ORIGINAL ARTICLE

Hereditary Spherocytosis : A Clinical Experience

by

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Abstract

Although hereditary spherocytosis is a common cause of hemolytic anemia among whites of Northern European descent, it is uncommon in Asia. In the past 8.5 years (from December 1978 to June 1987), we found only six cases of hereditary spherocytosis. They were 3 males and 3 females, and their ages ranged from 3 months to 8 years, with a mean age of 3.3 years. The most common presenting complaint was anemia (6 cases) followed by jaundice (4 cases) and splenomegaly (4 cases). Other symptoms were fever, abdominal pain and hepatomegaly. The mean hemoglobin concentration of these patients was 7.5 g/dl, in which 2 patients had severe anemia (less than 6 g/dl). Reticulocyte count ranged from 1.9% to 10% (mean 5.9%). All patients were found to have spherocytosis in their peripheral blood smears and an increased red blood cell fragility. Splenectomy was performed in one patient. There was no significant complication after operation in a 7-month follow up. The clinical manifestation returned to normal and the mean hemoglobin concentration increased. The existence of hereditary spherocytosis could not be proven in almost all parents of the patients. Based on this fact, is 'congenital spherocytosis' a more suitable term instead of hereditary spherocytosis?

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Introduction

Hereditary spherocytosis is a condition of abnormal red cell morphology seen microscopically as erythrocytes that have lost the central pallor characteristic of the biconcave disc shape. The cells are instead rounder, more fragile, and susceptible to extravascular hemolysis in the spleen. As a result patients with this disorder suffer from variable degrees of anemia, splenomegaly and acholuric jaundice (Miller et al., 1984). This familial hemolytic anemia has been variously termed as congenital microspherocytosis, familial jaundice, and familial acholuric jaundice, although the term 'hereditary spherocytosis' best delineates the major aspects of the disease: the familial pattern and the presence of spherocytes (Neerhout, 1983). Hereditary spherocytosis affects all races, but from the number of reported cases it seems to be more common in individuals of Northern European origin. The prevalence is about 220 cases per million (Oski and Naiman, 1982). In the United States the incidence is about 1 in 5000 and has been diagnosed at all ages, from 30 hours to 77 years. It has been found infrequently in blacks and members of other racial groups (Miller et al., 1984). The pattern of inheritance is autosomal dominant with 50% of siblings and offspring of the propositus being affected regardless of sex. However, in approximately 10% to 25% of cases, neither parent can be shown to have the defect (Lux and Wolfe, 1980 and Miller et al., 1984). From linkage studies, the dominant spherocytosis gene may be found on chromosome 6 or chromosome 12 (Kimberling et al., 1978 and Miller et al., 1984).

The purpose of this paper is to report a clinical experience of hereditary spherocytosis in children, in a 8.5 year period.

Report of Cases

In the past 8.5 years (from December 1978 to June 1987), we found only 6 cases of hereditary spherocytosis. The details of six cases are recorded in Table 1.

Table 1 : *Clinical findings*

Case	I	II	III	IV	V	VI
Age	8 yrs	4 yrs	3½ yrs	6 mos	3 mos	3½ yrs
Sex	F	M	M	M	F	F
Signs	Fever Abd. pain	Fever Abd. pain	Fever Pallor	Jaundice Pallor	Jaundice	Pallor
Symptoms	Anemia Jaundice	Anemia Jaundice	Anemia -	Anemia -	Anemia Jaundice	Anemia Jaundice
* Spleen	S II	S II	S II	-	-	S
* Liver	4 cm	3 cm	-	-	-	3 cm

There were 3 males and 3 females, and their ages ranged from 3 months to 8 years, with a mean age of 3.3 years. Anemia and jaundice were the most common complaints and occurred in 100% and 67% of the patients respectively. Four cases (67%) had a palpable spleen. The incidence of splenomegaly increased as the age advanced. The liver was enlarged in 3 cases. Two cases (case 1 and 2) came with fever, abdominal pain, splenomegaly and severe anemia that required blood transfusion. It had been suspected as an aplastic crisis. Unfortunately the bone marrow aspiration examinations were not documented.

Table 2 : *Laboratory findings*

Case	I	II	III	IV	V	VI
Hb.	5.0	3.2	9.7	10.3	8.8	7.9
Ery.	1980000	1430000	3210000	3630000	3890000	2760000
Retic.	20 %	19 %	95 %	-	-	100 %
Leuco.	18,100	13.300	9,800	8,700	7,400	11,200
Platelet	Suffic.	Suffic.	Suffic.	Suffic.	Suffic.	Suffic.
Spherocyte	(+)	(+)	(+)	(+)	(+)	(+)
Coomb's	(-)	(-)	(-)	(-)	(-)	(-)

The details of the laboratory findings are recorded in table 2. The mean hemoglobin concentration of these patients was 7.5 g/dl, in which 2 patients had severe anemia (less than 6 g/dl). Reticulocyte count was recorded only in 4 cases, it ranged from 1.9% to 10% (mean 5.9%). All of the patients were found to have spherocytosis in the peripheral blood smears and an increased red blood cell fragility (figure 1). Coomb's test were negative in all patients.

All parents were studied for the existence of hemolytic anemia characterized by the presence of spherocytes, and an increased osmotic fragility. Almost in all parents the existence of hereditary spherocytosis could not be proven, except that one mother (case 4) had an increased osmotic fragility without any evidence of spherocytes in her peripheral blood smear (table 3).

The course of the disease had been followed in a period of time, varying from 3 months to 8.5 years (mean 31.8 months) (table 4).

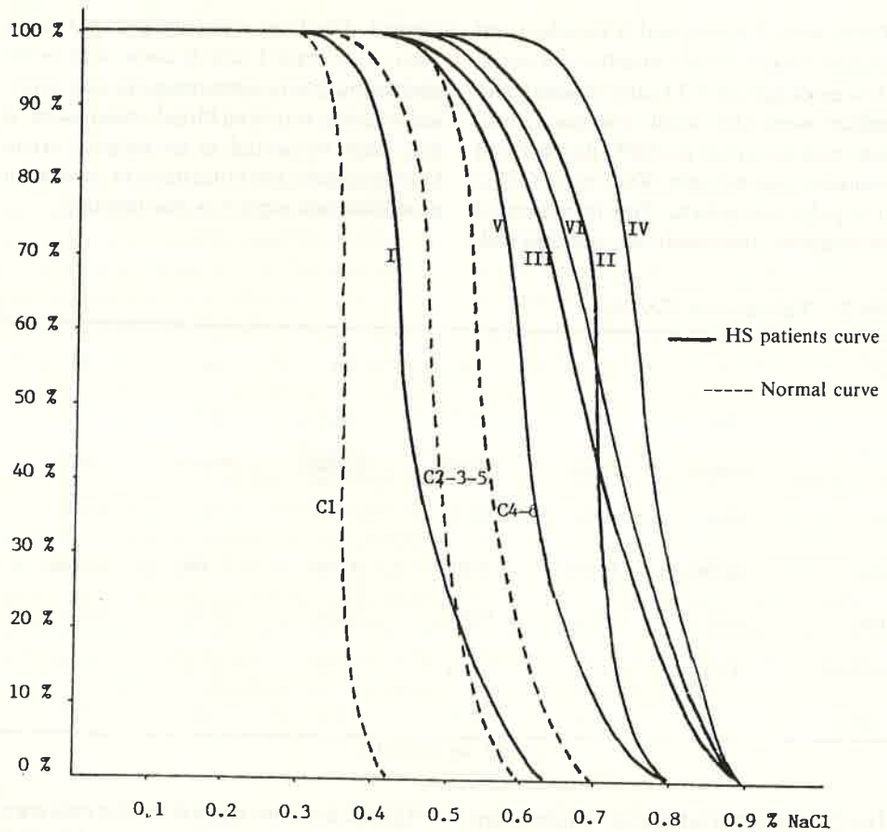

Figure 1 : *Osmotic fragility curve*

Table 3 : *Family study*

Case	I	II	III	IV	V	VI
Father :						
Hb.	13.7	12.9	15.5	15.3	15.3	14.1
Sphero.	(-)	(-)	(-)	(-)	(-)	(-)
O.F. Min.	0.55(0.55)	0.60(0.55)	0.50(0.50)	0.55(0.55)	0.50(0.50)	0.55(0.55)
Max.	0.20(0.30)	0.30(0.30)	0.30(0.30)	0.30(0.30)	0.25(0.30)	0.30(0.30)
Mother :						
Hb.	13.1					
Sphero.	(-)	(-)	(-)	(-)	(-)	(-)
O.F. Min.	0.55(0.55)	0.55.(0.55)	0.55(0.50)	0.70(0.55)	0.55(0.50)	0.55(0.55)
Max.	0.30(0.30)	0.20(0.30)	0.20(0.30)	0.25(0.30)	0.20(0.30)	0.30(0.30)

Table 4 : *Course of the disease*

Case	I	II	III	IV	V	VI
Follow up	102 mos	44 mos	24 mos	10 mos	8 mos	3 mos
Mean Hb.	10.0	7.9	8.5	9.5	9.0	7.3
Tansfusion	2 ×	13 ×	20 ×	0 ×	4 ×	0 ×
Splenectomy	(-)	(+)	Candidate	(-)	(-)	(-)
Follow up	-	7 mts	-	-	-	-
Mean Hb.	-	12.8	-	-	-	-
Transfusion	-	0	X	-	-	-

The hemoglobin concentration ranged from 7.3 g/dl to 10.0 g/dl (mean 8.7 g/dl). Two patients (case 4 and 6) did not need any transfusion in a 3 and 10 months follow up. Two other patients (case 2 and 3) required frequent transfusions (4 and 10 times a year). Splenectomy was performed in one patient (case 2). There was no significant complication after operation in a 7-month follow up. The clinical manifestations returned to normal and the mean hemoglobin concentration increased from 7.9 g/dl to 12.8 g/dl without any transfusion. The other patient (case 3) would be a candidate for splenectomy because of transfusion dependence and his age is already 5.5 years now.

Discussion

It is generally agreed that in hereditary spherocytosis the membrane of the red cell is defective. It is now known that within the classic categories of hereditory spherocytosis are individuals with different membrane skeleton protein abnormalities and different severity of anemia. The majority of patients with hereditary spherocytosis have red cells that range from discocytes to stomatocytes and only a small number have true spherocytes. These individuals have a compensated or mild anemia, and the molecular defect of their cells is not yet understood. In contrast, a small number of individuals with hereditary spherocytosis have marked spherocytosis and fragmented cells in their peripheral blood and have severe hemolysis. Within this group, at least two different molecular defects have been described. One defect is a quantitative decrease in red cell spectrin and the other is qualitative change in the spectrin molecule resulting in abnormal protein-protein associations, which produce a weakened membrane skeleton. Both the quantitative and qualitative defects in spectrin appear to give rise ro membrane instability and presumably the hemolysis (Chasis and Shohet, 1985). The hereditary spherocytic red cell has a near to normal membrane surface area when it is released from the bone marrow, but as the membrane surface is lost and the surface to volume ratio declines, it becomes progressively more spherical and less flexible. This change becomes critical when the hereditary spherocyte is no longer sufficiently deformable to squeeze through the narrow fenestrations that separate the splenic cords and sinuses (Lux and Wolfe, 1980).

Unsplenectomized patients with hereditary spherocytosis often show two populations of cells on peripheral blood smears and osmotic fragility tests, a minor population of hyperchronic 'microsherocytes' that is very fragile on the unincubated osmotic fragility and a major population whose fragility may be only slightly greater than normal. This phenomenon produces a specific osmotic fragility curve, not only shifted but typically demonstrates a tailing effect due to the small population of highly osmotically fragile cells. This highly sensitive population represents cells which have been conditioned by passage through the spleen (Lux and Wolfe, 1980, Miller er al., 1984 and Neerhout, 1983).

The disease is quite variable in its severity, however, most patients will, at some time, manifest one or more of the cardinal features of the disease: anemia, jaundice and splenomegaly (Lux and Wolfe, 1980). Anemia is variable: some patients are able to maintain a normal hemoglobin level while others may require frequent transfusions. Typically the anemia is mild infrequently with chronic levels of hemoglobin below 7 g/dl (Neerhout, 1983). Jaundice is usually intermittent and often occurs during viral infections when there may be splenic hyperfunction and increased hemolysis. Moderate (2 to 6 cm) splenomegaly appears in 50 per cent of children during infancy and in 75 to 95 per cent of older children and adults. The size of the spleen does not correlate with the severity of the disease (Lux and Wolfe, 1980). The most common presenting complaint in our study is anemia (100%) followed by jaundice and splenomegaly (67% each). The age at presentation correlates inversely with the severity of laboratory features. Hence, patients in infancy or early choldhood are often moderately anemic (hemoglobin = 8 to 11 g/dl) whereas older children and adults frequently have a compensated hemolysis and little or no anemia at all (hemoglobin 10 g/dl) (Lux and Wolfe, 1980; Oski 1982). Besides the two cases who were suspected as having an aplastic crisis, the mean hemoglobin concentration at presentation in our study was 9.2 g/dl.

At any age the reticulocyte count is usually greater than 8 per cent (Lux and Wolfe, 1980), but may range from 2% to over 90% (Miller et al., 1984). The peripheral smear classically contains many spherocytes. However, in 20 to 25 per cent of patients the typical conditioned microspherocytes are relatively infrequent and the smear may be considered normal even by experienced observers. The most useful diagnostic test for hereditary spherocytosis is the osmotic fragility test. When performed without preincubation the test quantitates the proportion of splenic conditioned cells in the circulation. However, close to 25 per cent of patients will have a normal unincubated osmotic fragility test prior to splenectomy, particularly the mildly affected patients and their relatives who are the most difficult to diagnose. The incubated osmotic fragility test, in contrast, is almost always positive since incubation conditions 'stress' the erythrocyte and enhance the fragmentation defect (Lux and Wolfe, 1980). The presence of an abnormal osmotic fragility curve tends to verify the presence of spherocytes but like the blood smear it is not entirely diagnostic for hereditary spherocytosis (Neerhout, 1983).

The erythrocyte autohemolysis test parallels in many ways the action of the spleen on hereditary spherocytic cells. In performing the test, red cells are allowed to incubate at 37°C for 48 hours in their own plasma under sterile conditions. As in the osmotic fragility test, the autohemolysis test can be cosidered as a confirmatory test for hereditary spherocytosis but is not in itself diagnostic. The results are variable from laboratory to laboratory, and in some laboratories large numbers of false positive are seen. In addition, the test is not specific (Lux and Wolfe, 1980). The correction of autohemolysis by addition of glucose is characteristic of hereditary spherocytosis and generally not seen in other hemolytic states with spherocytes (i.e., autoimmune hemolytic anemia and ABO incompatibility) (Neerhout, 1983). It is also of value in confirming the diagnosis in patients with hereditary spherocytosis and normal incubated osmotic fragility (Fukagawa et al., 1979).

Since there is no single pathognomonic test for hereditary spherocytosis, the diagnosis depends largely on demonstration of (1) microspherocytes on blood smear, (2) dominant pattern of inheritance, (3) increased osmotic fragility accentuated by 24 hour incubation at 37°C, and (4) increased autohemolysis after 48 hour sterile incubation at 37°C with correction by addition of glucose or ATP (Neerhout, 1983).

A sudden fall in hemoglobin level may be associated either with episodes of increased red cell destruction (hemolytic crisis) or decreased red cell production (aplastic crisis). The most frequent crisis in hereditary spherocytosis is the hemolytic crisis. Fortunately, hemolytic crises are rarely severe. They usually occur with febrile viral infections and are characterized by an increase in the degree of jaundice, reticulocytosis and splenomegaly.

The dangerous crisis in hereditary spherocytosis is the aplastic crisis. These crisis are less frequent clinically, but are more serious since severe anemia frequently occurs, particularly in children. It is usually heralded by fever, vomiting, abdominal pain, pallor and symptoms of anemia. Since all marrow elements can be involved in the hypoplasia, peripheral reticulocytopenia, leukopenia as well as thrombocytopenia may be

noted. Aplastic episodes are generally self-limited and on the average last 10 to 14 days.

Another type of crisis in hereditary spherocytosis is the megaloblastic crisis that occurs if the intake of folic acid is inadequate to support the hyperplastic bone marrow associated with hereditary spherocytosis (Lux and Wolfe et al., 1980, Miller, 1984 and Neerhout, 1983).

Individuals born with moderate to severe hemolysis should undergo splenectomy when they are old enough to withstand the procedure. Upon removal of the spleen, their red cell survival returns near to normal and they no longer are at risk for the develompent of on aplastic or megaloblastic crisis. Furthermore, the rate of gallstone formation is greatly reduced. However, to allow time of maturation of the immune system, splenectomy should be postponed until the child passes the age of 5 years because then the incidence of on overwhelming post-splenectomy infection by pneumococcal or H. influenzae organisms decrease approximately by 20 per cent in patients over the age of 4 years (mortality 0.6 per cent) compared to mortality at infancy. A second reason for postponing splenectomy is that the operation is technically easier and therefore safer in older patients (Chasis and Shohet, 1985). There is no evidence that further delay is useful and it may even be harmful since the risk of gallstones increase dramatically after the age of 10 years. Individuals with hereditary spherocytosis have a 5 per cent incidence of stone formation under the age of 10 years, a 40 to 50 per cent incidence between 10 and 50 years of age, and an incidence of approximately 85 per cent after the age of 50; the incidence of symptoms related to these stones is probably about 40 per cent. Occasionally transfusion dependence, recurrent aplastic crises, skeletal deformities, or delayed growth will prompt earlier splenectomy, but this should not be done before the age of three years (Lux and Wolfe, 1980). Thus, the infant and growing child must be supported until they are old enough for splenectomy. During the neonatal period, these babies are at appreciable risk for the development of kernicterus. Their bilirubin conjugation is impaired because of transiently reducted glucuronyl transferase activity. If the indirect bilirubin is higher than 20 mg/ml, they require exchange transfusion, and phototherapy may also be used. With milder elevations of bilirubin, phototherapy alone can be used. Infants and children should be observed at least every 3 months. During this time, they may require transfusions. In addition, they should be protected from aplastic crisis as carefully as possible. There patients, except those on formula feedings, should therefore be given supplemental folate, 1 mg/day, and any infection should be diagnosed and treated as quickly as possible (Chasis and Shohet, 1985).

In a patient with well compensated hemolysis, it is not easy to decide at what point to recommend splenectomy. Since splenectomy nearly normalized red cell survival, it removes the risk of aplastic crisis and greatly reduces the rate of gallstone formation. Therefore it is advisable to perform splenectomy in patients who have no unrelated contraindication to surgery (Chasis and Shohet, 1985). Splenectomy almost uniformly corrects the anemia and markedly diminished the hemolytic state. The red cell survival is still 22 per cent shorter than normal, attesting to the ongoing red cell defect. This mild degree of shortened life-span is easily compansated for by the marrow, and anemia does not result (Neerhout, 1983). The continued absence of splenic function can be confirmed by the sustained presence of Howell-Jolly bodies on the peripheral blood smear (Chasis and Shohet, 1985 and Lux and Waefe, 1980). Failure to do so should suggest the possibility of (1) accessory spleen, (2) a second defect in addition to hereditary spherocytosis (associated red cell enzyme deficiency, hemoglobinopathy, and thalassemia have been noted), and (3) a defect other than hereditary spherocytosis causing the sphereocytosis (Neerhout, 1983). After surgery, the parents should be carefully in formed about the risk of infection and instructed to call their physician immediately at any sign of infection (Chasis and Shohet, 1985).

As it has been mentioned before, the defect is believed to be inherited as a mendelian dominant, although in 10 to 25 per cent of cases this may not be demonstrable in either parent. It is interesting to notice that we could not find any genetic correlation in all of our cases, a phenomenon that had also been reported in Taiwan (Liaw et al., 1985). Such cases could be due to spontaneous mutation, variable expressity, or an autosomal recessive form of the disease (Miller et al., 1984). It has been found that hereditary spherocytosis is not a single disease, but is rather a term used to describe a variety of different molecular lesions of the erythrocyte membrane skeleton with similar clinical manifestation (Burke and Shotton, 1983). Based on these facts, is 'congenital spherocytosis' a more suitable term instead of hereditary spherocytosis?

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