JPPT | Case Report

Monogenic Familial Neonatal Diabetes in Preterm Infant With *ABCC8* Gene Mutation: Transition to Oral Sulfonylurea Therapy

Elizabeth Behre, DO; Sierra S. Donnell, MD; Nicole Larsen, MD; Guido Mora, MD; and Kousiki Patra, MD

Sulfonylurea treatment has been shown to improve both glycemic control and neurodevelopmental outcomes in neonatal diabetes (NDM) secondary to *ABCC8* gene mutations. Given these mutations are among the most common, an empiric sulfonylurea trial may be reasonable. We report a case of NDM secondary to an *ABCC8* mutation in an infant born at 34 6/7 weeks gestational age (GA) who was transitioned to oral sulfonylurea therapy at 38 2/7 weeks corrected GA. Empiric oral sulfonylurea therapy was initiated while genetic testing was pending, which later confirmed the diagnosis of monogenic NDM. Empiric transition to sulfonylurea therapy in a preterm infant with monogenic NDM is described for the first time in the literature. Furthermore, this report offers possible guidance relating to initial sulfonylurea dose at initiation and the utility of additional genetic testing in family members.

ABBREVIATIONS ACTH, adrenocorticotropic hormone; DOL, day of life; FDA, US Food and Drug Administration; K_{ATP}, ATP-sensitive potassium; MODY, maturity onset diabetes of the young; NDM, neonatal diabetes; NICU, neonatal intensive care unit; SUR1, sulfonylurea receptor 1 protein

KEYWORDS ABCC8; genetic diagnosis; glyburide; neonatal diabetes; neonatology; perinatal endocrinology; preterm; sulfonylurea

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Introduction

Hyperglycemia is common in preterm infants. Causes include inadequate insulin secretion, sepsis, stress-induced suppression of insulin and/or increased production of glucose, and iatrogenic causes like parenteral nutrition or steroids. Neonatal diabetes mellitus (NDM) from a single gene mutation, or monogenic diabetes, is a rare cause of neonatal hyperglycemia, occurring in 1 in 90,000 to 160,000 live births.[1] This uncommon disease is important to recognize early as diagnosis can help determine prognosis and guide treatment. NDM should be considered when hyperglycemia persists beyond 7 to 10 days of life. Furthermore, genetic testing should be considered in any case of diabetes diagnosed in infants under 6 months old, as the majority of these cases are due to single gene mutations. NDM may be transient with typical resolution in 3 to 6 months (~3/4 of cases) or less commonly, permanent, and is more common in infants born greater than 32 weeks' gestation.[1]

There are over 20 different genes implicated in NDM with heterozygous mutations in *ABCC8*, *KCNJ11*, 6q24-related, and *INS* gene alterations being the most common.[2] Genetic testing is essential to guide prognosis, long-term management, and to determine risks for family members. While insulin is the first-line treatment for most genetic mutations, sulfonylurea treatment has been shown to improve both glycemic control and neurodevelopmental outcomes specifically in NDM secondary to *ABCC8* and *KCNJ11* gene mutations, which represent one third to half of permanent cases.[3,4]

We hereby report a case of NDM secondary to an *ABCC8* mutation. The *ABCC8* gene encodes the sulfonylurea receptor 1 (SUR1) protein, a subunit of the ATP-sensitive potassium (K_{ATP}) channel on pancreatic beta cells that plays a vital role in K_{ATP} channel closure. Normally, closure of this channel depolarizes the beta cell membrane resulting in a calcium influx that prompts insulin release. However, *ABCC8* gene mutations can inhibit closure of the K_{ATP} channel thereby interfering with insulin release and causing hyperglycemia. Sulfonylureas increase insulin secretion through SUR1 subunit binding, which facilitates closure of the K channel. Mutations in *ABCC8* are more likely to cause transient NDM, and have also been found in patients with maturity onset diabetes of the young (MODY). Furthermore, multiple case reports have described the variable phenotypic expression of *ABCC8* mutations within a single family, ranging from NDM to impaired fasting glucose.[5–7] The presence of a strong family history of diabetes, particularly when poorly classified, should raise suspicion for diagnosis of NDM in infants with hyperglycemia. Diagnosis also warrants consideration

of genetic testing or diabetes screening in family members. This case describes the empiric transition to sulfonylurea therapy as well as the implications for family members in the setting of a genetic diagnosis.

Case History

A female infant is born small for gestational age (1795 grams, 0.2%ile) at 34 6/7 weeks gestation via cesarean section due to severe maternal preeclampsia. Her mother is a 28-year-old with a medical history notable for poorly controlled pre-gestational diabetes on insulin with chronic kidney disease, anemia, chronic hypertension and recurrent urinary tract infections. The patient is admitted to the neonatal intensive care unit (NICU) due to prematurity requiring intubation soon after admission due to respiratory failure secondary to respiratory distress syndrome. Initial labs are notable for anemia requiring blood transfusion, severe metabolic acidosis and hyperglycemia (~300 mg/dL). The infant is given 2 intravenous insulin boluses of 0.1 units/kg prior to initiation of an insulin infusion at 0.01 units/kg/hr due to worsening hyperglycemia on day of life (DOL) 1. Initial sepsis workup was unremarkable and empiric antibiotics and antifungals were discontinued after 3 days. Following normalization of blood glucose and overall clinical improvement, the insulin drip is discontinued on DOL 2 with extubation on DOL 3.

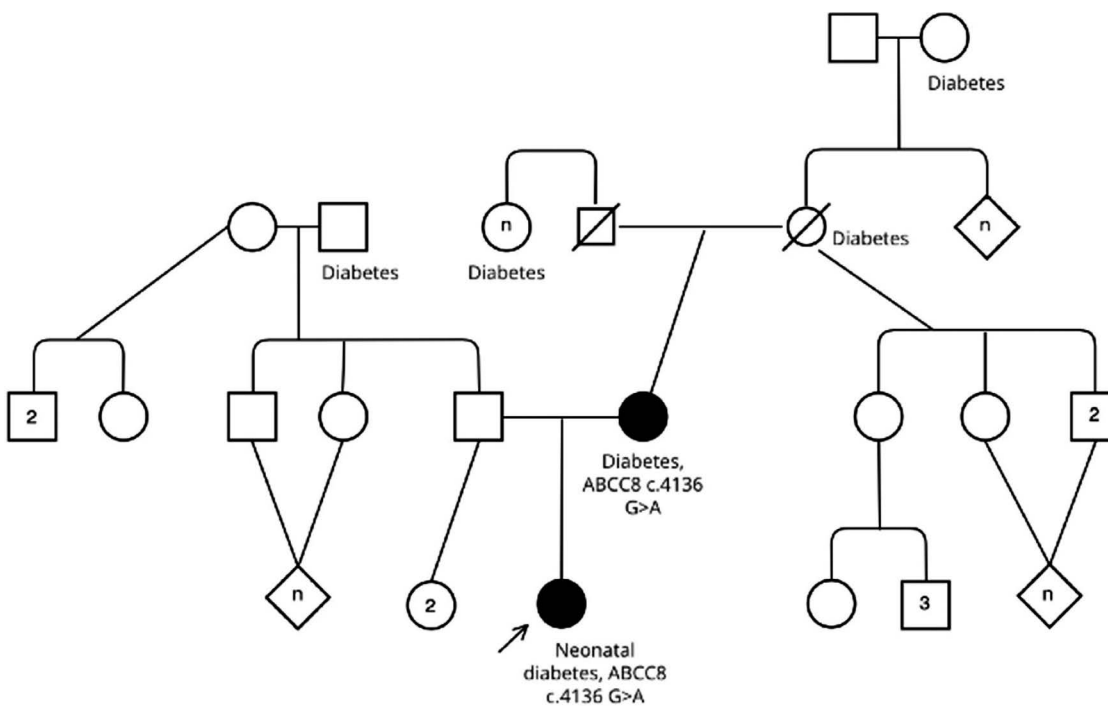
Additional history reveals an absence of maternal genetic testing and an equivocal diabetes diagnosis originally noted at age 16 as type II diabetes without obesity. She was later diagnosed with type I diabetes with elevated insulin antibodies and low C-peptide, but a new concern for MODY exists given a strong family history of diabetes (Figure) and intermittent insulin requirement.

The differential diagnosis of infant's hyperglycemia remains broad. Her lab evaluation includes normal cortisol and adrenocorticotropic hormone concentrations, negative type 1 diabetes antibodies. Abdominal ultrasound showed no pancreatic hypoplasia or anomaly. Pediatric genetics is consulted, who recommended sending the Prevention Genetics Monogenic Diabetes panel.

Blood glucose concentrations improved between DOL 3 to 8 without need for insulin, however, on DOL 8, the patient is again noted to have hyperglycemia (~300 mg/dL), prompting a pediatric endocrinology consult. She is started on lispro, a subcutaneous short-acting diluted insulin U10 (10 units/mL) following a sliding scale. This was preferred over a long-acting insulin regimen due to the infant's size in an effort to avoid hypoglycemia. A glucose target of 250 mg/dL was initially recommended and a low dose of 0.25 units of diluted insulin (~0.15 units/kg/dose) was initially given for blood glucose values above the target, with titration of the insulin dose depending on the glucose level. Preprandial insulin was given as needed every 3 hours. Long-acting insulin was not started because glycemic control was maintained adequately with bolus dosing.

After a week of intermittently requiring insulin therapy, and with genetic testing pending, pediatric

Figure. Family pedigree; numbers describe quantity of offspring, n indicates number of offspring unknown.



endocrinology recommended a sulfonylurea trial given high efficacy and insulin independence for patients with monogenic NDM due to *KCNJ11* or *ABCC8* mutations. Given its favorable half-life and presence in the literature, glyburide was chosen and initiated 0.1 mg/kg (0.24 mg) every 12 hours. Of note, glyburide is not commercially available as a liquid and as such was prepared by the hospital pharmacy using six 5 mg glyburide tablets and 30 mL of Ora-Blend to create a 1 mg/mL suspension, stored in the refrigerator with a shelf life of 14 days. Following this initiation at 38 2/7 weeks, sliding-scale insulin was completely weaned off within 12 hours. The glyburide was then titrated down 5 times due to hypoglycemia which occurred usually 2 to 4 hours after the dose was provided (Table). The lowest dose of 0.05 mg daily (0.02 mg/kg or 0.05 mL daily) was reached 10 days after the first titration. She is ultimately discharged on glyburide 0.05 mg daily (0.017 mg/kg or 0.05 mL daily) without any insulin requirement. On the day of discharge from the NICU, her genetics panel results were positive with a pathogenic variant in *ABCC8* c.4136G>A, p.Arg1379His, heterozygous, confirming a neonatal monogenic diabetes diagnosis.

Maternal genetic testing reveals the same pathogenic variant with significant implications for further management of mother's diabetes. The patient continues to be followed with outpatient pediatric endocrinology. Parents self-discontinued glyburide at an unknown age sometime between 4 and 8 months old. During the last visit at twelve months of age, good glycemic control and a normal hemoglobin A1c (5.4%) were documented. Given her continued growth with euglycemia, this most likely represents transient NDM.

Table. Glyburide Titration Dosing and Glucose Nadir

Day #	Glyburide PO Dose	Glucose Nadir Prompting Titration	Last Dose Held Prior to Titration?
0	0.1 mg/kg BID	42 mg/dL	no
1	0.08 mg/kg BID	42 mg/dL	yes
3	0.06 mg/kg daily	47 mg/dL	no
5	0.04 mg/kg daily	56 mg/dL	no
7	0.02 mg/kg BID	54 mg/dL	no
10	0.02 mg/kg daily	–	–

Discussion

Because of the low prevalence of NDM, diagnosis may be delayed with potentially profound negative effects. Treatment of hyperglycemia with delayed NDM diagnosis may result in complications from unnecessarily prolonged insulin use, such as hypoglycemia. If there is undetected hyperglycemia secondary to NDM, more serious sequelae including diabetic ketoacidosis, hyperosmolar dehydration, or neurologic complications can result.

Prompt diagnosis and appropriate transition to sulfonylureas has shown positive outcomes compared to other interventions for NDM resulting from *KCNJ11* or *ABCC8* mutations. In 1 study, those on sulfonylureas instead of insulin had better HbA1c values at 1 year, and glycemic control remained excellent at 10-year follow up.[8] This study also noted over 60% of subjects had neurologic features including developmental delay or learning difficulties, over 50% of which improved after transition to sulfonylureas. Other research involving sulfonylurea use in this population has noted more specific neurologic improvements in areas including hypotonia, visual attention deficits, and motor skills.[9]

There are few case reports that describe sulfonylurea use in very young infants. For example, Wambach et al[10] describe transition to sulfonylurea in a full-term infant on day of life 5. Our case represents the first with insulin to sulfonylurea transition in a preterm infant once corrected to full term. However, further research is needed to better understand dosage, administration times, effect on comorbidities, and potential complications in neonates, particularly those born preterm. Of note, our patient, several patients described in Carmody et al,[3] and the neonate described in Wambach et al[10] are the only published cases of *KCNJ11* or *ABCC8 associated* NDM started on a sulfonylurea under DOL 30. Both cases where sulfonylurea dose changes were provided, ours and Wambach et al,[10] involved starting glyburide 0.1 mg/kg twice daily, and both these cases had the initial dose decreased by more than 50% in the first 48 hours due to hypoglycemia.[10] This suggests smaller glyburide starting doses may be more appropriate in these patients at younger ages.

The *ABCC8* c.4136G>A mutation carried by our patient has been previously described in the literature.[11,12] However, relatively little is currently known about the individual mutations within the *ABCC8* gene regarding variability in clinical presentation and treatment response. Our case corroborates the previously well-established phenotypic variability within various *ABCC8* mutations associated with monogenic diabetes. To our knowledge, this represents the first case to describe phenotypic variability within a single family harboring the *ABCC8* c.4136G>A mutation specifically. Furthermore, genetic testing in our patient helped clarify her mother's long misclassified diagnosis and guided more appropriate maternal therapy.

Conclusion

Our case illustrates the importance of genetic testing in hyperglycemic neonates when family history suggests undiagnosed monogenic diabetes. Sulfonylurea use was started prior to genetic profile completion given possible benefits. Carmody et al[3] have noted

multiple advantages of empiric treatment, including the excellent safety profile of sulfonylurea use in children, reduction in treatment costs if successful, potential to ameliorate neurodevelopmental disability in some cases, and a potentially shortened inpatient stay. Disadvantages noted included a lack of FDA approval for infantile sulfonylurea use, a lack of a commercially available oral suspension, and a hypoglycemia risk during transition and in those with transient forms of neonatal diabetes.[3] Our case supports consideration of empiric sulfonylurea treatment prior to available genetic test results in neonates with strongly suspected NDM.

Article Information

Affiliations. Division of Endocrinology (EB), Seattle Children's Hospital; Division of Hospital-Based Medicine (SD), Ann and Robert H. Lurie Children's Hospital of Chicago; Department of Pediatrics (NL), Division of Neonatal-Perinatal Medicine, University of Michigan C.S. Mott Children's Hospital; Division of Endocrinology (GM), Ann and Robert H. Lurie Children's Hospital of Chicago; Department of Pediatrics (KP), Division of Neonatology, Rush University Medical Center.

Correspondence. Elizabeth Behre, DO; elizabeth.behre@seattlechildrens.org

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