Hydrops Fetalis Caused by Homozygous α -Thalassemia and Rh Antigen Alloimmunization

Report of a Survivor and Literature Review

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ABSTRACT

Hematologic causes of hydrops fetalis include homozygous α -thalassemia and immune hemolytic anemias. We report the case of a boy with hydrops fetalis who had homozygous α -thalassemia and alloimmune hemolytic anemia due to anti-E and anti-C blood group antibodies. He received intrauterine red blood cell transfusions and postnatal chronic transfusion with iron chelation therapy. A non-myeloablative sibling stem cell transplant failed. He is now 5 years and 6 months of age, hypothyroid with short stature, but in overall good health. He is one of the oldest reported homozygous α -thalassemia survivors and, to our knowledge, the only survivor with immune- and nonimmune-induced hydrops fetalis.

INTRODUCTION

Hydrops fetalis is a rare but important cause of perinatal morbidity and mortality caused by the accumulation of interstitial fluid in the fetus. Hematological causes of hydrops fetalis include immune- and nonimmune-mediated mechanisms. Maternal isoimmunization to Rh blood group antigens resulting in the production, for example, of anti-D, anti-E, and/or anti-C antibodies can cause hydrops and hemolytic disease of the newborn. Nonimmune-mediated hydrops can be caused by hemoglobinopathies. In fact, α -thalassemia is the most common cause of hydrops fetalis in Southeast Asia.

The thalassemias are the most common monogenic diseases and occur mostly in peoples from the Mediterranean to Southeast Asia, with α -thalassemias occurring mainly in the latter part of the region. The hallmark of this disease is an imbalance in globin-chain production in the adult $\alpha_2\beta_2$ -hemoglobin (Hb) molecule.

In homozygous α -thalassemia, deletion of both copies of each of the two α -globin genes on chromosome 16 occurs, thus no α -globin is produced (α^0). The tetramers that are made, Hb Bart's (γ_4) and Hb H (β_4), behave instead like myoglobin in that they do not readily give up oxygen at physiologic tensions leading to severe hypoxia. Affected infants have very high levels of Hb Bart's (which is unstable), and some have Hb Portland ($\zeta_2\gamma_2$) or Hb H.

Typically these newborns die *in utero* in the third trimester or in the early postnatal period from severe hypoxia, and have congestive heart failure, ascites, edema, and hepatosplenomegaly. This condition has been called hydrops fetalis, and Hb Bart's hydrops or Hb Bart's disease.

Prenatal diagnosis of homozygous α -thalassemia is possible via chorionic villous sampling between the 10th and 12th weeks of gestation. Signs of hydrops can also be detected on prenatal ultrasound. The ability to diagnose these fetuses combined with the advances made in interventional obstetric medicine (e.g., intrauterine blood transfusion and early delivery) has enabled a few babies to survive. Not only do these children have intrauterine hypoxia-related health complications, they also have lifelong dependency on blood products, and thus are at risk for contracting blood borne diseases and developing iron overload. Chelation therapy for iron overload is fraught with complications. Ultimately, the definitive treatment for these children is hematopoietic stem cell transplantation.

In this case, we describe one of the oldest children surviving with α^0 -thalassemia currently reported. He also is, to our knowledge, the only reported child with combined immune-mediated and Hb Bart's hydrops fetalis. In addition, we review homozygous thalassemia, chronic transfusion and chelation therapies, and outcomes after stem cell transplantation.

CASE REPORT

The parents of the child discussed in this case were both of Hmong descent. The mother was 20 years of age when she conceived and gave birth to this child. She has blood type O positive and was known by red blood cell antibody screening to have anti-E blood group antibodies. Her three previous pregnancies (gravid 4 para 3) resulted in healthy children. The mother's first obstetric evaluation for this pregnancy was at 27 weeks gestation and included a fetal ultrasound, which showed a hydropic fetus with marked ascites, hepatosplenomegaly, subcutaneous edema, cardiomegaly, and a small pericardial effusion. Intrauterine percutaneous umbilical vein blood sampling demonstrated profound fetal anemia with Hb concentration of 5.7 g/dl. The initial assessment was hydrops fetalis secondary to anti-E alloimmune hemolytic anemia. Four intrauterine umbilical vein packed red blood cell (PRBC) transfusions were administered over the course of 5 weeks, each time increasing the Hb concentration into the range of 10 g/dl to 12 g/dl. A fetal ultrasound at 31 weeks gestation showed resolution of fetal ascites but persistent cardiomegaly and hepatosplenomegaly.

The baby was born vaginally at 34 weeks gestation. Birth weight was 1685 grams, length 40.2 cm, and head circumference 28.6 cm. Apgar scores were 1 and 5 at 1 and 5 minutes, respectively. The baby required immediate intubation due to respiratory distress. On initial exam, the respiratory rate was 80, pulse 144, temperature 36.4°C,

blood pressure 77/36 mm Hg. The skin was jaundiced. There was poor air exchange bilaterally with rales. The heart rhythm was normal sinus with a grade 2/6 systolic ejection murmur. The abdomen was markedly distended secondary to hepatosplenomegaly. Blood tests within the first 2 days after birth revealed a white blood count of $7.6 \times 10^3/\mu\text{l}$, Hb 13.9 g/dl, mean corpuscular volume 83 fl, platelets $157,000 \times 10^3/\mu\text{l}$, reticulocytes 2.28%, total/direct bilirubin 9.7/1.3 mg/dl, total protein 5.4 g/dl, albumin 3.9 g/dl, blood group O positive, and direct antibody test (Coombs) positive. Antibodies eluted from fetal red blood cells were identified as reactive against E and C blood group antigens. Of note, the Coombs test remained positive until day 30 after birth. On the third day after birth the total/direct bilirubin had risen to 19.7/11.1 mg/dl. Chest x-ray confirmed cardiomegaly, hepatomegaly, and splenomegaly. An echocardiogram showed general cardiac dilatation with global hypokinesis along with dilatation of the main pulmonary artery and descending aorta. The ejection fraction was 44%. The congestive heart failure was treated with dopamine, dobutamine, and furosemide. Hyperbilirubinemia peaked on day 24 after birth with a total bilirubin of 52.6 mg/dl (direct bilirubin 42.5 mg/dl), which resolved by 3 months-of-age. The baby remained in neonatal intensive care for 2 months and received multiple PRBC transfusions. A Hb electrophoresis (done after the baby had received PRBC transfusions) revealed an unusually high quantity of Hb Bart's (γ_4). To detect deletion-type mutations within the α -globin gene cluster, Southern blot analysis was done. All four α -globin genes were deleted (two Southeast Asian type deletions) consistent with homozygous α -thalassemia. Monthly PRBC transfusions were started.

At 2 years of age, the child received a matched sibling hematopoietic stem cell transplant from his sister. A non-myeloablative conditioning regimen consisting of busulphan, fludarabine, antithymocyte globulin, and total lymphoid irradiation was used. Seven months after initial engraftment, the transplant failed with disappearance of donor DNA, and the patient's Hb decreased to 6 g/dl. Since that time, he has been on a chronic PRBC transfusion program and iron chelation therapy with subcutaneous deferoxamine.

Today, he is in overall good health, but has mild hypothyroidism and short stature. He is bilingual (Hmong and English) and his development is age appropriate.

DISCUSSION

Hematologic causes of hydrops fetalis include immune-mediated and nonimmune mechanisms.¹ The most common immune-mediated mechanism is Rh hemolytic disease of the fetus and newborn. Mechanisms not involving immune-mediated hemolysis of red blood cells include decreased production of normal Hb $\alpha_2\beta_2$ tetramers, and intrinsic red blood cell or Hb abnormalities. In Southeast Asia, one common cause for severe anemia *in utero* is homozygous α^0 -thalassemia resulting in hydrops fetalis, also

known as Hb Bart's disease. As in our patient, the α -globin gene mutation is commonly a 20 kilobase deletion of DNA referred to as the Southeast Asian (SEA) deletion (- - SEA / - - SEA).²

It is extremely uncommon for a fetus to have two separate but concurrent hematologic conditions predisposing to hydrops fetalis. In our patient, both immune- and nonimmune-mediated conditions were present, homozygous α^0 -thalassemia (- - SEA / - - SEA) and hemolytic disease of the newborn with anti-E and anti-C antibodies.

Homozygous α -thalassemia used to be a uniformly fatal disease in the prenatal and early postnatal course. The advent of early diagnosis through chorionic villous sampling and early treatment with intrauterine umbilical vein transfusions (IUT) has dramatically altered the clinical course of this common disease. The increase in survival is mostly attributable to IUT. One recent review describes 12 children with α^0 -thalassemia who survived due to IUT and intensive neonatal care.³ Numerous complications illustrate the difficulties in treating this disease. Ten of the 12 infants were born via Cesarean section, all were preterm (gestational ages 28 to 37 weeks), 10 out of 11 had an intensive postnatal course, congenital malformations were found in 50%, and developmental delay was found in 3 out of 10 children.³

IUT, while life saving, is physiologically not an ideal therapy. Hb A is transfused into a fetus that predominantly has Hb Bart's, Hb Portland, or Hb H. The difference in the oxygen dissociation curves leads to compensatory physiologic changes, such as increasing concentrations of 2,3-diphosphoglycerate. There have been cases of neonatal iron overload after IUT, most likely compounded by ineffective erythropoiesis.⁴ A benefit of IUT, however, is suppression of fetal hematopoiesis.

In a group of 155 fetuses with blood group immunization, treatment with IUT resulted in an overall survival rate of 83%.⁵ As anticipated, survival was affected by presence and degree of hydrops. A 90% survival was seen in those fetuses without hydrops versus 73% in those with hydrops. Hydrops seemed to respond briskly to IUT and resolved completely after the first transfusion in a smaller study.⁶ Interestingly, survival was not linked to gestational age.⁵

Three out of four children with α^0 -thalassemia who received IUT had normal neurologic development, whereas only one of four infants who received prompt postnatal transfusion is neurologically normal.⁷ *In utero* hypoxia is presumed to cause limb⁸ and urogenital (mainly hypospadias)⁹ abnormalities. Neurological and developmental abnormalities are encountered frequently in these children. IUT should therefore be considered as soon as the diagnosis of hydrops has been made in an attempt to reduce hypoxic organ damage.

These α^0 -thalassemia survivors have a lifelong transfusion-dependency. Chronic transfusions accomplish several goals including an adequate Hb level with normal oxygen dissociation capabilities essential for normal growth and development, and suppression of erythropoiesis that will prevent bone marrow expansion and extramedullary hematopoiesis. Chronic transfusion programs strive to meet these criteria by maintaining a pretransfusion Hb concentration of approximately 9 g/dl. This is usually accomplished with transfusions every 3 to 4 weeks.

Before starting chronic transfusion therapy, it is recommended to administer the hepatitis B vaccine and obtain a red cell antigen panel. One study found alloantibodies in 15% of 251 patients,¹⁰ demonstrating the utility of this information for future blood transfusions.

Every unit of PRBC contains about 250 mg of iron. The extra iron is stored in various organs, particularly the heart and endocrine glands in children. Excessive iron causes oxygen free radical reactions that damage mitochondrial respiratory processes and cellular function.¹¹ Iron deposits in the hypothalamus, pituitary, thyroid, and gonads lead to hypothyroidism, hypogonadism with delayed puberty, and short stature.¹² In one study, growth hormone-related growth failure was found in up to 8% of boys, 7 to 8 years of age, with severe thalassemia, and was partly corrected with growth hormone administration.¹³ In addition to overall decreased height, a short trunk with normal height has been reported in up to 40% of patients, the etiology of which appears to be multi-factorial.¹⁴ Insulin resistance, hyperinsulinemia, and diabetes mellitus can develop in older children on chronic transfusion regimens.¹⁵ Parenchymatous organs can be similarly affected. Renal proximal tubular abnormalities,¹⁶ as well as pulmonary function abnormalities,¹⁷ have been described. In 79% of patients, significant reduction in total lung capacity was found, and was worse at younger ages and with greater iron burdens.¹⁷ Over time, iron overload causes organ failure with the leading cause of death being cardiac failure.

Chelation therapy is usually started when the ferritin level exceeds 1000 ng/ml. Given the implications of iron overload and the side effects of chelation, the decision of when to start chelation is not to be undertaken lightly. Unfortunately, the most exact way to quantify body iron stores is iron content in a dry liver biopsy. Due to the invasiveness of the procedure, serum ferritin is most frequently used, although alternate means such as superconducting quantum interference devices are being developed.

Chelation therapy has significantly prolonged the lifespan of people on chronic transfusion therapy. The agent most commonly used in the United States is deferoxamine, which must be given subcutaneously over numerous hours causing problems with therapeutic compliance. The severe consequences of poor compliance are illustrated in a statistic on patients with β -thalassemia major, where 90% of

well-chelated children survived into their thirties. With poor compliance, this number dropped to a dismal 10% to 20%.¹⁸ Deferoxamine is also fraught with complications. A change in body proportions, mainly a shortened trunk, has been described, as have retinopathy¹⁹ and sensorineural hearing loss.²⁰ An increased incidence of bacteremia is noted, particularly with *Yersinia*. A potential long bone dysplasia attributed to deferoxamine is controversial.²¹ An oral chelating agent, deferiprone, has been in use in other parts of the world for over 10 years in people 2 to 85 years of age.²² With a similar therapeutic index, it has the advantages of oral route of administration (hence better compliance), lower toxicity, and decreased cost. More importantly, deferiprone seems to more effectively remove iron from the heart.^{22,23} A new agent, ICL670 (deferasirox) is currently being tested in children in a phase III clinical trial (personal communication, Prof. Antonio Piga, University of Turin, Italy). Despite chelation therapy, heart failure continues to be the leading cause of death in people with iron overload.²³

The potential for curing α^0 -thalassemia lies in a successful hematopoietic stem cell transplant (SCT). One case of HLA-matched sibling SCT,¹⁷ two with matched sibling bone marrow transplant,^{24,25} and one case using sibling cord blood mismatched at 1 MHC (major histocompatibility complex) locus²⁶ are described in the literature. Hb Bart's decreased to undetectable values within 3 weeks after transplant in one child. Two of the children ended up being stable mixed chimeras. However, all transplants resulted in a hematological cure. One child who did not receive IUT has developmental delay.

The birth of babies with α^0 -thalassemia is partly prevented with pre-conception education and antenatal screening. The potential for survival with the advent of early intervention (in the form of IUT) and curative treatment (in the form of SCT) is bound to change the prevalence of this once universally fatal disease. Despite increasing population shifts, thalassemia still is predominantly a disease of "developing" countries. As technological advances in the "countries of the few" change the picture of diseases, the ethical implications of salvaging every fetus with homozygous α -thalassemia merit thoughtful consideration. Meanwhile, much research remains to be done regarding the neurodevelopmental outcome of the surviving children, the availability of oral chelating agents in the United States, as well as the optimal transplant regimen.

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