Case of Neonatal Fatality from Neuromuscular Variant of Glycogen Storage Disease Type IV

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Abstract Glycogen storage disease type IV (GSD-IV), or Andersen disease, is a rare autosomal recessive disorder that results from the deficiency of glycogen branching enzyme (GBE). This in turn results in accumulation of abnormal glycogen molecules that have longer outer chains and fewer branch points. GSD-IV manifests in a wide spectrum, with variable phenotypes depending on the degree and type of tissues in which this abnormal glycogen accumulates. Typically, GSD-IV presents with rapidly progressive liver cirrhosis and death in early childhood. However, there is a severe congenital neuromuscular variant of GSD-IV that has been reported in the literature, with fewer than 20 patient cases thus far. We report an unusual case of GSD-IV neuromuscular variant in a late preterm female infant who was born to non-consanguineous healthy parents with previously healthy children. Prenatally, our patient was found to have decreased fetal movement and polyhydramnios warranting an early delivery. Postnatally, she had severe hypotonia and respiratory failure, with no hepatic or cardiac involvement. Extensive metabolic and neurological workup revealed no abnormalities. However, molecular analysis by whole-exome sequencing revealed two pathogenic variants in the *GBE1* gene. Our patient was

thus a compound heterozygote of the two pathogenic variants: one of these was inherited from the mother [p.L490WfsX5 (c.1468delC)], and the other pathogenic variant was a de novo change [p.E449X (c.1245G>T)]. As expected in GSD-IV, diffuse intracytoplasmic periodic acid-Schiff-positive, diastase-resistant inclusions were found in the cardiac myocytes, hepatocytes, and skeletal muscle fibers of our patient.

Introduction

Glycogen storage diseases (GSDs) are a group of rare inherited metabolic disorders caused by abnormal synthesis or breakdown of glycogen, leading to accumulation of abnormal quantity, quality, or both, of glycogen in the tissues. Glycogen is synthesized by the enzymes glycogen synthase and glycogen branching enzyme (GBE), which function in forming α -1,4 and α -1,6 glucose linkages, respectively (Tay et al. 2004). The α -1,6 branching in the glycogen molecule increases its solubility by decreasing the osmotic strength. Additionally, the action of glycogen phosphorylase on the branched structure of the glycogen molecule makes more glucose monomers available for metabolic needs. Accumulation of this abnormal glycogen molecule that has a long outer chain and poor solubility causes irreversible tissue and organ damage, especially in the liver and muscles.

There are multiple forms of GSDs, each with a predilection for a certain age group. GSD-IV (also called Andersen disease, amylopectinosis, or polyglucosan body disease) is a rare autosomal recessive disease, with an estimated incidence of 1 in every 760,000–960,000 births (Tang et al. 1994). It results from deficient GBE activity. Human GBE cDNA has been cloned and has a length of ~3 kb (Thon et al. 1993). The coding sequence contains

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2,106 bp, encoding 702 amino acids. Human GBE protein is located on chromosome 3p (Thon et al. 1993). In the absence of GBE, an abnormal glycogen called polyglucosan is formed; it has fewer branching points and longer outer chains than normal glycogen (Tay et al. 2004). This polyglucosan accumulates in all tissues to various degrees and results in different manifestations of disease.

The more classic form of GSD-IV, originally described by Anderson in 1956, involves the liver, leading to progressive cirrhosis of the liver (Andersen 1956). However, there also exists a neuromuscular variant of GSD-IV. This variant is distinguished into four different groups categorized by the age of onset: perinatal, congenital, juvenile, and adult forms. To our knowledge, fewer than 20 cases of genetically characterized fatal congenital neuromuscular variant of GSD-IV have been reported in the literature thus far (Tay et al. 2004; Tang et al. 1994; Zellweger et al. 1972; Bao et al. 1996; Assereto et al. 2007; Bruno et al. 2004, 2007; Lamperti et al. 2009).

Case Report

We describe a female infant born at 36 weeks and 4 days of gestation by an urgent cesarean delivery for concerns of non-reassuring fetal testing, biophysical profile of 6, and marked polyhydramnios. Ultrasound immediately prior to delivery was significant for IUGR < 5th percentile, small fetal stomach, and polyhydramnios with AFI of 39. These findings were concerning for tracheoesophageal fistula. The infant was delivered limp, with no respiratory effort and undetectable heart rate. The infant required extensive resuscitation, including intubation, chest compressions, and epinephrine in the delivery room. Apgar scores were 1, 1, 1, 2, 3, and 5 at 1, 5, 10, 15, 20, and 25 min of life. The infant was taken to the NICU, and a therapeutic hypothermia protocol was initiated based on the extensive resuscitation measures, initial gases, and seizures within first hour of life. On initial assessment, the infant's neurological status was Sarnat stage 3. The admission exam was consistent, with a birth weight of 2,230 g, head circumference of 33.5 cm, and length of 48 cm. There was no spontaneous eye opening or limb movements. The suck, gag, rooting, moro, and deep tendon reflexes were absent. There was no response to noxious stimuli. The infant's tone was flaccid. She had no dysmorphic features or arthrogryposis. Flexion creases were normal. There was no cardiac murmur or organomegaly.

On further history, mother is a 24-year-old woman with two prior healthy children. She reported a sudden 20-pound weight gain over the last three weeks and decreased fetal movements since ~6 months of gestation, which had been attributed to her class III obesity. She denied exposure to or use of any drugs, tobacco, or alcohol during pregnancy.

Both parents were reportedly healthy, had no significant family history of neuromuscular disorders, and denied consanguinity. The infant's exam remained unchanged over the course of the following weeks, other than for occasional movements of her finger and tongue. Initial echoencephalogram showed a structurally normal brain with no bleeds. Echocardiography showed a structurally normal heart, with signs of pulmonary hypertension on the initial day of life. Electroencephalogram was consistent with mild encephalopathy. Brain MRI and MR venogram showed no evidence of acute ischemia or sinus venous thrombosis. Extensive metabolic workup, including blood gases, blood glucose, serum amino acids, urine organic acids, ammonia, lactate, thyroid studies, acylcarnitine profile, gamma-glutamyltransferase, transaminases, aldolase, creatine kinase, and initial and repeat newborn screens, were all within normal limits. The sepsis workup done during hospital stay was negative. Additionally, the placental pathology was unremarkable. Single nucleotide polymorphism (SNP) array, whole-exome sequencing, and sequential analysis with deletion testing of the mitochondrial genome were performed.

The infant was noted to have hypercarbia when challenged with low ventilator settings and was thought to be ventilator-dependent. On day 29 of life, after extensive discussion with the family, the parents agreed to withdraw care because of the unfavorable prognosis. The patient was extubated and expired within minutes after the extubation. An unrestricted autopsy was performed immediately after death. At time of the autopsy, the baby weighed 2,590 g and the crown-heel length was 43 cm. There were no apparent dysmorphic features or evidence of congenital malformations. The most significant histological findings included diffuse intracytoplasmic, pale basophilic inclusions in the cardiac myocytes, hepatocytes, and skeletal muscle fibers [Fig. 1, upper panel (a–d)]. These inclusions were strongly positive for periodic acid-Schiff (PAS) staining [Fig. 1, middle panel (e–h)] and resistant to diastase digestion, i.e., positive for PAS-diastase staining [Fig. 1, lower panel (i–l)], which are consistent with indigestible abnormal polysaccharide material and support the diagnosis of type IV glycogen storage disease.

SNP array performed on the patient's peripheral blood did not reveal any clinically significant microdeletion or micro-duplication. Five small regions of homozygosity were identified, and the gene of interest was not a part of it. Subsequently, whole-exome sequencing further confirmed the diagnosis. The patient was noted to have two pathogenic variants in the *GBE1* gene, one resulting from a de novo change p.E449X (c.1345G>T) and the other inherited from the mother p.L490WfsX5 (c.1468delC). Pathogenic variants in *GBE1* gene are known to cause autosomal recessive GSD-IV. Clinical presentation, along with positive pathology findings suggestive of GSD-IV and

Fig. 1 Histopathological features of diffuse intracytoplasmic inclusions in the myocardial fibers (**a**, **e**, **i**), hepatocytes (**b**, **f**, **j**), intercostal skeletal muscle fibers (**c**, **g**, **k**), and thigh skeletal muscle fibers (**d**, **h**, **l**). Top panel (**a** through **d**): Tissues with hematoxylin and eosin staining demonstrate intracytoplasmic, pale basophilic inclusions (indicated by yellow arrows). Middle panel (**e** through **h**): Tissues

with periodic acid-Schiff (PAS) staining show strong PAS-positive intracytoplasmic eosinophilic inclusions (indicated by blue arrows). Lower panel (**i** through **l**): tissues with PAS-diasase staining highlight PAS-positive diastase-resistant intracytoplasmic eosinophilic inclusions (indicated by black arrows)

molecular findings of two pathogenic variants of the *GBE1* gene, is consistent with most severe neonatal neuromuscular presentation of autosomal recessive GSD-IV.

Discussion

GSD-IV is a heterogeneous disorder that presents with marked clinical variability. The most classic form is the hepatic form that presents with hepatosplenomegaly and failure to thrive by 18 months of age, followed by progressive liver failure, and death by 5 years of age (Andersen 1956; Bao et al. 1996). The milder form involves nonprogressive hepatic dysfunction, which has little impact on life expectancy and does not necessitate liver transplantation (McConkie-Rosell et al. 1996). In addition to the more common hepatic form, there exists a neuromuscular variant,

which is further classified into four forms based on age at manifestation. The perinatal form of this variant presents with fetal akinesia, arthrogryposis, fetal hydrops, and death in the perinatal period (Alegria et al. 1999). The congenital form manifests with polyhydramnios, profound hypotonia, respiratory failure, and death in early infancy (Tay et al. 2004; Tang et al. 1994; Zellweger et al. 1972; Bao et al. 1996; Assereto et al. 2007; Bruno et al. 2004, 2007; Lamperti et al. 2009; McMaster et al. 1979). The juvenile form presents with hypotonia and/or cardiomyopathy (Bao et al. 1996; Reusche et al. 1992). Lastly, the adult-onset disease presents with diffuse central and peripheral nervous system dysfunction (Bruno et al. 1993).

Literature search yielded a handful of case reports on congenital GSD-IV, all with some variations in their clinical presentation. In 1972, Zellweger et al. reported

one of the earliest demonstrated GBE-deficient cases of infantile onset of GSD-IV with hypotonia (Zellweger et al. 1972). Tang et al. described a neonate with severe hypotonia and dilated cardiomyopathy without liver involvement, but amylopectin-like inclusions were found in hepatocytes, as seen in our patient (Tang et al. 1994). Tay et al. reported two unrelated patients with the congenital variant of GSD-IV, confirmed by pathogenic variants in the *GBE1* gene (Tay et al. 2004). Both pregnancies were complicated by polyhydramnios, and both neonates showed hypotonia and poor respiratory effort at birth. Autopsy results showed pale, atrophic skeletal muscles, and PAS-positive, diastase-resistant globules in the liver, heart, skeletal muscle, and neurons of the brain and spinal cord. Assereto et al. described two unrelated newborns who showed severe hypotonia at birth and died of cardiorespiratory failure at ages 4 and 12 weeks, respectively (Assereto et al. 2007). Both pregnancies were complicated by polyhydramnios and reduced fetal movements. *GBE1* activity in cultured fibroblasts was less than 5% in both cases. Molecular analysis identified a homozygous null mutation in the 2 gene in each patient.

Bruno et al., Burrow et al., and Fernandez et al. reported a total of four cases of non-lethal congenital hypotonia due to GSD-IV (Bruno et al. 2004; Burrow et al. 2006; Fernandez et al. 2010). All patients had significant delays in motor development, which plateaued at some point, leaving them wheelchair-bound. The degree of fine motor, language, and social impairments in these cases varied from none to moderately affected. These findings support the current theory of GSD-IV being a phenotypic spectrum with varying degrees of organ involvement, age of onset, and evolution of disease process, all dependent on the residual GBE activity (Fernandez et al. 2010). All cases of perinatal or neonatal death from GSD-IV have been associated with the near-complete absence of GBE activity (Assereto et al. 2007; Bruno et al. 2004, 2007).

We have reported here the clinical, pathological, and molecular data of an infant affected with GBE deficiency caused by de novo disease-causing one variant and another disease-causing variant inherited from the mother in the *GBE1* gene. Our patient's de novo p.E449X (c.1345G>T) variant in the *GBE1* gene is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. This variant has not been previously reported as a pathogenic variant nor as a benign variant, but for our patient, it was interpreted as a pathogenic variant. The maternally inherited p.L490WfsX5 (c.1468delC) variant in the *GBE1* gene has been reported previously in GSD-IV. This variant causes a frameshift starting with a codon Leucine 940, changes this amino acid to a tryptophan, and creates a premature stop codon at position 5 of the new reading frame.

Our patient demonstrated features of severe congenital GSD-IV, with profound hypotonia, polyhydramnios, respiratory failure, and no clinical liver or heart involvement. Diagnosis for our patient was made based on the accumulation of PAS-positive, diastase-resistant intracytoplasmic inclusions in hepatocytes, cardiac myocytes, and skeletal muscle fibers. In cases of autosomal recessive disorders, we normally expect both parents to be carriers of the disease-causing variants, but this was not the case for our patient. Only the mother of our patient was found to be a carrier for this variant; the second disease-causing variant happened as a new genetic change (de novo) in our patient. The risk for these parents to have another child affected with GSD-IV is minimal in this scenario.

The neuromuscular variant of GSD-IV is very rare. However, there is a strong possibility of underdiagnosis. The neuromuscular variant of GSD-IV should be considered one of the differential diagnoses in neonates with hypotonia and in pregnancies complicated with polyhydramnios, fetal hydrops, and reduced fetal movement of unknown etiology. The presence of PAS-positive and diastase-resistant inclusion bodies in the muscle is the hallmark for this disease, and gene sequencing is the gold standard for diagnosis.

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Compliance with Ethics Guidelines

Tavleen Sandhu, Michelle Polan, Zhongxin Yu, Rufe Lu, and Abhishek Makkar declare that they have no conflicts of interest.

Tavleen Sandhu and Abhishek Makkar were the members of the primary medical team for the patient and were involved in planning, conduct, and reporting of the case. Michelle Polan, Zhongxin Yu, and Rufe Lu were part of the consultancy team and were involved in reporting of the case. Abhishek Makkar is the guarantor for this manuscript.

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