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 αβ2-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 (α0). The tetramers that are made, Hb Bart’s (γ4) and Hb H (β4), 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 (ζ2 γc) 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 viachorionic 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 α0-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 (gravida 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 hydrotic fetus with marked ascites, hepatosplenomegaly, and perinatal 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 x 10³/µl, Hb 13.9 g/dl, mean corpuscular volume 83 fl, platelets 157,000 x 10³/µl, 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 dilation 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). 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. 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 α2β2 tetramers, and intrinsic red blood cell or Hb abnormalities. In Southeast Asia, one common cause for severe anemia in utero is homozygous α0-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-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-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-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 limb³ and urogenital (mainly hypospadia)⁸
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-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 pretreatment 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
The potential for curing α-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-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.

REFERENCES