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Case Report

Permanent neonatal diabetes mellitus: a genetic switch gone wrong

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ABSTRACT

Permanent neonatal diabetes mellitus (PNDM) is a rare monogenic disorder characterized by persistent hyperglycemia presenting before six months of age. Mutations in genes encoding the ATP-sensitive potassium (KATP) channel, particularly ABCC8, are an important cause of PNDM and have significant therapeutic implications, as many affected patients can be successfully transitioned from insulin therapy to oral sulfonylureas following genetic confirmation. A 7-month-old female infant, initially diagnosed with diabetes at 2 months of age, presented with recurrent hyperglycemia. Laboratory evaluation showed random blood glucose 450 mg/dL, HbA1c 9.5%, C-peptide 0.2 ng/ml, low insulin levels, and negative pancreatic autoantibodies. Genetic analysis using whole-exome sequencing identified a heterozygous pathogenic variant in the ABCC8 gene, confirming permanent neonatal diabetes mellitus. The patient was initially managed with subcutaneous insulin (0.8 U/kg/day) and subsequently transitioned to oral glibenclamide beginning at 0.2 mg/kg/day under continuous glucose monitoring. The dose was gradually escalated while insulin was tapered and discontinued within three days. The infant achieved stable euglycemia without recurrent hypoglycemia or hyperglycemia on glibenclamide monotherapy. At six months of follow-up, HbA1c improved from 9.5% to 5.8%, with normal growth, satisfactory developmental progress, and sustained glycemic control. This case highlights the importance of early genetic testing in infants presenting with diabetes before six months of age. Identification of an ABCC8 mutation enabled precision-based treatment with sulfonylurea, resulting in successful insulin discontinuation and excellent metabolic control. Early molecular diagnosis facilitates individualized therapy, improves long-term outcomes, and supports appropriate genetic counseling.

Keywords: Permanent neonatal diabetes mellitus, ABCC8 mutation, Monogenic diabetes, Sulfonylurea therapy, Precision medicine

INTRODUCTION

Permanent neonatal diabetes mellitus (PNDM) is a rare monogenic form of diabetes characterized by persistent hyperglycemia occurring within the first six months of life due to impaired pancreatic β-cell function rather than autoimmune destruction. Unlike type 1 diabetes mellitus, which typically develops later in childhood and results from autoimmune β-cell destruction, neonatal diabetes arises from single-gene defects affecting insulin synthesis, secretion, or pancreatic development. The estimated incidence of neonatal diabetes ranges from 1 in 90,000 to 1 in 260,000 live births, with approximately half of the affected infants having permanent disease requiring lifelong treatment. Early recognition is crucial because many genetic forms of neonatal diabetes have targeted therapeutic options that can dramatically improve glycemic control and quality of life while avoiding unnecessary lifelong insulin therapy.[1,2] Advances in molecular genetics have transformed the understanding of PNDM over the past two decades. More than 30 genes have been implicated in neonatal diabetes, with mutations in KCNJ11, ABCC8 and INS accounting for the majority of permanent cases. The KCNJ11 and

ABCC8 genes encode the Kir6.2 and sulfonylurea receptor-1 (SUR1) subunits, respectively, of the ATP-sensitive potassium (K-ATP) channel in pancreatic β-cells. Under physiological conditions, increased intracellular ATP generated by glucose metabolism closes the K-ATP channel, resulting in membrane depolarization, calcium influx, and insulin secretion. Activating mutations in these genes prevent channel closure, impairing insulin release despite adequate glucose levels and leading to persistent hyperglycemia from early infancy.[3-5]

Among the known genetic causes, ABCC8 mutations demonstrate considerable phenotypic variability. Depending on the nature and inheritance of the mutation, affected individuals may develop transient neonatal diabetes, permanent neonatal diabetes, or diabetes later in life. Importantly, many patients with activating ABCC8 mutations respond remarkably well to oral sulfonylurea therapy because these drugs close the K-ATP channels through an ATP-independent mechanism, restoring endogenous insulin secretion. Successful transition from insulin injections to oral sulfonylureas has been associated with improved metabolic control, reduced treatment burden, and enhanced neurodevelopmental outcomes, highlighting the importance of establishing an accurate molecular diagnosis.[3,6,7] The clinical presentation of PNDM usually includes persistent hyperglycemia within the first six months of life, intrauterine growth restriction, failure to thrive, dehydration, polyuria, poor weight gain, and diabetic ketoacidosis in severe cases. Certain genetic mutations, particularly those involving K-ATP channel genes, may also be associated with neurological manifestations including developmental delay, epilepsy and muscle weakness, collectively referred to as developmental delay, epilepsy and neonatal diabetes (DEND) syndrome. Consequently, comprehensive clinical evaluation combined with early genetic testing has become an integral component of the diagnostic approach in infants presenting with diabetes before six months of age.[2,5,8] This case highlights the pivotal role of precision medicine in neonatal diabetes by demonstrating how identification of an activating ABCC8 mutation fundamentally altered therapeutic management. Recognition of the underlying genetic defect enabled successful transition from insulin therapy to oral sulfonylurea, emphasizing that early molecular diagnosis not only confirms the etiology but also directly influences treatment decisions, improves long-term glycemic control, reduces dependence on insulin injections, and enhances overall patient outcomes.

CASE REPORT

A 7-month-old female infant was referred for evaluation of persistent hyperglycemia. She had been born at term with no significant perinatal complications. At the age of 2 months, she developed recurrent fever, lethargy, and poor weight gain. Initial laboratory investigations revealed a random blood glucose level of 450 mg/dL. She was diagnosed with neonatal diabetes mellitus and stabilized with subcutaneous insulin therapy at a dose of 0.8 IU/kg/day, following which she was discharged. At 5 months of age, the child was readmitted with recurrent hyperglycemia and similar symptoms. Further evaluation was undertaken to identify an underlying genetic cause of diabetes. Laboratory investigations showed HbA1c of 9.5%, C-peptide of 0.2 ng/ml, and low fasting insulin levels, suggestive of impaired endogenous insulin secretion. Autoimmune markers were negative. Genetic testing using next-generation sequencing (NGS) identified a compound heterozygous pathogenic variant in the ABCC8 gene, confirming the diagnosis of permanent neonatal diabetes mellitus (PNDM). Based on the genetic diagnosis, insulin therapy was gradually transitioned to oral glibenclamide (0.2 mg/kg/day) under continuous blood glucose monitoring. The glibenclamide dose was progressively escalated over several days while insulin doses were correspondingly reduced.

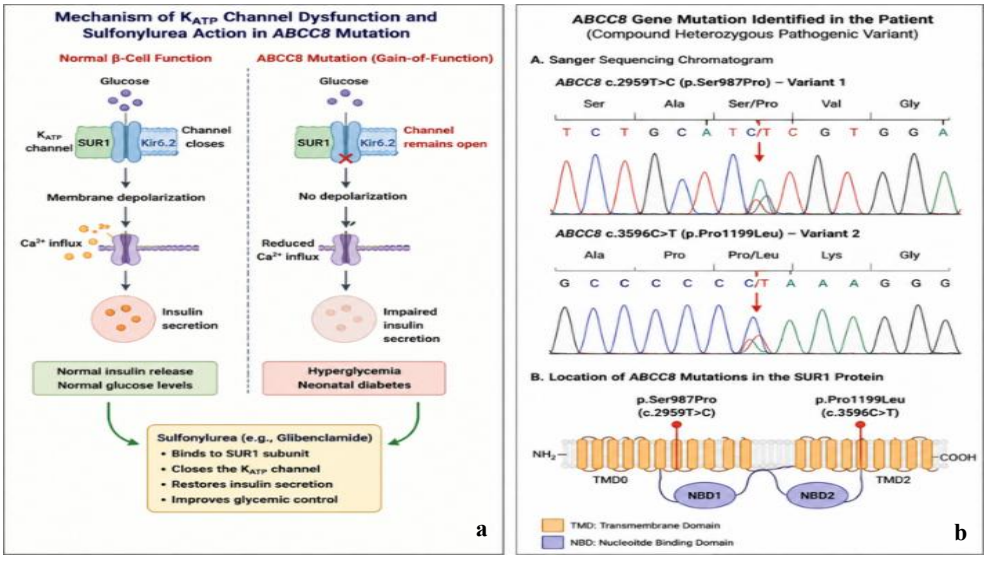


Figure 1 (a and b): Sulfonylurea action in ABCC8 mutation.



Figure 2 (a and b): Children affected with permanent neonatal diabetes mellitus.

Insulin was successfully discontinued on the fourth day of starting glibenclamide, and the patient maintained stable blood glucose levels without episodes of hypoglycemia or recurrent hyperglycemia. On follow-up, the child remained euglycemic on oral sulfonylurea therapy with dose (0.3mg/kg/day). Glycemic control improved substantially, with HbA1c decreasing to 5.8% at six months of follow-up. Growth parameters improved, and developmental milestones showed significant progress. This case highlights the importance of early molecular diagnosis in infants presenting with diabetes before six months of age, as identification of an ABCC8 mutation enabled successful transition from lifelong insulin therapy to oral sulfonylurea treatment, resulting in excellent metabolic control and improved quality of life.

Table 1: Clinical and laboratory profile of the patient with permanent neonatal diabetes mellitus.

Parameter	Findings
Age at presentation	2 months
Sex	Female
Current age at report	7 months
Presenting complaints	Fever, lethargy, poor weight gain, persistent hyperglycemia
Random blood glucose	450 mg/dl
Initial treatment	Subcutaneous insulin (0.8 IU/kg/day)
HbA1c before genetic diagnosis	9.5%
C-peptide	0.2 ng/ml
Fasting insulin	Low
Autoimmune markers	Negative
Genetic analysis	Compound heterozygous pathogenic variant in ABCC8 gene
Final diagnosis	Permanent Neonatal Diabetes Mellitus (PNDM)
Targeted therapy	Oral glibenclamide (starting dose 0.2 mg/kg/day)
Insulin discontinuation	Day 4 after initiation of glibenclamide
Follow-up HbA1c	5.8%
Clinical outcome	Euglycemia maintained on oral sulfonylurea with improved growth and developmental milestones

Table 2: Timeline of clinical course and management.

Age	Clinical event	Management/Outcome
Birth	Full-term birth	No significant perinatal complications
2 months	Fever, lethargy, poor weight gain and hyperglycemia (RBS 450 mg/dL)	Diagnosed with neonatal diabetes; insulin started (0.8 IU/kg/day)
7 months	Recurrent hyperglycemia	Detailed metabolic and genetic evaluation initiated
7 months	HbA1c 9.5%, C-peptide 0.2 ng/ml, low fasting insulin	Suspected monogenic diabetes
7 months	NGS identified pathogenic ABCC8 mutation	Diagnosis of PNDM confirmed

Continued.

Age	Clinical event	Management/Outcome
At admission	Day 0 starting sulfonylurea	Patient was admitted to the hospital before starting sulfonylurea. Required: continuous glucose monitoring
IPD	Day1	Insulin regime was continued [short and long] morning dose Glibenclamide [0.1mg/kg] Prior to evening meal [0.1mg/kg] glibenclamide
	Day 2	Stopped long-acting insulin during transfer process. Continue to administer rapid acting insulin analogue before meals Glibenclamide dose 0.2mg/kg/day
	Day 3	Monitoring glucose monitoring and continue glibenclamide (0.2mg/kg/dose) Reducing pre meal insulin dose by 50% Glibenclamide Total dose: 0.4mg/kg/day
	Day 4	monitoring euglycemic with CGM Glibenclamide Total dose 0.4mg/kg/day Insulin was stopped with assuring response to glibenclamide.
12 months	HbA1c -5.8%	Maintained euglycemic on oral sulfonylurea, growth and development improvement seen

DISCUSSION

Permanent neonatal diabetes mellitus (PNDM) is an uncommon monogenic disorder presenting within the first six months of life and requires prompt recognition because genetic diagnosis directly influences therapeutic decisions. In the present case, a 7-month-old female infant developed persistent hyperglycemia at 2 months of age, with a random blood glucose of 450 mg/dl, HbA1c of 9.5%, C-peptide of 0.2 ng/ml, low fasting insulin levels, and negative autoimmune markers. Genetic testing identified a compound heterozygous pathogenic variant in the ABCC8 gene, confirming PNDM. Following initiation of oral glibenclamide (0.2 mg/kg/day), insulin therapy was successfully discontinued by the third day of treatment, and at six months of follow-up the child maintained excellent glycemic control with an HbA1c of 5.8%, accompanied by significant improvement in growth and developmental milestones. These findings demonstrate the clinical utility of precision medicine in neonatal diabetes, where molecular diagnosis enables individualized therapy.

Our findings are consistent with previous reports highlighting the importance of genetic evaluation in infants presenting with diabetes before six months of age. A study describing the first intronic INS mutation causing PNDM reported a female infant diagnosed with permanent diabetes at 2 months of age, who remained insulin-dependent throughout childhood because INS mutations impair proinsulin processing and do not respond to sulfonylurea therapy.[9] Similarly, Ahamed et al reported a 4-month-old male infant with an INS (C96Y) mutation, fasting blood glucose of 177 mg/dL, HbA1c of 8.2%, and C-peptide of 0.6 ng/ml, who required lifelong insulin therapy because INS mutations result in defective proinsulin folding and β-cell apoptosis.[10] In contrast, our patient harbored an ABCC8 mutation, allowing successful transition from insulin to oral sulfonylurea, emphasizing the therapeutic importance of identifying the underlying genetic defect.

The response observed in our patient also closely parallels previous reports involving ABCC8-associated PNDM. Manyazewal et al described a 45-day-old infant with an ABCC8 mis-sense mutation who achieved euglycemia after successful transition from insulin to oral sulfonylurea monotherapy following genetic confirmation.[11] Likewise, Abraham et al reported a 2-month-old female infant with a novel ABCC8 mutation who was initially managed with insulin and subsequently switched to glibenclamide, achieving improved glycemic control with HbA1c of 6.8% and C-peptide of 2.7 ng/ml after three months of therapy.[12] The improvement observed in our patient, with HbA1c decreasing from 9.5% to 5.8%, further supports the effectiveness of sulfonylurea therapy in K-ATP channel-related neonatal diabetes.

Recent evidence also demonstrates the marked genetic heterogeneity of neonatal diabetes. Perri et al identified a novel ABCC8 variant in transient neonatal diabetes mellitus associated with fetal growth restriction, illustrating that different ABCC8 mutations may produce distinct clinical phenotypes.[13] Similarly, Cao et al reported that 75% of patients with KATP channel mutations were completely or partially transitioned from insulin to oral sulfonylureas, whereas patients with other genetic defects continued to require lifelong insulin replacement.[14] The present case reinforces these observations by demonstrating that early molecular diagnosis of an ABCC8 mutation permitted targeted oral sulfonylurea therapy, successful insulin withdrawal, and excellent short-term metabolic control, highlighting the

pivotal role of genetic testing in optimizing treatment and prognosis in permanent neonatal diabetes mellitus.

CONCLUSION

Permanent neonatal diabetes mellitus is a rare monogenic disorder in which early genetic diagnosis plays a pivotal role in guiding appropriate therapy. In the present case, identification of a pathogenic ABCC8 mutation enabled successful transition from insulin to oral glibenclamide, resulting in discontinuation of insulin within three days, improvement in HbA1c from 9.5% to 5.8%, and sustained euglycemia with favourable growth and developmental outcomes over six months of follow-up. This case highlights that infants presenting with persistent hyperglycemia before six months of age should undergo prompt genetic evaluation, as precision-based treatment can significantly improve metabolic control, simplify long-term management and enhance overall prognosis.

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