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Congenital Erythroblastic Hypoplasia

Treatment of Transfusion Hemosiderosis with Desferrioxamine B

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Periodic case reports of congenital erythroblastic hypoplasia indicate the disease is well defined. Treatment, however, remains unsatisfactory because therapeutic measures either fail to induce remission or produce serious side effects. The patient reported below demonstrates the natural course of the disease and its unresponsiveness to multiple therapeutic agents. The problems of management will be discussed with special reference to treatment of transfusion hemosiderosis by a new iron chelating agent.

Case Report

A white male child was born at the Henry Ford Hospital in July, 1940, after an uneventful gestational period. Delivery was normal and birth weight was six pounds, eight ounces. The immediate neonatal course was uneventful. The patient's growth and development were normal for the first 18 months. He then began passing frequent bulky foul smelling stools. Growth and development became retarded, and shortly thereafter he was referred to Henry Ford Hospital. The impairment of physical development was confirmed and no abnormal pigmentation, renal anomalies, strabismus or skeletal deformities were noted. Hemoglobin concentration was found to be 8.8 gm per 100 ml. "Celiac disease" was diagnosed and treatment was initiated with a high protein diet. Stools became normal in consistency and less frequent, while growth and development improved.

However, the anemia was progressive and within six months he was readmitted with a hemoglobin of 4.2 gm per 100 ml. The white cell count was 5,050 per cubic mm and the reticulocyte count was 0.1 percent. An apical systolic murmur was interpreted as being secondary to the anemia. Hypoplasia of the red cell series was noted in the marrow examination, but platelet and white cell production were normal. Blood transfusions were given, but within a few weeks the hemoglobin concentration again fell. Transfusions subsequently became necessary every six to ten weeks in order to maintain life.

At age four years, the patient underwent splenectomy at another institution despite clinical evidence of a normal size spleen and without evidence of excessive hemolysis. At operation, the spleen was slightly enlarged, but was histologically normal. No therapeutic benefit resulted, and regular transfusions again became necessary eight weeks after splenectomy. Various hematinics, including folic acid, vitamin B_12 and iron, were given without improvement. Four years later, the patient received a full trial of adrenocorticotropicin therapy without favorable effect. One year later, because of both retarded somatic development and the suggested erythropoietic effects of androgens, he was treated with methyl testosterone for several months without success. Pyridoxine and rutin were administered without objective benefits. Oral corticosteroids were started when he was 14 years of age and have been continued since that time. Repository testosterone therapy was

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The natural history of congenital erythroblastic hypoplasia is well illustrated by the lifelong observation of the case reported. A unique therapy for transfusion hemosiderosis is reported.—Ed.
begin when the patient was 15 years of age and continued to the present time. Desiccated thyroid also has been continued. Figure 1.

Growth and development have always been poor. From age 13 to 15, he grew 3.8 cm. At age 17, bone age was retarded two years and no gonadotropins were recovered from the urine. Between age 17 and 19 during repository testosterone administration, he grew at an annual increment of 2.0 cm. Although secondary sexual characteristics developed slowly, the testes have remained prepuberal in size, and potency is very low. Despite intensive anabolic hormonal therapy, osteoporosis of the vertebral column was noted in roentgenograms made when the patient was 18 years of age. At this time assay for urinary gonadotropins failed to detect any, and it was concluded that the patient suffered from hypophyseal failure.

From age 2 to 18 years, he received repeated blood transfusions, totalling more than 300. Marrow, platelet and white cell counts remained normal while hypoplasia of the red cell series was repeatedly noted (Fig. 2.) Peripheral smear reticulocyte counts averaged 0.1 percent. He was studied extensively at several other medical centers and these observations were confirmed. Red blood cell fragility and Coombs' tests remained negative.

At age 16, the patient was found to have an enlarging liver and gradual graying of color of the skin. Since hemosiderosis was demonstrated in bone marrow, gastric mucosa (Fig. 3) and liver (Fig. 4), it was concluded that transfusion hemosiderosis was the cause of the somatic retardation and multisystem failure. During the 17th year of life and without change of his medical program, the requirements for blood replacement began to lessen and transfusions were necessary only every four or six months. The reticulocyte count increased gradually to 1.0 and 2.0 percent, while the bone marrow changed from a normal cellular marrow with erythroblastic hypoplasia to marked hypercellularity with a striking increase in normoblasts and the appearance of megaloblasts (Fig. 5). Subsequent hemoglobin concentrations averaged 10 gm per 100 ml during this period. His physical
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Figure 2
Aspirate section of marrow. Note erythroblastic hypoplasia. Dark deposits are hemosiderin.

Figure 3
Stomach section. Iron stain reveals pigment in the fundus of gastric glands is hemosiderin.
Figure 4
Liver section. Iron stain reveals excessive dark deposits of hemosiderin.

Figure 5
Aspirate section of marrow after remission. Note restoration of normal cellularity.
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activity increased. He resumed full time schooling and living approached a near normal routine. Endocrine replacement was continued without evidence that a specific agent was responsible for the hematologic remission. The last transfusion was given in January, 1959. Because severe hemosiderosis was present and since partial hematologic remission had been firmly established, repeated venesections were done at weekly or biweekly intervals in an attempt to reduce total body iron content. It soon became apparent that venesections in amounts of 50 or 100 ml could not be done without dropping the hemoglobin to critical levels. Therefore, in November, 1962, an attempt to reduce total body iron stores with the use of desferrioxamine B*, a new iron chelating agent, was undertaken. At that time, the patient's height was 155 cm and weight was 59.5 kilo. He was weak and short of breath on exertion, remained boyish in appearance, was moderately obese, and showed pseudogynecomastia, an ashen-gray skin and a tender enlarged liver.

Of the patient's three siblings, two, aged 34 and 36 years, are alive and well. The third, a brother, had been unsuccessfully treated elsewhere for aplastic anemia. He died at one year of age, and at postmortem the diagnosis of congenital erythroblastic hypoplasia was confirmed. No other family member gave a history of anemia or blood disease.

Laboratory Values

Laboratory studies in recent years show a hemoglobin of 8.5 gm per ml, hematocrit 25 percent, white blood count 7,400 per cubic mm with normal differential, reticulocyte count 4.3 percent, urinalysis negative, and platelet count 462,000 per cubic mm. Electrophoresis of serum proteins include total protein 7.9 gm per ml, albumin 5.50, alpha-1 globulin 0.22, alpha-2 globulin 0.47, beta globulin 0.98, and gamma globulin 0.73 gm per 100 ml. Bromsulfa!ine retention is 25 percent in 45 minutes, serum iron is 299 mcg per 100 ml with an iron binding capacity of 299 mcg per 100 ml. Other chemical determinations are serum creatinine 0.5 mg per 100 ml, blood urea nitrogen 16 mg per 100 ml, fasting blood sugar 80 mg per 100 ml. Electrocardiogram demonstrates abnormalities compatible with myocarditis.

Discussion

Since 1936, over 75 cases of erythroblastic hypoplasia have been reported in the literature under the titles of congenital (erythroid) hypoplastic anemia,1 primary red cell aplasia, erythrogenesis imperfecta,2 Diamond-Blackfan anemia,3 etc. The disease usually appears in early neonatal life and has been recognized as early as one or two months of age. Common abnormalities in the peripheral blood include a hemoglobin of 1.7 to 9.4 gm per 100 ml, a normocytic anemia and reticulocytopenia. Initially, white blood cells and platelets are normal in quality and quantity, though hypersplenism may alter this picture later. Bone marrow examination reveals a decreased myeloid-erythroid ratio of 6:1 to as high as 240:1, erythroblastic hypoplasia with normal white blood cell and platelet elements. The response to ordinary modes of therapy is generally unrewarding, but prognosis is not necessarily poor as long as transfusions maintain adequate red cell values. With modern clinical procedures the child with erythroblastic hypoplasia can be expected to survive into the second decade and may achieve adulthood as the result of transfusion maintenance, corticosteroid therapy, spontaneous remission or a combination of these.

The case presented demonstrates the familial incidence of this disease as shown previously by Loeb, Burgert,4 Diamond and others. Unlike Fanconi's anemia, which has been shown to have autosomal recessive sex-linked transmission, no hereditary relationship has been established for erythroblastic hypoplasia.5,6

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Treatment

Methods of therapy of this disease fall generally into four categories: A. blood transfusions, B. empiric hematopoietic stimulation, particularly with corticosteroids, C. supportive measures, and D. removal of transfusion iron. Transfusion therapy is the only measure common to all cases which have survived. Regardless of subsequent course, initial and periodically repeated blood transfusions are needed to support the anemic circulation. In any chronic blood disorder, careful blood typing and cross matching is essential to reduce the likelihood of acquired hemolytic anemia. As in the case presented, the use of sedimented red cells for correction of anemia is advisable. Whenever therapy has been attempted with hematinic agents, such as iron, folie acid, B12, crude liver extract, testosterone, cobalt, or vitamin C, no consistent response has occurred. Currently, the only well-documented therapeutic hematologic remissions have occurred in response to adrenocorticotropin or corticosteroid therapy with or without splenectomy. In the largest series reported, Diamond reports that of 22 patients treated, 12 encountered steroid induced remission.7

Jeune,8 Pearson,1 and others record successfully treated cases, though Loeb9 reports splenectomy was needed for complete remission. Splenectomy seems to be useful in isolated cases, but has been inconsistently beneficial when used with steroids, and of questionable value when employed alone.3,10 Expectant management with supportive therapy is rewarded with remission of the disease in many instances. Our case typifies the lack of response to hematinics and corticosteroids as well as the unexpected remission, both of which have occurred in periods from late infancy to early adulthood. Diamond reports six of his 30 cases had spontaneous remissions while receiving intermittent transfusions and he mentions four other cases in the literature.3

Complications of Treatment

Our case records complications of treatment which occur most frequently in patients given multiple blood transfusions. Growth retardation, failure of secondary sexual maturation and osteoporosis (as side effect to corticosteroid therapy) all occur. Perhaps the most common and serious complication is diffuse increase in iron deposition demonstrated by skin, stomach, heart and liver hemosiderosis. Hemosiderosis with pigmentation of the skin and enlargement of the liver was noted by Cathie4 and Lelong11 in patients with this disease. Liver biopsies performed on patients four and one-half years old and seven years of age, as well as patients having had long term blood transfusion maintenance, showed hemosiderin deposits with varying degrees of fibrosis. In some instances, portal hypertension was present without associated gastrointestinal bleeding.

Because transfusions are required at monthly or bi-monthly intervals to maintain life, the amount of iron deposited may amount to 500 mg. of elemental iron a month. Until remission occurs, which may not be for many years, venesection for the removal of iron in body stores usually cannot be performed. Although exact measurement is impossible, we estimate that in over 300 transfusions which our patient received, more than 40 gm of iron had been deposited in elemental form. Because of the severe
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degree of hemosiderosis produced and secondary multiple organ failure, removal of iron in the total body stores was thought desirable. Venesection was employed for several months after hematologic remission had occurred, but subsequently was discontinued because removal of small quantities of blood produced marked lowering of hemoglobin values.

Treatment With Desferrioxamine B

In November, 1962, desferrioxamine B, a new iron chelating agent, was utilized in an attempt to remove iron from the body without producing anemia. Ferrioxamine is a member of the sideramine family produced by actinomyces fermentation, as are ferrimycin, albomycin and grisein. Bickel,\textsuperscript{12} in 1960, described two new iron containing compounds, ferrimycin and ferrioxamine B. Clinical trials using ferroxamine B indicated that when this drug was injected intravenously it would cause a rise in serum iron concentrations, but the injected iron would not be combined with, or available for active production of blood. He determined, therefore, that the iron in the compound was bound quite strongly and before long an iron-reduced complex of ferrioxamine B was produced, namely desferrioxamine B, which could chelate circulating trivalent iron. Smith\textsuperscript{13} points out that in patients with excess storage of iron, significant urinary iron excretion can be achieved by the parenteral administration of desferrioxamine B. His work indicates that patients with oversaturation of the plasma iron binding capacity will excrete 11 to 40 mg of elemental iron per gram of desferrioxamine B. Bannerman\textsuperscript{14} points out, however, that in “iron overload” the amount of iron removed by desferrioxamine B is small compared to that removed by venesection. Therefore, the latter remains the method of choice for removal of iron. It has been shown that 1200 mg of desferrioxamine B will remove five mg of iron daily in normal subjects, 15 mg in persons with secondary hemosiderosis and 50 to 80 mg of iron daily in cases of idiopathic hemochromatosis.\textsuperscript{15}

Desferrioxamine B therapy was begun on our patient with an initial daily dose of 1200 mg intravenously (IV) and then 800 mg IV and 400 mg intramuscularly (IM). This schedule was continued for 11 days. The patient was discharged from the hospital and treatment was continued at home with 400 mg twice daily intraglutely. Because of local discomfort, on the 22nd day the dose was reduced to 400 mg once daily which was better tolerated. On the 57th day, in an attempt to increase iron excretion, the 400 mg dose was increased to 600 mg desferrioxamine B dissolved in a single injection of 3 ml daily. This dose was tolerated well and was continued until the 121st day when the 600 mg dose was given every other day to determine the effect on urinary iron excretion. Since the 200th day, 1000 mg of the drug has been given daily subcutaneously (SC) without discomfort or other side effects. Clinical examination during this time revealed marked clearing of the ashen-gray color of the skin of the patient as well as marked reduction in the size of the liver from 4 to 5 cm below the costal margin to only palpable at the costal margin. An unexplained rise in hemoglobin level to 11.5 gm per 100 ml was noted in the month after cessation of phlebotomies and institution of desferrioxamine B therapy. However, the hemoglobin gradually fell to pretreatment levels.
During the period of study, it is estimated 3.5 gm of elemental iron was excreted in response to treatment. Urinary iron excretion has remained proportional to the amount of drug administered (Figure 6). An average of 14.7 mg of iron was excreted daily in response to 1200 mg of desferrioxamine B therapy. Serum iron levels remained unchanged until the eighth month of treatment. At that time serum iron fell from 226 mg per 100 ml to 183 mg per 100 ml. Serum iron binding capacity fell from 233 mg per 100 ml to 210 mg per 100 ml. During IM administration, frequency and total dosage were limited only by local tissue tolerance. For this reason, the IV route is preferred if higher than 1200 mg single doses are to be given. But if this dose or less is to be administered daily, the SC route is preferred because of its freedom from discomfort and ease of administration. No systemic side effects directly related to desferrioxamine B have been observed.

Conclusions

Clinical evidence suggests that reduction of body iron by chelation with desferrioxamine B in transfusion hemosiderosis is possible with the duration of treatment depending on total amount of accumulated body iron. However, it seems that in cases of anticipated repeated transfusions best results could be obtained with daily desferrioxamine therapy initiated with the beginning of transfusions. In this way, iron excretion would possibly equal iron administration, and side effects of hemosiderosis would be prevented.
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Summary

Transfusion hemosiderosis occurred in a patient with congenital erythroblastic hypoplasia treated with multiple transfusions. Treatment by venesection was hazardous; therefore, desferrioxamine B, a new iron chelating agent, was administered and removed significant amounts of iron. A description of the results of the therapy and the case history is presented.

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