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CASE REPORT

Successful treatment of fetal hemolytic disease due to glucose phosphate isomerase deficiency (GPI) using repeated intrauterine transfusions: a case report

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Key Clinical Message

Hemolytic anemia due to GPI deficiency can be severe and life threatening during fetal life. When parents decline invasive testing, ultrasound monitoring of fetuses at risk is feasible. Intrauterine transfusion can be effective for the treatment of severe fetal anemia due to GPI deficiency.

Keywords

Fetal anemia, GPI deficiency, intrauterine transfusion.

Introduction

Glucose-6-phosphate isomerase (GPI) deficiency is the third most common red blood cell enzymopathy, after glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiency and is similarly associated with hereditary nonspherocytic hemolytic anemia (HNSHA). An estimated 55 families with GPI deficiency have been reported. The sole clinical manifestation in the majority of patients is chronic HSNHA, ranging from mild to severe. Most cases of GPI deficiency are diagnosed during the neonatal and childhood period. To date, only two cases of prenatal diagnosis of GPI deficiency have been reported. [1, 2]. Additionally, cases of postnatal diagnoses of hydrops caused by GPI deficiency were documented, usually without survival of the affected child [2, 3].

In this case report, we describe a family in which two siblings have congenital HSNHA due to GPI deficiency. The first child was diagnosed at the age of 3 years, the second was monitored antenatally with repeated Doppler ultrasound and was eventually treated for fetal anemia with repeated intrauterine transfusions. To our knowledge, this is the first case of prenatal diagnosis of GPI deficiency in cord blood, followed by successful intrauterine treatment of GPI-deficient fetal anemia.

Case History

A 33-year-old woman was referred to our center at 17 weeks of gestation because of an increased risk of fetal anemia. The parents were nonconsanguineous, but originated from the same village. Neither had a family history of GPI deficiency or unexplained anemia. Their first child, a 5-year-old girl, was born after an uneventful pregnancy and did not suffer from extreme neonatal jaundice or anemia. She was diagnosed with GPI deficiency at the age of 3 years after her first documented acute hemolytic episode with signs of jaundice, severe anemia, and

hemoglobinuria. Following extensive investigation she was found to have reduced GPI enzyme activity in her red cells. DNA analysis showed the girl to be homozygous for the c.1615G>A, p.(Asp539Asn) missense mutation in *GPI*. This mutation is previously reported in association with GPI deficiency [4, 5]. Both the mother and father were found to be heterozygous for the same mutation.

At present, the girl remains clinically well, has normal growth and neuropsychological development but has evident chronic hemolysis treated with folic acid. She has had infrequent exacerbations of hemolysis associated with minor childhood infections but nonsevere enough to warrant erythrocyte transfusions.

The current pregnancy was the fourth pregnancy of this couple, following two early miscarriages. The parents refrained from early diagnostic chorionic villus biopsy or amniocentesis (because of the risk of miscarriage), but instead opted for ultrasound monitoring for signs of fetal anemia (measurement of the MCA Doppler peak systolic velocity (MCA-PSV)). The pregnancy was followed up on a weekly basis, from 16 weeks of gestation onward. At 26 weeks of gestation, fetal anemia was suspected, based on an increased MCA-PSV of >1.5 Multiples of the Median (MoM) (Fig. 1). No signs of fetal hydrops were present.

After parental counseling, an intrauterine blood transfusion (IUT) was planned. The first IUT was given transplacentally in the umbilical cord root at 27 weeks of gestation. Pretransfusion cord blood was obtained for diagnostic testing, the fetal hemoglobin level was 7.4 g/dL. An uncomplicated intravenous transfusion of donor blood was performed, resulting in a posttransfusion hemoglobin concentration of 13.5 g/dL. Genetic analysis of fetal cells confirmed that the second child was also homozygous for the aforementioned mutations in the *GPI* gene.

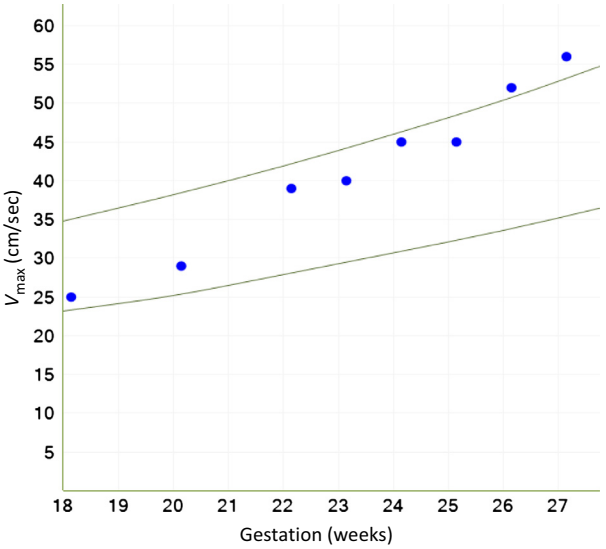

Figure 1. Peak systolic velocities (V_{max}) in the middle cerebral artery of the fetus. The lowest line represents 1.0 MoM. The highest line represents 1.5 MoM. There is suspicion of fetal anemia when V_{max} in the middle cerebral artery exceeds 1.5 MoM.

After the diagnosis was made, folic acid was prescribed to the mother in a daily dosage of 5 mg. The fetus was monitored weekly by ultrasound and MCA Doppler. Another two IUT's were performed at gestational weeks 30 and 34 (Table 1). The fetal condition remained good throughout pregnancy, with no signs of hydrops. Based on the fact that the fetus needed repetitive intrauterine transfusions from 27 weeks of gestation onwards, labor was induced at 37 weeks to avoid further intrauterine transfusions. A girl was born vaginally with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The cord blood PH was 7.25 and her weight was 3620 g. Neonatal jaundice was apparent immediately after birth. Intensive phototherapy was given from days 1 to 4. The child required no exchange or top-up transfusions and was discharged at day 7. At 4 weeks of age, despite resolving hemolytic parameters (decreasing bilirubin and LDH) the girl remained reticulocytopenic and required an additional blood transfusion for symptomatic anemia. Two weeks after transfusion, spontaneous recovery of hemoglobin concentration was observed, with rising reticulocytes (105×10^9/L), normal bilirubin (11 μmol/L), normal LDH (241 U/L), and low haptoglobin (<0.1 g/L) concentrations, consistent with compensated chronic hemolysis. She remains well and transfusion-independent at the current age of 5 months, while receiving folic acid replacement therapy.

Discussion

GPI is a dimeric enzyme which catalyzes the reversible conversion of glucose-6-phosphate and fructose-6-phosphate, the second step in glycolysis. GPI deficiency is a disorder with autosomal recessive inheritance. The GPI

Table 1. Intrauterine transfusion data for the treatment of fetal anemia.

Gestational age (weeks)	Estimated fetal weight (g)	Volume transfused (mL)	Pretransfusion Hb(g/dL)	Posttransfusion Hb(g/dL)
27	1230	46	7.4	13.5
30	1697	50	8.6	12.8
34	2979	87	9.0	13.1

Volume transfused: volume of transfused red blood cells. Pre and posttransfusion Hb: hemoglobin level in the fetus before and after intrauterine transfusion

gene is located on the long arm of chromosome 19 and 31 mutations in the *GPI* gene are currently listed in the Human Gene Mutation Database (www.hgmd.cf.ac.uk). The majority of these mutations are missense mutations affecting key interactions of the enzyme's active site [5]. GPI-deficient patients are either homozygous or compound heterozygous for such mutations, and are clinically characterized by chronic hemolytic anemia with hemolytic crises during infection or after ingestion of hemolytic drugs [6]. The current therapy consists of blood transfusions and splenectomy for the most severe hemolytic cases [3, 7]. It has been suggested that mutant GPI is inactivated faster with increasing RBC cell age than the wild-type enzyme [8]. The manifestation in affected fetuses might therefore be milder because of the shorter lifespan of fetal RBCs. However, if fetal hydrops develops due to GPI deficiency, the prognosis is usually very poor [2, 9].

In the literature, there is scarcity of publications on prenatal diagnosis of GPI deficiency [1, 2]. Whitelaw et al. performed the first prenatal GPI deficiency diagnosis at 28 weeks of gestation by assessing the GPI characteristics in amniotic fluid cells. GPI deficiency was considered after the neonatal death of a previous child with hydrops. The second child in this family was diagnosed antenatally as compound heterozygous for two different mutant *GPI* alleles and received an exchange transfusion after birth, which took place at 35 weeks of gestation [2]. Dallapiccola et al. provided a first trimester GPI deficiency diagnosis on trophoblast cells obtained from chorionic villus sampling [1].

In the present case, the couple declined invasive prenatal testing. Instead, close fetal surveillance by ultrasound scanning was performed on a weekly basis, to monitor for signs of fetal anemia. The increasing MCA-PSV raised the suspicion of GPI deficiency. The diagnosis was confirmed by genetic analysis of DNA of cord blood cells, sampled before the first IUT. The major benefit of this strategy was the avoidance of invasive prenatal testing.

IUT is universally accepted as an efficient treatment for fetal anemia. In the Leiden University Medical Center, serving as the Dutch national referral center for fetal therapy since 1965, it was the first time IUTs were performed for fetal anemia due to GPI deficiency. The timing of IUTs was based on findings of repeated ultrasound monitoring.

Patients with anemia are known to have an increased folic acid consumption. We prescribed folic acid supplementation to the mother to prevent the occurrence of megaloblastic anemia in the fetus. This strategy is supported by previous publications [6]. Postdelivery the girl also received folic acid, as is standard in patients with hemolytic anemia. However, despite a reduction in hemolytic parameters, she also needed a transfusion. This is a well-known phenomenon in children that received intrauterine transfusions and is thought to be induced by reduction in their own erythropoietin production. An alternative to transfusion postpartum could be exogenous erythropoietin [10]. In this case, that was not considered for after the first transfusion neonatal reticulocyte count recovered spontaneously.

Both children in this family are homozygous for the same two *GPI* mutations. The parents are both heterozygous for both mutations suggesting that although they were reported to be nonconsanguineous it is very likely that they stem from a common ancestor.

It is unknown why the second child was more severely affected. One possibility could be early exposure to oxidant agents which can trigger episodes of hemolysis. However, obstetric history of the second pregnancy showed no infection or known ingestion of oxidant drugs or food. Whitelaw et al. also reported a family of two affected siblings with different disease severity [2]. Kugler et al. pointed out that patients with the same mutation and deficient GPI activity can present with varying degrees of anemia and clinical impairment [7]. Our findings confirm that the hemolytic episodes caused by GPI deficiency are unpredictable and emphasize the importance of prenatal monitoring of fetuses at risk.

In conclusion, hemolytic anemia due to GPI deficiency can be severe and life threatening during fetal life. We recommend frequent ultrasound monitoring for prenatal management of pregnancies in which there is an increased risk of fetal GPI deficiency, when parents decline early invasive testing. In this case, repeated intrauterine blood transfusions appeared to be effective for the treatment of severe fetal anemia due to GPI deficiency and may additionally have prevented the development of fetal hydrops and demise.

Conflict of Interest

None declared.

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