International Journal of Scientific Reports
Phadke AK et al. Int J Sci Rep. 2025 Nov;11(11):412-417
http://www.sci-rep.com
pISSN 2454-2156 | eISSN 2454-2164
DOI: https://dx.doi.org/10.18203/issn.2454-2156.IntJSciRep20253328

Case Report

Transient neonatal diabetes in a moderate preterm neonate: tailoring therapy beyond insulin

Abhishek K. Phadke, Ali Kumble, Shuhadamol Arif Khan*, Shadiya T. M.

Department of Pediatrics, Indiana Hospital and Heart Institute, Mangalore, Karnataka, India

Received: 30 July 2025
Revised: 11 September 2025
Accepted: 18 September 2025

***Correspondence:**
Dr. Shuhadamol Arif Khan,
E-mail: shuhudamol@gmail.com

ABSTRACT

Congenital diabetes is a rare form of neonatal diabetes mellitus (NDM), typically resulting from monogenic mutations that impair pancreatic beta-cell development, insulin secretion, or function. It is broadly classified into two types: transient NDM (TNDM), which typically resolves within weeks to months but may relapse later in life, and permanent NDM (PNDM). Unlike type 1 or type 2 diabetes, congenital diabetes manifests within the first six months of life and often requires a distinct diagnostic and therapeutic approach. We present a rare case of congenital diabetes in a 32-week preterm female neonate, born small for gestational age, who developed persistent hyperglycemia from the first day of life. Initial management with intravenous fluids and insulin therapy yielded limited glycemic control, raising the suspicion of insulin resistance. Based on clinical grounds, oral sulfonylurea therapy was initiated, leading to rapid glycemic stabilization and notable catch-up growth. This case underscores the importance of early recognition of monogenic diabetes, the potential effectiveness of sulfonylureas even in preterm neonates, and the need for a high index of suspicion in atypical neonatal hyperglycemia. We describe the clinical course, diagnostic evaluation, and successful management strategy in this infant.

Keywords: Congenital diabetes, Monogenic mutations, Preterm, Insulin, Sulfonylurea

INTRODUCTION

Neonatal hyperglycemia most commonly observed within the first 3 to 5 days of life and typically resolves within a few days; however, it can occasionally be seen up to 10 days after birth. Contributing factors include excessive parenteral glucose administration, sepsis, stress-induced elevations in counter-regulatory hormones, and medications such as corticosteroids.[1] If hyperglycemia persists beyond 10 days of life, especially in the absence of identifiable secondary causes, it warrants evaluation for congenital or neonatal diabetes.

NDM is an uncommon form of diabetes that presents in infants under 6 months of age with incidence of 1 in 90,000 live births.[2] Unlike type 1 diabetes, which is typically autoimmune in nature, NDM is often caused by monogenic mutations that impair insulin secretion from the pancreas. Among the known genetic causes, mutations in the KCNJ11 gene (encoding the Kir6.2 subunit of the ATP-sensitive potassium channel) are one of the most common causes of NDM.[3] TNDM is produced by 6q24 mutations, which include paternal uniparental disomy, partial duplication of paternal origin, or a relaxation of maternal imprinting. ZFP57 (6p22.1) mutations, whether homozygous or compound heterozygous, have also been linked to TNDM.[4]

Clinical symptoms of neonatal diabetes include IUGR, hyperglycaemia, glycosuria, polyuria, severe dehydration, and failure to thrive.[5] Other associate anomalies include facial dysmorphism and deafness, developmental delay, learning difficulties in late life. Involvement of multiple systems like nervous system, cardiac, renal, or urinary tract anomalies also reported in some cases.[6]

Sulfonylureas, which stimulate insulin secretion, can be an effective treatment for certain genetic mutations, offering a potential alternative to lifelong insulin therapy. In approximately half of NDM cases, the illness is lifelong and is known to be PNDM. In the rest, the illness is temporary and disappears during infancy-TNDM, although there is a potential that it will recur later in life.[7] For permanent neonatal diabetes lifelong therapy is required.

We present a unique case of a moderate preterm infant diagnosed with neonatal diabetes, had diabetic ketoacidosis, poor weight gain and high blood sugar values on insulin therapy. The baby was successfully managed with oral hypoglycaemic drugs and now thriving well. This case highlighting the diagnostic process and challenges faced during the treatment and management with oral sulfonylureas.

CASE REPORT

A 32-week preterm female neonate was born to a 29-year-old G4P3L3 mother via emergency lower segment caesarean section (LSCS) due to severe pregnancy-induced hypertension. The parents were third-degree consanguineous. Antenatal ultrasound revealed bilateral uterine artery reduced flow. The mother had received one complete course of antenatal corticosteroids prior to delivery.

The baby had a very low birth weight (1.2 kg) and was small for gestational age. She required neonatal intensive care due to respiratory distress syndrome and apnea of prematurity. From day one of life, the infant had persistent hyperglycemia, despite adjustments in intravenous fluids and glucose infusion rates. Initial differential diagnoses included steroid-induced hyperglycemia and hyperglycemia secondary to caffeine or lipid infusions. However, even after stopping caffeine and lipid infusions, the blood glucose levels remained consistently elevated.

Sepsis workup was negative. During the first week of life, the neonate exhibited classic signs of hyperglycemia, including polyuria and failure to thrive. Blood glucose levels ranged from 300 to 450 mg/dL. Urinalysis showed glucosuria without ketonuria. Both serum and urine ketone levels were normal. Blood insulin and C-peptide levels were within normal limits, suggesting insulin resistance rather than insulin deficiency. Urine gas chromatography-mass spectrometry (GCMS) and tandem mass spectrometry (TMS) were normal, ruling out inborn errors of metabolism.

Of note, the baby's father had early-onset diabetes mellitus, requiring insulin therapy since the age of 20, raising suspicion of a familial or monogenic form of diabetes. Genetic testing of the infant and both parents was sent for evaluation of NDM.

In consultation with a pediatric endocrinologist, subcutaneous long-acting insulin (glargine) was initiated on day 10 of life. However, despite insulin therapy, glycemic control remained poor. The infant continued to lose weight and became lethargic, dehydrated, and showed poor skin turgor by the end of the second week. Blood gas analysis revealed severe metabolic acidosis. Intravenous fluids were initiated to correct dehydration, followed by an insulin infusion and a high-calorie diet. Despite these measures, hyperglycemia persisted.

Given the suspicion of insulin resistance, oral sulfonylurea therapy (glibenclamide at 0.1 mg/kg/day) was started. Remarkably, within 36 hours of initiating sulfonylurea therapy, blood glucose levels normalized to 70-120 mg/dL. The infant’s polyuria decreased significantly, and she began gaining weight. There were no episodes of hypoglycemia, and the infant remained well hydrated with stable weight gain.

The baby was discharged at a corrected gestational age of 36 weeks. At the 1-month post-discharge follow-up, blood glucose levels remained within normal limits, and the infant continued to thrive. She was closely monitored for potential sulfonylurea-related side effects, including hypoglycemia, hepatic dysfunction, and excessive weight gain. No adverse effects were observed.

Molecular genetic testing using Sanger sequencing for 33 known NDM-associated genes revealed no pathogenic mutations. However, considering the strong clinical phenotype suggestive of a monogenic form of diabetes, and given the limitations of Sanger sequencing in detecting large deletions, duplications, intronic variants, and mutations in novel or untested genes, further genetic evaluation using next-generation sequencing (NGS) such as a targeted gene panel or whole-exome sequencing (WES) was recommended.

Based on the clinical presentation, laboratory results, and response to sulfonylureas, a diagnosis of TNDM was considered likely. Parents were counseled regarding the nature of the condition, its potential for relapse later in childhood or adolescence, and the importance of regular monitoring.

At the 3-month follow-up, glycemic control remained stable. Sulfonylureas were gradually tapered and eventually discontinued. At the age of one year, the infant continues to have normal blood glucose levels without the need for pharmacological therapy.

This case highlights the importance of early recognition and targeted therapy in congenital diabetes. The dramatic response to sulfonylureas underscores the potential for oral agents in managing selected cases of neonatal diabetes. Long-term follow-up is essential, given the risk of recurrence and the evolving nature of monogenic diabetes syndromes.

Analyses performed:

I. DNA extraction.

II. Sequencing analyses: Thirty-three genes associated with NDM and other similar forms of monogenic diabetes were screened and analyzed for pathogenic variations using direct sequencing by Sanger method. These are given below.

HNF4A	*INS*	*EIF2AK3*	*NKX2-2*	*SLC29A3*
GCK	*ABCC8*	*GATA6*	*NKX6-1*	*SLC2A2*
HNF1A	*KCNJ11*	*GLIS3*	*PLAGL1*	*STAT1*
IPF1	*AGPAT2*	*INSR*	*PTF1A*	*ZFP57*
HNF1B	*APPL1*	*JAK1*	*RFX6*	*WFS1*
NEUROD1	*BSCL2*	*MAFA*	*SLC16A1*	
CEL	*DNAJC3*	*MNX1*	*SLC19A2*	

Figure 1: Analyses performed.

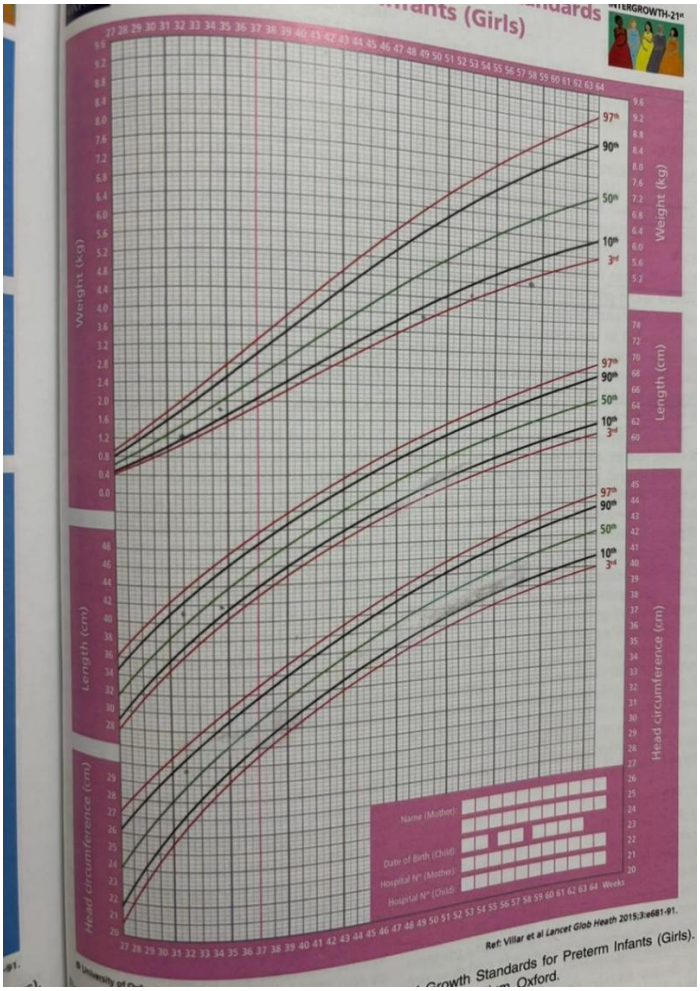

Figure 2: Child was monitored regularly and growth parameters were plotted on the intergrowth 21st chart. Baby's weight gain was found suboptimal.

DISCUSSION

NDM is a rare but important cause of hyperglycaemia in infants typically presents within the first 6 months of life with persistent hyperglycemia, failure to thrive, dehydration, and often intrauterine growth retardation.[8] It may be transient or permanent and is frequently associated with low insulin levels, absence of autoantibodies, and underlying genetic mutations. The disorder usually follows a triphasic course, beginning with neonatal diabetes, followed by a temporary remission, and later a recurrence of diabetes.[9]

Pathophysiology of NDM is described as, defective insulin production or secretion, often due to mutations in genes critical for pancreatic development or β-cell function.[10] This leads to hyperglycemia, dehydration, and in severe cases, diabetic ketoacidosis (DKA). Genetic and molecular mechanisms of TNDM is most commonly caused by abnormalities on chromosome 6q24, which include: paternal uniparental disomy (UPD), paternal duplication and hypomethylation of the maternal allele. These abnormalities lead to overexpression of the PLAGL1 (ZAC) and HYMAI genes, which negatively affect insulin secretion and β-cell function.[11] Insulin secretion is temporarily impaired, and diabetes typically remits by 12-18 weeks of life, although recurrence is possible later.

PNDM is caused by mutations in genes regulating insulin secretion from β-cells, notably: KCNJ11 and ABCC8 (encode components of the ATP-sensitive potassium channel [K-ATP channel]), INS (insulin gene mutations). Others include GCK, EIF2AK3, FOXP3, GLIS3, and more[11]. K-ATP channel mutations impair the channel's closure in response to ATP, preventing membrane depolarization and calcium influx needed for insulin release. These mutations may respond well to sulfonylurea therapy, which closes the K-ATP channels independent of ATP.

NDM may occur in isolation or as part of syndromes with exocrine pancreatic insufficiency, neurological abnormalities (e.g., developmental delay with KCNJ11 mutations) and dysmorphic features or growth restriction (especially in TNDM).

Preterm infants with congenital diabetes often present with severe hyperglycemia that may require more aggressive intervention than what is typically necessary for diabetes of later onset. Since the pancreatic islet cells in preterm infants may already be underdeveloped, the impaired insulin secretion exacerbates the challenges in managing such cases.

The management of NDM depends on the underlying genetic mutation. In cases with KCNJ11 mutations, oral sulfonylureas are the treatment of choice, as they bind to the sulfonylurea receptor on the beta-cell membrane, leading to the closure of ATP-sensitive potassium channels and stimulation of insulin secretion. Sulfonylurea therapy has been shown to be effective in normalizing blood glucose levels in many patients with KCNJ11-related NDM, reducing the need for insulin therapy and improving long-term quality of life.[12]

Genetic testing has become a cornerstone of diagnosis for neonatal diabetes, as it can pinpoint the exact mutation responsible and help differentiate between the various genetic causes of NDM. Importantly, genetic testing is also crucial for tailoring treatment, as the therapeutic approach may differ based on the underlying genetic defect. In particular, KCNJ11-related NDM is sulfonylurea-responsive.

Despite the absence of identifiable pathogenic mutations on Sanger sequencing of 33 genes associated with NDM in this case, the clinical presentation was strongly suggestive of TNDM. The infant exhibited hallmark features of TNDM, including onset of hyperglycemia within the first week of life, small for gestational age status, dehydration, polyuria, and failure to thrive. The marked response to oral sulfonylurea therapy and subsequent spontaneous resolution of hyperglycemia further support the diagnosis. Additionally, the father's early-onset diabetes raises the possibility of a familial monogenic etiology. The inability to detect mutations may be due to limitations of Sanger sequencing, which does not identify epigenetic changes such as 6q24 methylation abnormalities, uniparental disomy, or mutations in non-coding or novel regions. Thus, while genetic confirmation remains ideal, the clinical course and therapeutic response in our patient align with a typical TNDM phenotype, underscoring the importance of recognizing such cases and the potential utility of advanced molecular diagnostics like methylation-specific PCR or whole exome sequencing.

A similar case was reported by Tarasiewicz et al where a term IUGR neonate presented with early-onset hyperglycemia and was diagnosed and managed as transient neonatal diabetes.[13] Despite extensive genetic analysis including next generation sequencing for genes causing monogenic diabetes, no pathogenic mutations were identified by them.

Another case of transient neonatal diabetes was described by Tas et al in a 7-month-old diagnosed with diabetes had been born prematurely at 33 weeks of gestation, and he had hyperglycemia that required a short course of insulin treatment in the NICU during the newborn period, which cured spontaneously within two weeks.[14] In contrast, our case exhibited persistent hyperglycemia with poor response to insulin, but showed significant improvement following initiation of oral sulfonylureas. This comparison highlights the clinical variability in transient neonatal diabetes and emphasizes the need for individualized treatment approaches based on therapeutic response and comprehensive genetic assessment.

Management of neonatal diabetes: sulfonylureas as a treatment option

The treatment of congenital diabetes depends on the specific genetic mutation identified. For infants with KCNJ11 gene mutations, the preferred treatment is the oral use of sulfonylureas, which work by binding to the sulfonylurea receptor on the beta-cell membrane. This binding blocks the ATP-sensitive potassium channels, which leads to membrane depolarization and the subsequent release of insulin from the pancreas. This therapeutic approach is highly effective in patients with KCNJ11 mutations and allows many patients to transition from insulin therapy to oral medication.

In our case, the early initiation of sulfonylurea therapy resulted in rapid normalization of blood glucose levels and resolution of the symptoms of hyperglycemia, such as frequent urination. The patient's weight improved, and no further episodes of dehydration or failure to thrive were noted. This reflects the growing body of evidence supporting sulfonylurea treatment in neonatal diabetes. A comparable case was reported by Jang et al where an infant with congenital diabetes was started on oral sulfonylurea (glimepiride) at 2 months of age.[15] With gradual dose escalation, insulin therapy was successfully discontinued by 3 months of age and they found infant's blood glucose levels have remained well controlled without any significant episodes of hypoglycemia.

Long-term monitoring is necessary to assess for hypoglycemia, which can occur as a result of over-treatment or changes in the infant's feeding patterns. In this case, the patient's response to treatment was positive, with no incidents of hypoglycemia.

The successful management of congenital diabetes with sulfonylureas in a moderate preterm infant underscores the importance of early diagnosis and appropriate treatment. While long-term outcomes for children with congenital diabetes can vary, early and effective treatment significantly improves the prognosis. Early diagnosis allows for optimal glycemic control, reducing the risk of long-term complications, such as retinopathy, nephropathy, and neuropathy, that are commonly seen in patients with poorly controlled diabetes.[16]

Regular follow-up is crucial in these patients. Monitoring should include blood glucose levels, growth parameters, and developmental milestones. Additionally, ongoing genetic counselling is vital to assess the potential implications for future pregnancies and to provide the family with information about inheritance patterns, particularly in the case of familial mutations.

CONCLUSION

This case highlights the importance of considering neonatal diabetes in the differential diagnosis of hyperglycemia in infants. Genetic testing, including sequencing of both parents plays a crucial role in confirming the diagnosis and guiding treatment decisions. The case serves as a reminder that neonatal diabetes should be considered in any infant presenting with unexplained hyperglycemia, when other common causes are excluded. Early identification of the genetic cause of neonatal diabetes allows for implementation of targeted therapies, such as sulfonylureas, which can significantly improve clinical outcomes and prevent lifelong insulin dependency. Early and accurate diagnosis, along with appropriate treatment, is essential for improving the prognosis and quality of life of affected children.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Lemelman MB, Letourneau L, Greeley SAW. Neonatal Diabetes Mellitus: An Update on Diagnosis and Management. Clin Perinatol. 2018;45(1):41-59.
2. Beltrand J, Busiah K, Vaivre-Douret L, Fauret AL, Berdugo M, Cavé H, et al. Neonatal Diabetes Mellitus. Front Pediatr. 2020;8:540718.
3. Flechtner I, Vaxillaire M, Cavé H, Froguel P, Polak M. Neonatal diabetes: a disease linked to multiple mechanisms. Arch Pediatr. 2007;14(11):1356-65.
4. Orphanet: Transient neonatal diabetes mellitus. Available at: https://www.orpha.net/en/disease/detail/99886. Accessed on 15 June 2025.
5. De León DD, Pinney SE. Permanent Neonatal Diabetes Mellitus. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle. 1993.
6. Iafusco D, Zanfardino A, Bonfanti R, Rabbone I, Tinto N, Iafusco F, et al. Congenital diabetes mellitus. Minerva Pediatr. 2020;72(4):240-9.
7. Mohora R, Stoicescu SM. Congenital Diabetes Mellitus. Mædica. 2016;11(2):154.
8. Temple IK, Mackay DJ. Diabetes Mellitus, 6q24-Related Transient Neonatal. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle. 1993.
9. Priyadarshi A, Verge CF, Vandervliet L, Mackay DJ, Bolisetty S. Transient Neonatal Diabetes Mellitus followed by recurrent asymptomatic hypoglycaemia: a case report. BMC Pediatrics. 2015;15(1):200.
10. Neonatal diabetes mellitus: Clinical features, diagnosis, and management-UpToDate. Available at: https://www.uptodate.com/contents/neonatal-diabetes-mellitus-clinical-features-diagnosis-and-management. Accessed on 15 June 2025.
11. Naylor RN, Greeley SAW, Bell GI, Philipson LH. Genetics and pathophysiology of neonatal diabetes mellitus. J Diabetes Investig. 2011;2(3):158-69.
12. Long-term Follow-up of Glycemic and Neurological Outcomes in an International Series of Patients With

Sulfonylurea-Treated ABCC8 Permanent Neonatal Diabetes. 2021;44.
13. Tarasiewicz M, Pietrzykowska A, Włodarczyk J, Seget S, Gadzalska K, Jakiel P, et al. Transient Neonatal Diabetes Mellitus with an Unknown Cause in a 1-Month-Old Infant: A Case Report. Healthcare (Basel). 2024;12(13):1257.
14. Tas E, Al-Hosain E, Movva S, Colangelo T, Gurtunca N. Neonatal diabetes mellitus May Offer the Missing Link to monogenic diabetes in family members: A case report. J Clin Translat Endocrinol. 2024;32:100171.
15. Jang S, Yang M, Ahn SY, Sung SI, Chang YS, Park WS. Neonatal Diabetes Mellitus Due to KCNJ11 (KIR6.2) Mutation Successfully Treated with Sulfonylurea. Neonatal Med. 2021;28(2):94-8.
16. Polak M, Cavé H. Neonatal diabetes mellitus: a disease linked to multiple mechanisms. Orphanet J Rare Dis. 2007;2:12.

Cite this article as: Phadke AK, Kumble A, Khan SA, Shadiya TM. Transient neonatal diabetes in a moderate preterm neonate: tailoring therapy beyond insulin. Int J Sci Rep 2025;11(11):412-7.