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Premature Identical Twin Neonates With Sleep Apnea

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Case Report

A pair of 3-month-old twin girls were admitted to our hospital for evaluation of severe obstructive and central sleep apnea. Maternal medical history was unremarkable; this was the mother's first pregnancy. Prenatal course was notable for twin gestation. The parents were both of Irish, English, German ancestry and consanguinity was neither known nor suspected. The pregnancy was complicated by premature rupture of membranes at 28 weeks' gestation, leading to delivery by cesarean section at 28.6 weeks' gestation at an outside hospital. Growth parameters for the twins were appropriate for gestational age.

Soon after birth, the twins required noninvasive positive pressure ventilation for respiratory support. Skin examination showed scaly, dry skin over the trunk consistent with neonatal ichthyosis. Axial arching and increased tone were noted on neurological examination. Mild anemia (hemoglobin 9–10 g/dL) and thrombocytopenia (90000–110000 platelets/mm³) were noted. State newborn metabolic screens were within normal limits. Given the finding of ichthyosis, a single-nucleotide polymorphism chromosome microarray analysis was sent to evaluate for genetic disorders, which ultimately revealed no abnormality but did confirm monozygosity. The twin girls were transferred to a rehabilitation facility at 2 months of age for management of problems attributed to prematurity, including feeding intolerance and hypoxia requiring supplemental oxygen. At the rehabilitation facility, the feeding problems persisted, with oral aversion and recurrent emesis. Given persistent hypoxemia, sleep studies were performed which demonstrated severe obstructive and central sleep apnea with resting end-tidal CO₂ ranging from 54 to 56 mm Hg and severe desaturations ranging from 72% to 74% on room air, precipitating transfer to our hospital for further management.

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Author Contributions

AR conceptualized and wrote the manuscript. JDiaz, JDuis, and CL contributed to and revised the manuscript. LN and GM provided expert guidance and reviewed and revised the manuscript. DSJ performed the laboratory analyses on the patients' cells.

Declaration of Conflicting Interests

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On admission, their physical examinations were notable for bradypnea, with resting respiratory rates between 10 and 15 breaths per minute, flattened facies, downturned mouth, and micrognathia. No hepatomegaly was appreciated, but the spleen tips were palpable. Scaly skin was noted on the trunk and extremities. Neurological examination in both patients was notable for minimal interaction with the environment, absent blink-to-threat responses, marked extensor tone in the trunk and bilateral lower extremities, multiple beats of lower extremity clonus, and diffuse hyperreflexia. Nasal bilevel positive airway pressure (BiPap) was initiated for decreased respiratory drive and hypercarbia. Continuous nasogastric tube feeds were initiated secondary to emesis and inability to tolerate oral feedings. Brain magnetic resonance images were negative for evidence of anatomic abnormalities, or gray-white matter disease. Electroencephalography did not reveal epileptiform foci. Ear, nose, and throat evaluation demonstrated no structural causes accounting for the obstructive sleep apnea. Mild anemia (hemoglobin of 10.5 g/dL) and thrombocytopenia (platelets 96 000/mm³) persisted.

Hospital Course

Given the severity of the neurological findings, further evaluation for genetic causes of the twins' symptoms was pursued. The progressive neurological dysfunction with persistent thrombocytopenia prompted testing for Gaucher disease (GD). The total blood dried-blood spot (DBS) glucocerebrosidase (GCase) enzymatic activity was 0.4 and 0 nmol/h/mg of protein (reference range >1.2 nmol/mL/h) in each twin, consistent with a diagnosis of GD. In the same DBS, the chitotriosidase enzymatic activities were elevated at 191 and 224 nmol/mL/h of protein (reference range <30 nmol/h/mg). Further studies were performed in established fibroblast cell lines (Figure 1). Given the diagnosis and associated poor prognosis, palliative care was consulted. The family ultimately decided to focus on comfort and maximizing quality of life. Over the next few weeks, seizures, persistent desaturations, and opisthotonus developed. The twins died within 24 hours of each other at 5 months of age.

The parents chose to pursue natural conception for subsequent pregnancies. After the death of the twins, the couple had a spontaneous first trimester abortion. In their next pregnancy, chorionic villus sampling at 11 weeks' gestation revealed that the fetus was a carrier of the paternal-derived *GBA* gene mutation, and thus, an unaffected carrier of Gaucher disease.

Final Diagnosis

Gaucher disease type 2.

Discussion

GD is an autosomal recessive lysosomal storage disease with an incidence in the general population of approximately 1/17 300 to 1/50 000.^{1,2} In the Ashkenazi Jewish population, its incidence may be as high as 1/800.³ The most common type of Gaucher disease is type 1 (GD-1), which presents in childhood with hepatosplenomegaly. Laboratory findings in GD-1 include anemia, leukopenia, and thrombocytopenia.⁴ Patients with Gaucher disease types 2

(GD-2) and 3 (GD-3) have neurological, visceral, hematological, and skeletal manifestations.⁴

GD is caused by decreased function of the catabolic enzyme glucocerebrosidase (GCase), leading to accumulation of its primary substrate glucocerebroside in the reticulum endothelial system of cells in the bone marrow and brain. This leads to the classic pathological finding of lipid-engorged macrophages with “crumpled tissue” cytoplasm from biopsies of the bone marrow, liver, or spleen. The definitive diagnosis is made by measurement of GCase activity in peripheral leukocytes.⁵ Since GD is an autosomal recessive condition, identification of 2 disease-causing alleles in the *GBA* gene confirms the diagnosis.

The wide clinical variability of GD-2 has been recognized over the past several years. In the “classic” form of GD-2, infants present with neurological symptoms in the first year of life and rapidly decline, resulting in death in early childhood.^{6,7} Somatic symptoms of GD-2 include dysmorphic features, thrombocytopenia, anemia, and progressive organomegaly.^{6,7} The perinatal lethal phenotype is a rare form of GD-2 that presents with neonatal ichthyosis. Histopathologically, ichthyosis is caused by the deficiency of GCase in the epidermis resulting in the predominance of glucosylceramide compared to ceramide, leading to epidermal dehydration.

We describe a case of premature monozygotic twins who presented in the neonatal period with GD-2. Clinicians must maintain a high index of suspicion to pursue an underlying diagnosis in the face of common symptoms that might otherwise be attributed to prematurity. In hindsight, the early findings of abnormal tone, feeding difficulties, respiratory distress, and thrombocytopenia were suggestive of GD-2, but were overlooked or mistakenly attributed to prematurity. The presence of ichthyosis did trigger evaluation with SNP array, but the skin findings were mild and improved with emollient creams, so further genetic evaluation was not pursued. Of note, it has been shown that patients affected with GD-2 demonstrate improvement in the ichthyosiform lesions with time.^{6,7} As the twins grew older and their neurologic examination worsened, it remained imperative to continue to reexamine the clinical evidence and revisit the differential diagnosis in order to arrive at the final diagnosis.

Multiple ethical issues arose during the care of the twins. Before the diagnosis was established, invasive procedures, including tracheostomy or gastrostomy tube placement were being considered to address the twins’ most pressing medical concerns. However, given the high suspicion of an underlying genetic disorder, invasive interventions were deferred pending a definitive diagnosis.

The care of twins with identical phenotypes of a terminal illness provided additional challenges. Multidisciplinary care was required to assist family members in coping. Social work, nursing, pastoral care, and child life were all integral in providing support to the family. Attention was given to ensure that the family was able to celebrate their daughters’ milestones despite being in the hospital, such as having the twins baptized by the hospital chaplain.

Sequencing of the *GBA1* gene in the twins identified mutations in both the maternal and paternal alleles, indicating compound heterozygosity: c.887 G>A in exon 8 predicted to result in the substitution of glutamine for arginine in codon 257 (p.Arg257Gln) and c.1246 G>T in exon 10, predicted to result in the substitution of cysteine for glycine in codon 377 (p.Gly377Cys). The p.Arg257Gln mutation, in heterozygosity with the recombinant allele *RecNciI*, was first described in an Australian child who presented with ichthyosis at birth and died at 3 weeks of age from GD-2.⁸ The p.Gly377Cys mutation is a novel mutation identified in the twins. A substitution of glycine for serine in the same codon (p.Gly377Ser) was previously described in patients with GD-1 and GD-2 of Portuguese and Spanish ancestry.^{9–11} The p.Gly377Cys results in a disruptive amino acid substitution from a small and nonpolar amino acid (glycine, Gly) to a sulfur-containing amino acid (cysteine, Cys). This results in lower GCase enzymatic activity in comparison with other mutants (Figure 1), predicting an earlier onset and rapidly progressive clinical course as observed in the twins reported here.

For parents who are known carriers of genetic disease, prenatal and preimplantation genetic diagnosis (PGD) allows for the early identification of fetuses and embryos with a particular diagnosis. While PGD has been associated with significant controversy, it has allowed many couples to have healthy children. Additionally, reproductive options in families where both the mother and father are carriers of the same disease include adoption, use of a donor egg or sperm, and invasive prenatal diagnosis after conception to allow for the family to make a decision regarding whether to continue the pregnancy in the case of an affected fetus.

Conclusion

This case of twins born prematurely who developed signs of neurologic dysfunction and were ultimately found to have GD-2 is a compelling reminder of the challenges parents and providers face in the care of premature infants. Distinguishing unique features of a genetic disease from those typical of infants born prematurely is important for early diagnosis and appropriate care of patients and families. A novel mutation was identified in the *GBA1* gene causing significantly reduced GCase activity and resulting in the rapid clinical decline observed in the twins. Pursuit of genetic testing is integral for preconception genetic counseling for parents considering subsequent pregnancies.

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Figure 1.

Glucocerebrosidase (GCase) enzymatic activity levels in the affected twins with Gaucher disease type 2 (GD-2). Primary cultured fibroblast lines were established from the twins, represented here as patients 2 and 3. (A) The fibroblast GCase enzymatic activity was dramatically reduced in patients 2 and 3 in comparison with both control and fibroblast GCase from a patient with GD-1 carrying homozygous Asn370Ser mutation (patient 1). (B) Using a specific GCase antibody, Western blotting showed GCase levels of patients 2 and 3 substantially reduced in comparison with control and patient 1 with GD-1 (Asn370Ser). The recombinant GCase was used as a reference control with molecular weight of ~60 kD.