



Case Report

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Reproductive Implications of Consanguinity: Recurrent Hydrops and a Fetal Diagnosis of Lethal Gaucher Disease

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Abstract

Consanguinity is defined as a relationship with one ancestor in common. We present a Muslim couple with known consanguinity and their fetal outcomes over multiple pregnancies.

This patient is a 28-year-old G4P0A3L0 who is married to her third cousin. Her first pregnancy was in Egypt during which a fetal demise was diagnosed at 21 weeks. Her second pregnancy ended in another fetal demise at 27 weeks and significant hydrops was noted post-mortem. This couple had an expanded carrier screening (ECS) panel using a targeted genotyping approach for over 160 recessive conditions and no mutations were identified. During her third pregnancy, fetal hydrops with no apparent anomalies was noted at 21 weeks and a fetal demise confirmed at 22 weeks.

She consented to a trio whole exome sequence using fetal tissue from the 3rd pregnancy. This confirmed a homozygous nonsense mutation c.1534A > T in the GBA gene. The mutation was found in the heterozygous state for each parent. Homozygosity for this mutation is associated with the perinatal lethal form of Gaucher disease, type 2. Their ECS did include the GBA gene but not their specific mutation. Thus, ECS failed to identify them as a carrier couple.

When the diagnosis in the third pregnancy fetal tissue was confirmed, she was already 13 weeks of gestation in a new pregnancy. Chorionic villus sampling (CVS) was performed and the fetus was negative for the GBA mutation and thus unaffected. This fourth pregnancy progressed to a healthy term vaginal delivery.

While there are several case reports describing Gaucher disease type 2, this patient highlights the relevance of consanguinity. This case highlights the utility of whole exome sequencing in the setting of prenatal diagnosis and illustrates the significant limitations of expanded carrier screening when a genotyping panel is utilized with limited mutations per gene evaluated.

Keywords

Gaucher disease, Consanguinity, Fetal hydrops, Whole exome sequencing, Chorionic villus sampling

Introduction

Consanguinity is defined as a relationship with one recent ancestor in common. While this is uncommon in western countries, over one seventh of the world's population is estimated to live in countries where 25-50% of marriages are consanguineous [1]. This varies significantly from one population to another depending on many factors including religion, culture, public attitude, legislation, socio-economic condition and geography. It is most prevalent in North and Sub-Saharan Africa, West, Central and South Asia [2,3]. Rates in the Middle East have remained consistently high or increased [4,5] and Arab Muslim countries have the highest rates of consanguineous marriage in the world ranging from 50-70% [6]. This is thought to be a pre-Islamic tradition and is deeply culturally rooted [7-9]. There is no encouragement of consanguineous marriage in Islamic religious text [10].

These relationships are known to be associated with increased risk of miscarriages, fetal anomalies and stillbirth due to autosomal recessive conditions. The general population risk of having a child with a birth defect is ~2-3%. First

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cousin marriages increase the risk 2 times above the general population risk of a birth defect (~4-6%) [11]. The Latin-American Collaborative Study for Congenital Malformations found a significant association with three congenital anomalies: Hydrocephalus, postaxial hand polydactyly and bilateral cleft lip +/- palate [12]. A study published in the *Annals of human biology* in March 2017 urged that pre-marital and pre-conception counseling about the potential harmful consequences of consanguinity should be an integral part of health policy [13]. Obeidat, et al. showed an increased risk of low birth weight, preterm labor and birth with congenital anomalies associated with consanguinity [14]. We present one couple with known consanguinity and their fetal outcomes over multiple pregnancies.

Presentation of Case

Our patient and her husband are 3rd cousins of Egyptian descent who are both Muslim ([Supplementary File](#)). She presented as a 28-years-old G4P0A3L0 with three previous second trimester losses. Her first loss occurred in Egypt at approximately 21 weeks of gestation, diagnosed during a routine prenatal visit. Limited information is known about this pregnancy regarding other factors. She proceeded to have an uncomplicated induction of labor and delivered a male fetus, but no autopsy or genetic studies were performed.

Her second pregnancy was two years later after immigration to the US and once again there was no fetal heart rate at 27 weeks of gestation. A fetal autopsy was performed and no anomalies were identified. The fetus was noted to be hydropic and most of the organs were autolyzed and or partial autolyzed. Karyotype on the products of conception confirmed a male fetus, 46 XY. The placenta was noted to be large with mild inflammation of the membranes and an unremarkable 3 vessel cord. Infectious studies were negative for Cytomegalovirus (CMV), Herpes simplex virus (HSV) and Epstein-Barr virus (EBV).

Following this second pregnancy, she was seen by a genetic counselor with plans for microarray testing of preserved fetal tissue from her second pregnancy. However, there was insufficient tissue to perform microarray analysis. Maternal chromosome analysis was performed and the karyotype was 46, XX. Her spouse declined karyotype analysis secondary to financial constraints. The patient was found to be an alpha thalassemia carrier. However, her spouse had a normal mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and hemoglobin electrophoresis. They both had an expanded carrier screening panel which included over 120 conditions, including the GBA gene associated with Gaucher, performed by targeted genotyping. No mutations were identified for the patient or her partner by this specific panel. She also had a negative antiphospholipid antibody work-up and despite her Rh-negative status, there was no evidence of red blood cell alloimmunization.

After an initial Maternal Fetal Medicine consult, saline sonohysterography was performed and showed no evidence of uterine anomalies. She was seen at our high risk clinic for her third pregnancy when she was 11 weeks and the first trimester screen results were low risk for common

aneuploidies with a normal nuchal translucency. At 21 weeks, the patient presented for her level II ultrasound. The nuchal fold was increased measuring 10 mm and the fetus was hydropic with pleural effusion and significant ascites. The umbilical artery demonstrated an elevated Systolic to Diastolic ratio and middle cerebral artery (MCA) doppler had elevated peak systolic flow (1.57 multiples of the median), suggesting fetal anemia.

Based on the fetal ultrasound findings, an amniocentesis was performed. Fetal studies revealed negative polymerase chain reaction (PCR) for Parvovirus B19, normal female karyotype and the single nucleotide polymorphisms (SNP) microarray analysis did not reveal any copy number variants. However, as expected based on consanguinity, the microarray revealed long contiguous regions of homozygosity in chromosome 1 and 12 (total 37.9 Mb). A repeat ultrasound performed at 22 weeks confirmed a fetal demise and slight worsening of fetal hydrops. The patient elected for induction of labor and had an uneventful vaginal delivery. On postpartum day one, she was noted to have increased vaginal bleeding and a dilation and curettage was performed for retained products.

Discussion

At this time, the patient had 2 pregnancies complicated by hydrops fetalis. This may result from a wide range of conditions and is classified as immune or nonimmune. The pathophysiology of hydrops remains unclear. Immune hydrops results from transplacental passage of maternal antibodies that obliterate fetal red blood cells. Although our patient was Rh negative, she had no evidence of red blood cell alloimmunization, ruling out immune hydrops.

Nonimmune hydrops is a larger umbrella term, accounting for 90% of cases. The majority are due to cardiovascular anomalies (21%) but this category also includes many other causes ranging from chromosomal, metabolic, structural defect or placental etiology. The etiology is dependent on gestational age at diagnosis. When diagnosed prenatally as our patient was, 20% is due to aneuploidy, 15% cardiovascular and 14% infections, the most common being parvovirus B19 [11]. These causes had already been investigated and ruled out for our patient based on normal karyotype, microarray, and infectious studies.

The patient was counseled that since the second fetus also had hydrops, this could potentially be caused by an autosomal recessive condition due to consanguinity. She consented to a trio whole exome sequence (WES). DNA from the patient, her spouse and the third pregnancy was used for this analysis. All the coding regions were sequenced and the variant curation focused on disease causing mutations with specific emphasis on chromosome 1 and 12 (where the fetus had loss of heterozygosity by microarray). The fetus was found to have a homozygous nonsense mutation c.1534A > T in the GBA gene. This gene is located on chromosome 1 within the region of loss of heterozygosity. The c.1534A > T alteration, located in exon 12 (coding exon 11) of the GBA gene, consists of an A to T substitution at nucleotide position 1534. This changes the amino acid from a lysine to a stop

codon at amino acid position 512. This alteration occurs in the last exon of the GBA gene, so while it is truncating, the mRNA is predicted to escape nonsense mediated decay (NMD) and a truncated mutant protein could still be expressed. Co-segregation analysis of the c.1534A > T alteration revealed that both of the parents are heterozygous for this alteration. Homozygosity for this mutation is associated with the perinatal lethal form of Gaucher disease, type 2.

Given an established molecular diagnosis, the patient was counseled regarding the 25% risk of recurrence, the option for diagnostic prenatal testing and the option of pre-implantation genetic diagnosis. However, the patient was already 13 weeks of gestation when these results became available. After genetic counseling, she opted for a chorionic villus sampling (CVS) procedure. Fetal studies confirmed a 46, XX karyotype and that the fetus had not inherited any copies of the c.1534A > T mutation and was therefore unaffected. A fetal microarray was also performed and revealed that the fetus had loss of heterozygosity in a region of chromosome 7. This is different from the previous fetus but was still presumed to be due to the consanguinity. However, in case this represented uniparental disomy, knowing chromosome 7 has an imprinted gene associated with Russell Silver syndrome. Parental studies were performed and biparental inheritance of chromosome 7 was demonstrated. We reviewed the residual risk given their consanguinity, but reassured them that the disease in the previous fetus will not affect their current pregnancy. The patient proceeded to have an uncomplicated pregnancy and a vaginal delivery at term.

Gaucher disease is the most common lysosomal storage disease seen worldwide. It is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme glucocerebrosidase. The affected gene is located on chromosome 1q21 and more than 300 variants have been reported to date [15]. Specifically type 2 can have been reported to be associated with hydrops fetalis characterized by abnormal accumulation of fluid. The pathophysiology is not well understood, however, most fetuses die in utero, as was the case for this patient's history [16].

While there are several case reports describing the Gaucher disease type 2, this case highlights the relevance of consanguinity. This is also the first recorded case of Gaucher disease with this specific nonsense mutation. This case highlights the utility of WES in the setting of prenatal diagnosis. Consanguineous couples are more likely to have offspring with autosomal recessive conditions and WES may be the only tool to elucidate a diagnosis in any of these cases. Interestingly, this patient had expanded carrier screening which included the GBA gene. However, only seven mutations were evaluated, and this patient's mutation was not included. This case also illustrates the significant limitations of expanded carrier screening when a genotyping panel is utilized with limited mutations per gene evaluated.

Our report focuses on the importance of considering metabolic disorders and autosomal recessive conditions when evaluating a fetus for hydrops, especially when parental consanguinity is known or loss of heterozygosity is demonstrated by the fetal microarray. Given most mutations are rare, whole

exome sequencing should be considered for these cases as the mutation is likely to be homozygous in the affected proband and present in only one copy in the parents. In addition, the gene of interest may be more likely to be located in the region where loss of heterozygosity is demonstrated on the proband's microarray. In essence, variant curation from WES may be easier in the affected fetus of a consanguineous couple.

Conclusion

Particularly for consanguineous couples who have an affected pregnancy with fetal hydrops, the cause is more likely to be genetic in nature and inherited in an autosomal recessive manner. Therefore, fetal studies should include a WES after the more common causes are ruled out. Securing a molecular diagnosis allows these higher risk couples to have preimplantation genetic diagnosis or prenatal testing.

The authors of this paper have no conflicts of interest to disclose.

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