7]. The aim of this retrospective study was to assess the frequency of growth-failure in children with HS, and to evaluate improvement in growth, if any, following splenectomy.

METHODS

The study included children with HS, younger than 15 years, from a single center. Case-records over a period of 27-years (1985-2011) were retrieved. Diagnosis was based on the presence of spherocytosis in the peripheral smear, an increased osmotic fragility test and a negative direct-antiglobulin test, in the background of a suggestive clinical profile. Eosin-5'-maleimide binding assay was not available during the study-period [2]. Disease-severity was classified based on the British Committee for Standards in Haematology (BCHS) guidelines, including hemoglobin, bilirubin and reticulocyte count [1,5]. Records of height (Herpenden stadiometer, accuracy 1mm) and weight (digital scale, accuracy 100 g) were retrieved. Body mass index (BMI) was calculated. *Z* scores for height, weight and BMI were derived using WHO AnthroPlus [8]. Stunting was defined as a height-for-age *Z* score <-2SD. A weight-for-age (<10-years) or BMI-for-age (>10-years) *Z* score <-2SD defined 'underweight'. Stunting or underweight was considered 'severe' when the *Z* score was <-3SD [8,9]. In splenectomized patients, repeated-measure-ANOVA was utilized to compare the *Z* scores at 3-points: initial presentation, 1-year following surgery, and at the last clinic visit. Statistical analysis was performed using SPSS v20.0 (IBM). The Institutional Ethics Committee approved the study.

RESULTS

Records of 82 children were retrieved for analysis. The mean age (SD) was 6.7 (2.8) years (range 0.08,15 y). Forty-two (51%) had severe disease; 18 (22%) moderately severe, 16 (20%) moderate and 6 (7%) had a mild disease. Records of weight were available for 78 children; 25 (32%) were underweight and 10 (12.8%) were severely underweight. Among the 25 underweight children, 22 (88%) had moderate/moderately severe, 2 (8%) had moderate and 1 (4%) had mild disease. Records of height were available in 69 children; 18 (26%) were stunted; 8 (11.6%) were severely stunted. Among the 18 stunted children, 16 (89%) had moderately severe/severe HS, while 2 (11%) had moderate HS. Underweight children had a lower hemoglobin (*P*=0.037) and a more

severe disease (P<0.001). Children who presented at a later age were more likely to be stunted (P=0.006). The proportion of stunted children progressively increased across the age groups: <4 years (3/17; 17.6%), 4-8 years (5/25; 20%), 8-12 years (6/23; 26%) and >12 years (4/4; 100%) (P=0.006). Symptom-interval was greater (P=0.003) for children with stunting. In addition, they had a severe disease (P=0.01) (***Table* I**). The median number of transfusions were not different in children who had normal weight and height in comparison to those who had growth failure (***Table* I**).

Twenty six (31.7%) children had a total splenectomy at a mean (SD) age of 7.9 (3.7) years. The median (range) follow-up was 4.5 (0-3, 19) years. The mean (SD) hemoglobin [6.8 (1.6) g/dL] improved to 12.1 (2.5) g/dL following splenectomy (P<0.001). The pre- and post-splenectomy anthropometric data were available for 24 and 23 children, respectively. At diagnosis, 9/24 (37.5%) children were stunted and 10/24 (41.7%) were underweight. The prevalence of stunting was nearly similar at 1-year following surgery (9/23, 39.1%) (P=1.0), and did not reduce to a significant extent at the last follow-up visit (5/23, 21.7%; P=0.34). Reduction in the number of underweight children (10/24, 41.7%) was not statistically significant a year following surgery (5/23, 21.7%; P=0.21); prevalence remained the same at the last follow-up visit (5/23, 21.7%) (P=0.21).

The comparison of Z-scores for height and BMI at the stated time-points is illustrated in ***Fig. 1***. Repeated-measures-ANOVA failed to demonstrate a significant increase in Z scores for height (P=0.84) or BMI (P=0.14) following splenectomy. Even in children who underwent splenectomy at an earlier age (<6 years), the height-for-age failed to improve significantly [mean (SD) Z scores at baseline: -1.6 (1.3); 1-year following splenectomy: -1.4 (1.8); P=0.6].

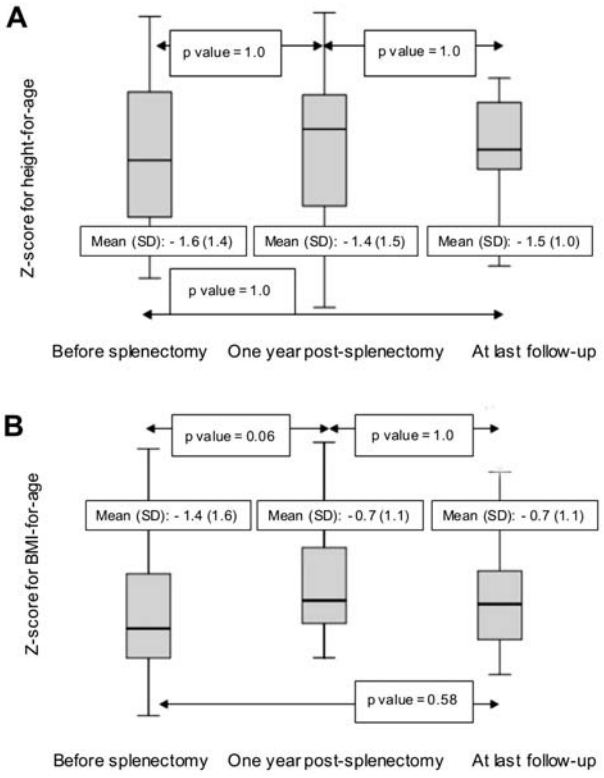

FIG. 1 *Comparison of Z scores before splenectomy, one year following surgery, and at the last follow-up visit, for (a) height-for-age, and (b) BMI-for-age, in children with hereditary spherocytosis.*

DISCUSSION

The current study reports 32% and 26% children with HS to

TABLE I VARIABLES INFLUENCING GROWTH FAILURE IN CHILDREN WITH HEREDITARY SPHEROCYTOSIS

Parameters	*All children (n=82)*	**Records of weight available(n=78)*			**Records of height available(n=69)*		
		Underweight (n= 25)	*Normal weight (n=53)*	*P value*	*Stunting (n=18)*	*No stunting (n=51)*	*P value*
$Age (y); mean (SD)	6.7 (2.8)	7.6 (3.9)	5.9 (3.5)	0.055	8.9 (3.8)	6.3 (3.2)	0.006
Females; No. (%)	28 (34)	12 (48)	13 (24.5)	0.06	5 (27.8)	14 (27.4)	0.55
#Symptom-onset to diagnosis interval (y)	2.0 (0.17-4)	2.5 (0.25,7.25)	1.0 (0.2,3.5)	0.115	6.5 (1.93-9.25)	2 (0.18,3)	0.003
$Hemoglobin (g/dL)	76 (24)	6.8 (2.5)	8.1 (2.1)	0.037	7.3 (2.2)	7.9 (2.4)	0.87
Severe/moderately severe disease; No. (%)	60 (73)	22 (88)	18 (34)	<0.001	16 (89)	33 (64.7)	0.01
#Number of transfusions prior to presentation	1.0 (0-2)	1.0 (0.2)	1.0 (0,2)	0.59	1.5 (0,2)	1.07 (0,2)	0.18

**Data pertains to details recorded at the first visit to the clinic; #Median (IQR); $Mean (SD).*

WHAT THIS STUDY ADDS?

- Frequency of underweight (32%) and stunting (26%) in children with hereditary spherocytosis in India was similar to the prevalence in the community.
- Underweight children had severe disease and a lower hemoglobin. Stunted children were older in age, had severe disease and a prolonged symptom interval.
- Splenectomy failed to alleviate growth-failure despite correction of anemia; a continuing environment of pre-existing sub-optimal nutrition could have blunted the growth-spurt.

be underweight and stunted, respectively. Underweight children were more likely to have either severe/moderately severe disease with a lower hemoglobin. Stunting was more frequent in children with severe disease, although the hemoglobin was similar to those with normal height. Hemoglobin improved significantly following splenectomy, yet growth failed to improve significantly.

The main limitation of the present study is the retrospective nature of the data. The anthropometry, though recorded in the clinic by trained health care workers, would have operator- or instrument-related bias over the long study period. In addition, the evaluation and the follow-up is likely to be non-uniform. Moreover, there were no controls to compare the growth pattern.

Severe HS, without regular transfusions or splenectomy, results in growth retardation and delayed sexual maturation [10]. Long standing anemia is the plausible cause of failure to thrive. A lack of acuity of symptoms contributes to delay in seeking healthcare, and exacerbates the growth-failure [4]. Splenectomy corrects anemia and the compensatory exuberant erythropoiesis that causes growth-failure. Bader-Meunier, *et al*. [7] reported an increase in height equivalent to 2SD in the growth curve following surgery in five pre-pubertal children with HS. Sub-optimal growth is often considered a relative indication for splenectomy in children with HS [5,11].

It was intriguing to observe a lack of improvement in growth following splenectomy, particularly as the hemoglobin levels had improved significantly. There could be several contributory factors. The size of the cohort could be a limiting factor. Mechanisms beyond anemia and chronic tissue hypoxia could be contributory. Though formal iron studies were not conducted, median number of transfusions did not differ in children with and without growth-failure, therefore, transfusional iron overload is unlikely. However, non-transfusional overload related to heterozygous state for the hemochromatosis gene has been previously reported in children with HS [12]. We could not test for this in this retrospective cohort. Interestingly, it was noted that the prevalence of growth-failure was similar to that previously reported from the community (underweight: 24-29%; stunting: 38%) [13,14]. Indeed, factors responsible for undernutrition in the community, including poverty, malnutrition and recurrent infections, would have likely contributed to the growth-failure in this cohort of patients with HS as well. We hypothesize that a continuing environment of pre-existing sub-optimal nutrition could have blunted a likely growth-spurt following splenectomy.

In conclusion, growth-failure was frequent in children with severe HS and in older children with delayed presentation. Notwithstanding the correction of anemia, splenectomy failed to alleviate growth-impairment at a median follow-up of 4.5-years. Given the risks of sepsis and thrombosis following splenectomy, studies performed on larger cohorts need to evaluate factors contributing to impaired growth, and to evaluate if growth-failure by itself should be a robust indication for splenectomy in similar settings [15].

Contributors*: DB: planned the study. AD: collected the data and prepared the manuscript; AT: contributed to patient enrollment and RD: reported the hematology. All authors contributed to manuscript writing and its final approval.*
Funding*: None;* Competing interest*: None stated.*

REFERENCES

1. Bolton-Maggs PH, Langer JC, Iolascon A, Tittensor P, King MJ. General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update. Br J Haematol. 2012;156:37-49.
2. Joshi P, Aggarwal A, Jamwal M, Sachdeva MU, Bansal D, Malhotra P, *et al*. A comparative evaluation of Eosin-5-maleimide flow cytometry reveals a high diagnostic efficacy for hereditary spherocytosis. Int J Lab Hematol. 2016;38:520-6.
3. Gallagher PG, Glader B. Hereditary spherocytosis, hereditary elliptocytosis, and other disorders associated with abnormalities of the erythrocyte membrane. *In*: Greer JP, Foerster J, Rodgers GM, Paraskevas F, Glader B, Arber DA, *et al.*, editors. Wintrobe's Clinical Hematology. 12th ed. Philadelphia: Lippincott Williams and Wilkins; 2009: p. 911-20.

4. Das A, Bansal D, Das R, Trehan A, Marwaha RK. Hereditary spherocytosis in children: Profile and post-splenectomy outcome. Indian Pediatr. 2014;51:139-41.
5. Schilling RF. Risks and benefits of splenectomy versus no splenectomy for hereditary spherocytosis - a personal view. Br J Hematol. 2009;145:728-32.
6. Diamond LK. Splenectomy in childhood and the hazard of overwhelming infection. Pediatrics. 1969;43:886-9.
7. Bader-Meunier B, Gauthier F, Archambaud F, Cynober T, Miélot F, Dommergues JP, *et al*. Long-term evaluation of the beneficial effect of subtotal splenectomy for management of hereditary spherocytosis. Blood. 2001;97:399-403.
8. WHO AnthroPlus for Personal Computers: Software for Assessing Growth of the World's Children and Adolescents [computer program]. Version 1.0.4. Geneva: World Health Organisation. Available from: *http://www.who.int/growthref /tools/en/*. Accessed March 10, 2016.
9. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: International survey. BMJ. 2007;335:194.
10. Eber S, Lux SE. Hereditary spherocytosis - defects in proteins that connect the membrane skeleton to the lipid bilayer. Semin Hematol. 2004;41:118-41.
11. Englum BR, Rothman J, Leonard S, Reiter A, Thornburg C, Brindle M, *et al*. Hematologic outcomes after total splenectomy and partial splenectomy for congenital hemolytic anemia. J Pediatr Surg. 2016;51:122-7.
12. Fargion S, Cappellini MD, Piperno A, Panajotopoulos N, Ronchi G, Fiorelli G. Association of hereditary spherocytosis and idiopathic hemochromatosis. A synergistic effect in determining iron overload. Am J Clin Pathol. 1986;86:645-9.
13. Bharti B, Shava U. Changing spectrum of malnutrition in urban cities. Indian Pediatr. 2011;48:910.
14. Rapid Survey on Children 2013-2014. India Factsheet. Ministry of Women and Child Development. Government of India. Available from: *http://wcd.nic.in/issnip/National_ Fact%20sheet_RSOC%20_02-07- 2015.pdf.* Accessed June 14, 2016.
15. Das A, Bansal D, Ahluwalia J, Das R, Rohit MK, Attri SV, *et al*. Risk factors for thromboembolism and pulmonary artery hypertension following splenectomy in children with hereditary spherocytosis. Pediatr Blood Cancer. 2014;61:29-33.