SPHEROCYTIC ANEMIA IN THE NEWBORN *

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Jaundice in the newborn period is a frequently occurring problem, but neonatal icterus continues to present difficulties both in diagnosis and management. Among the considerations in the differential diagnosis of neonatal icterus is the not too commonly encountered entity of hereditary spherocytosis. In a recent review of the literature, only 18 cases of hereditary spherocytosis in the neonatal period have been described [1,2,3] since the original paper was published by Vanlair and Masius in 1871. [4] As spherocytosis is the most frequent type of hemolytic anemia, the physician must be aware of its occurrence in the newborn. The present communication describes a case of spherocytosis occcurring in the neonatal period.

Case Report

F. A., a white male, delivered to a 21 year old gravida II, para I, blood group O, Rhesus positive, serology negative, following an uncomplicated 6 hour and 45 minutes labor. The delivery was spontaneous and the infant was given an Apgar score of 8. On physical examination, the patient was found to be well-developed with a birth weight of 6 pounds, length 19 inches. He had a lusty cry, good suck and Moro reflexes. Heart and lungs were considered normal, the abdomen soft and liver and spleen not palpable.

At age 17 hours the patient was noted to be clinically icteric. Detailed questioning of the father revealed that he had recurrent episodes of jaundice during early childhood and had undergone splenectomy at age 7 years without being made fully aware of the nature of his illness. Furthermore, other members of the paternal family had episodes of unexplained jaundice, cholelithiasis and cholecystectomy, as well as splenectomy (see fig. 1). With such a significant family history, the possible causes of familial icterus were considered and additional laboratory studies were performed on the patient revealing (table 1): hemoglobin 13.6 Gm. per 100 ml.; hematocrit 43 %; blood group O; Rhesus positive; Coombs negative; blood culture no growth in 24 and 48 hours; erythrocytes on peripheral smear were described as microcytic and polychromatic; the serum bilirubin totaled 9.7 mg. per 100 ml., with direct 0.35 mg. and indirect fraction 9.35 mg. Follow-up studies showed the bilirubin to rise to 12.6 mg. total with indirect 12.15 mg. at 38 hours of age. It reached the high point at 61 hours when total bilirubin was 17.20 mg., indirect 16.95 mg.; hemoglobin was 12.6 Gm. and the hematocrit 36 %.

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TABLE 1

LABORATORY FINDINGS OF NEWBORN INFANT, HIS FATHER AND ELDER SIBLING WITH HEREDITARY SPHEROCYTOSIS

	G.E.A. (FATHER)	E.T.A. (ELDER SIBLING)	F.J.A. (PATIENT)
Hemoglobin Gm./100 ml.	15.4	14.4	10.2
Hematocrit	47	39	31
Red blood cells millions/c.mm.	4.17	4.18	2.37
Coombs test	Negative	Negative	Negative
Bilirubin mgm./100 ml. Total	3.00	0.30	17.20
Direct	0.80	0.10	1.00
Indirect	2.20	0.20	16.20
Reticulocytes/100 rbc	1.2	0.9	2.5
Spherocytes/100 rbc	19.5	18.0	22.0
Blood Type and Rh	0 Pos	0 Pos	0 Pos
Hemoglobin Electrophoresis	A	A	A and F
SGO-T	16	—	24
Serology	Negative	Negative	Negative

The diagnosis of spherocytosis was confirmed by positive red cell fragility tests in the patient, his elder sibling and father (table 2).

The infant continued to nurse well and weight stabilized at 5 pounds 14 cunces. At age 83 hours the bilirubin was 16.0 mg. total with indirect 15.9 mg. By the time of discharge at age 6 ½ days, the bilirubin had fallen to total of 11.2 mg. with indirect being 10.2 mg.; thymol turbidity was 1.2 units and the serum transaminase (SGOT) was 17 units.

Following discharge the infant continued to eat well and gain weight at an acceptable rate. He was breast-fed until the age of 2 months when he

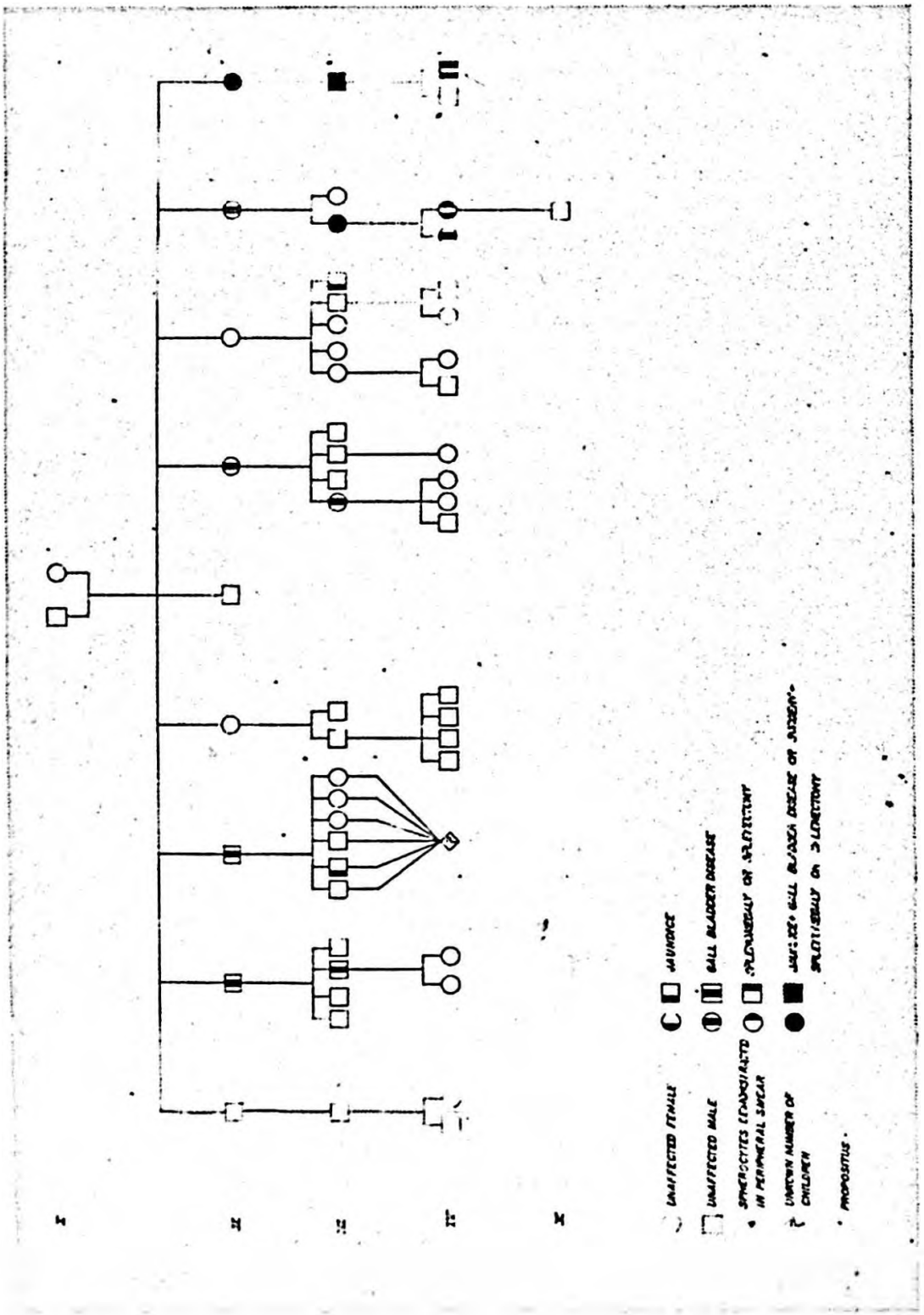

Fig. 1. Five generation family pedigree containing over 57 members. Fifteen demonstrated evidence of spherocytosis.

was changed to an evaporated milk formula and continued to do well. The patient was followed in the out-patient department with serial blood counts and examinations. Roentgenography of skull showed no bony abnormalities. At age 4 weeks when hemoglobin fell to 7.7 Gm. per 100 ml., hematocrit 23 %, RBC of 2,400,000 and only 2 % reticulocytes, it was decided to give him a booster transfusion. He was transfused with fresh whole blood at 20 cc./kilogram, and received a total of 75 cc. of whole blood. At age 8 weeks, a follow-up hemoglobin had fallen to 7.3 Gm. with a corresponding fall in RBC and hematocrit and 1 % reticulocyte count. At this time another booster transfusion was given; the patient received a total of 90 cc. of fresh whole blood without reaction. Total bilirubin prior to this transfusion was 0.15 mg. per 100 ml., and after transfusion the hemoglobin rose to 9.6 Gm. and has remained between 8 and 9 Gm. since then. The most recent examination was at age 7 months when the reticulocyte count was 3 per cent.

On follow-up physical examinations, the patient's growth and development have been normal, he appears active, has had no clinical icterus and only slight pallor has been observed. His liver has not been palpable, but the splenic tip has been felt since the age of 3 $^1/_2$ months.

A detailed family history was obtained from the grandmother of the patient. The family pedigree is depicted in fig. 1 and contains 57 known members in five generations. There are a number of unknown members who have not been shown. Gallbladder disease is the most commonly appearing feature with jaundice and splenomegaly less frequently encountered. Apparently anemia and its associated signs and symptoms have not been recognized in this family except for the propositus, which is in contrast to most other published reports of hereditary spherocytosis. [2,8,9]

TABLE 2

INCREASED RED CELL FRAGILITY IN HYPOTONIC SALINE DEMONSTRATED IN THREE CASES OF HEREDITARY SPHEROCYTOSIS

	CONTROL	G.E.A. (FATHER)	E.T.A. (ELDER SIBLING)	F.J.A. (PATIENT)
Saline concentration at which red cell lysis begins	0.48%	0.57%	0.51%	0.60%
Saline concentration at which red cell lysis completed	0 30%	0.33%	0.36%	0.36%

The only other members of the family to be examined by us were the patient's father, age 24, and elder brother, age 3, whose

peripheral smears revealed spherocytosis. Increased red cell fragility was also demonstrated. Table 2. A subsequent work - up of the father revealed radiolucent gall - stones which were removed and demonstrated to be composed mainly of bilirubin.

Discussion

This form of hemolytic anemia is characterized by spherocytosis, diminished red corpuscle resistance to hypotonic saline solutions, a variable degree of anemia of a hemolytic type and splenomegaly. The disease entity is known by a variety of names, each of which describes certain of its characteristics and obscures others. Congenital hemolytic jaundice, familial hemolytic jaundice, acholuric jaundice, congenital hemolytic anemia, hereditary spherocytic anemia, hereditary spherocytosis, familial hemolytic anemia and global - cell anemia have all been used to name this disease complex.[5]

The hereditary aspects of this disease have been intensively studied.[5,6,7] The disease is felt to be inherited as a Mendelian dominant gene, which by definition indicates transmission by either one of the parents. Havever, in testing large families, there often seems to be a paucity of affected relatives. Race[6] points out that to accept the simple dominant theory, one would have to postulate a high rate of gene mutations in order to account for many cases appearing without a family history. In the present case, the abnormal gene is found in the paternal relatives.

The ease of diagnosis is influenced by the fact that the degree of both anemia and icterus varies from patient to patient, due to varying rates of red cell destruction and production. There is also a poor correlation between clinical icterus and anemia. In several of the cases of hereditary spherocytosis in the newborn, pallor was the prominent feature and icterus was considered slight.[2,8,9] However, Betke[10] reported jaundice as a definite part of the symptom complex, although blood incompatibility cannot be excluded in several of his cases.

Anemia, as determined by hemoglobin concentration, may occur in the immediate neonatal period or may not be noted until later in life.[4] There is what has been called mild «forme fruste» or a latent form of hereditary sperocytosis,[3] which is found in clinically non - affected persons related to individuals with the active form. Such an instance is found in the sibling of our patient who, although clinically well, has laboratory findings confirmatory of spherocytosis, emphasizing that expression of the disease can be

different in members of the same generation and suggesting that there is a difference in penetrance in the gene or in the modifying genes on this dominantly transmitted defect.

The presence of splenomegaly remains variable, considered by some as an outstanding physical finding [11] and by others almost insignificant. [8] Our patient's spleen although not palpable in the newborn period has since been easily felt.

In the neonatal period, jaundice is dependent upon several factors, including the relative polycytosis of the neonate, and the immaturity of the hepatic enzyme systems. Added to these factors are the unknown roles that fetal hemoglobin plays, the action of the spleen in utero and the effect of the birth process influencing hemolytic crisis. These and other factors may explain the relatively few cases of spherocytosis reported in the newborn. Clinical findings, family history and comparatively simple laboratory studies usually suffice to make the diagnosis in the adult, but in the newborn these confirmatory signs and symptoms may be modified. One must proceed in the work-up of such a case by elimination of the commonest causes of neonatal jaundice.

In the consideration of the differential diagnosis of jaundice in infancy, one finds the list quite extensive. The clinician must rule out hemolytic processes associated with erythroblastosis from isoimmunization due to ABO, RH-HR and other blood group systems, [12,13] sepsis, [14] toxoplasmosis, [15,16] cytomegalic inclusion disease [17,18] congenital syphilis, [6] infectious hepatitis, thrombocytopenic purpura, congenital leukemia, galactosemia, familial nonhemolytic jaundice, [19,20] atresia or cystic dilatation of the bile ducts, icterus neonatorum, inspissated bile syndrome, Weil's disease and the infiltrative types of diseases. Many of these diseases can be readily differentiated by the history, clinical findings and results of laboratory tests.

It is imperative to establish an early diagnosis in each instance in order to institute proper therapy and to give general supportive treatment for possible anemia and the prevention of kernicterus. Despite much controversy the generally accepted management of hyperbilirubinemia, regardless of the cause, is that of exchange transfusion in order to maintain the serum bilirubin below 20 mg. per 100 ml. [21]

With spherocytosis, as with other hemolytic processes, there is what is called a «compensation index,» or balance between increased

erythropoiesis and hemolysis.[22] This equilibrium stabilizes the hemoglobin level which remains fairly constant in any given patient, except for periods of crisis, and this is found to vary considerably among different patients. The periods of crisis in spherocytosis are felt by some to represent episodes of cessation or marked diminution of erythropoiesis and may be associated with systemic infections, however, the actual cause often remains obscure. Owren, Battle and Dameshek[23,24,25] support the theory of an aplastic crisis by citing cases having diminished reticulocytes during an acute crisis with a subsequent reticulocytosis as the crisis subsides. However, other authors[20] found evidence of increased hemolysis during crisis. Our patient demonstrated minimal reticulocytosis despite a drop in the hemoglobin as contrasted to the infant reported by Shapiro[2] who had a persistently elevated reticulocyte count.

Complications: Biliary lithiasis is very common in hereditary spherocytosis with an incidence as high as 95 per cent in a group of patients over the age of 15 years[5] and these stones, as shown in the father of our patient, are typical pigment calculi which arise from chronically high hemoglobin pigment excretion. In Young's series,[5,33] 12 of 14 patients past childhood had cholelithiasis demonstrated by roentgen ray, which correlates with the high incidence of gallbladder disease seen in our pedigree.

Another feature of the disease, although reported less frequently, is the occurrence of leg ulcers similar to varicose ulcerations, the cause of which remains unknown.[27] Mental retardation and infantilism[28] are rarely associated anomalies. The bone thickening often found in other diseases with increased erythropoiesis is uncommon with spherocytosis. We were unable to demonstrate bone pathology in our patient, his father or sibling.

Pathogenesis: The majority of symptoms and findings in spherocytosis can be traced to the shortened lifespan of the erythrocytes and their destruction in the body. When an enlarged spleen is found in association with any hemolytic process the important question is one of causality. Is the destruction of the erythrocytes due to the presence of a large and possibly abnormal spleen, or is the splenomegaly the result of an intrinsic degeneration of the red cells?

Insight to this question is gained by means of techniques used for estimating the survival time of erythrocytes and their localization after destruction. The Ashby differential agglutination

method [28] and radioactive chromium (Cr 51) tagged cells [30] are used for this purpose. It has been established, with highly consistent results, that the rbc's in patients with spherocytosis have a shortened lifespan, with a half life calculated to be about seven days as compared to the normal of about 23 days. [23,26,28,31]

In an interesting experiment utilizing the Ashby technique, Emerson et al. [32] transfused blood from a patient with spherocytosis into a normal patient who had had a splenectomy and found the spherocytes to have a normal life span. This points out that spherocytes will survive normally in the absence of the spleen, but that the spleen of patients with spherocytosis does not destroy normal cells. It is further felt by Emerson et al. and Young [33] that the osmotic fragility of spherocytes is much greater in the spleen than in the remainder of the circulation, whereas the fragility of normal cells is nearly the same in both. Also in experiments performed with perfusion of freshly isolated spleens, Young discovered that this organ was capable of retaining the abnormal spherocytic corpuscles and permitting the normal cells to pass through.

The Red Blood Cell: A sphere has the minimum amount of surface per volume of any shape, and therefore any expansion of the contents of a spherocytic red cell, as seen with osmotic transfer of fluid into the cell, will result in rupture of the cell membrane. It is this spherical shape which is responsible for an increase in osmotic fragility noted in the spherocytes, which itself may be caused by a variety of mechanisms. [34,35] This is demonstrated by measuring the hemolysis, that is the amount of free hemoglobin of cells in saline solutions of varying hypotonicity.

The reason for the shape of the spherocyte remains unknown. There has been described an abnormality of glucose metabolism of the spherocyte which has not been defined but manifests itself by impaired incorporation of plasma phosphate into adenosine triphosphate. [20,35]

Crosby [36] describes the relationship of iron metabolism to hereditary spherocytosis, and was able to demonstrate the change of the characteristic rbc configuration by decreasing the total serum iron, however, the life span of these cells was not improved.

There does not appear to be an immune mechanism causing the hemolysis of the spherocytes as the Coombs test is invariably negative.

Therapy: Splenectomy should be considered the treatment of choice in hereditary spherocytosis often resulting in immediate and dramatic relief of symptoms although in no way affecting the primary disease. [33,36,37,38] Following splenectomy the red cell count and the hemoglobin usually approach normal values, the reticulocyte count decreases and the icterus and evidence of hemolysis subsides. These improvements are consequent to the elimination of or marked reduction in the hemolytic effect despite the persistence of spherocytic erythrocytes. Aplastic crises and anemia have not been reported in follow-ups of over 17 years after splenectomy. [5] The osmotic and mechanical fragility of the erythrocytes, however, is not usually modified by this procedure. [27,28] This was illustrated by the father of the present patient who had a splenectomy performed 17 years previously, but still had increased red cell fragility.

There have been reported poor responses following splenectomy and one possible explanation has been the presence of accessory spleens not removed at the time of original surgery. [39]

Recent interest in the relationship between splenectomy in young infants and the subsequent high incidence of severe infections brings us to the debate as to whether this operation should be postponed and, if so, for how long. It is generally accepted that there is a high incidence of fatal or life-threatening infection, namely sepsis or meningitis, following splenectomy in the young infant. [40]

Robinson and Sturgeon [41] in a report of over 100 patients, postsplenectomy, noted a distinct difference in the incidence of infection between those patients whose basic disease or treatment is associated with an increased susceptibility to infection, and those patients in whom the primary disease is essentially curative. Children with hereditary spherocytosis fall into the second category and it was concluded that splenectomy for them carries a relatively low incidence of postperative infection when performed after the age of 6 months.

King and Shumaker [42] reported 5 cases of spherocytosis who had splenectomies before the age of 6 months. Four of these infants developed meningitis in from 6 weeks to 3 years after the operation and of these one died.

On the other hand, Walter and Chaffin [43] in reporting 37 cases of splenectomy for spherocytosis, 10 in children less than 7 months of age, noted no severe infections in follow-ups of between

10 months and 13 years. It is the policy of some [2] that splenectomy should be performed for the child with established spherocytosis even if less than one year of age, when the clinical status requires, it whereas others recommend postponement of splenectomy until after the first year. [1] It is generally agreed that for 2 years postoperatively any infection, no matter how slight, should have antibiotic therapy.

Because of the extremely high incidence of cholelithiasis, [5] splenectomy is advised in these patients before the age of 10 years, or at an earlier age in symptomatic children. [22]

Coleman and Finch [26] have tried steroid therapy for patients with spherocytosis, and showed improvement of several laboratory parameters including a rise in hematocrit and fall in reticulocytosis in 3 intact patients and essentially no change in another patient following splenectomy. Their conclusion attributed the steroid effect to a non-specific effect on the spleen which decreased cell destruction or sequestration.

In some cases a small blood transfusion may be deemed advisable [8] when the circulating hemoglobin of the infant is dangerously low, but others advise not transfusing for low hemoglobin levels when clinical symptoms are absent. [2] It is agreed that transfusions may be helpful in controlling a transitory phase during which the anemia is the result of medullary hypoactivity, but it is unreasonable to continue with such measures more than a few months if these efforts have only a slight or temporary effect. [1]

There have also been reported cases [1,10,44] of hereditary spherocytosis where exchange transfusions in the neonatal period for elevated serum bilirubin were utilized to prevent kernicterus.

Immediate management would necessarily consist of periodic examinations to observe the patient with spherocytosis for the possibility of increasing anemia or related symptoms. The parents of these children must be fully informed as to the possibility of aplastic crises and alerted to observe their children properly for increased pallor, icterus or fatigability. Supportive measures, including small transfusions, should be administered for self-limited crises as required. The parents should furthermore be made to appreciate the advisability of splenectomy and this procedure should be performed prior to age 10 after evaluation on an individualized basis.

Summary

A case is presented of hereditary spherocytosis diagnosed in a newborn infant who was found to be icteric on the first day of life.

The establishment of the diagnosis is discussed, along with possible complications and therapy. A detailed family pedigree is presented.

The pathogenesis of hereditary spherocytosis and the question of splenectomy in infants with this disease are also discussed.

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