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Case Report

Transient neonatal diabetes mellitus with subtype ZFP57 genetic defect in 6q24: familial recurrence in a sibling

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ABSTRACT

Transient neonatal diabetes mellitus (TNDM) is a rare, monogenic form of diabetes presenting within the first six months of life, often linked to chromosome 6q24 abnormalities. We report a female neonate born to consanguineous parents, both heterozygous carriers of the ZFP57 p.(Arg269Gln) variant, with a history of an affected sibling. The patient presented with intrauterine growth restriction, perinatal complications, and persistent hyperglycemia requiring insulin therapy. Genetic testing confirmed maternal hypomethylation at 6q24, consistent with ZFP57-related TNDM. Insulin requirements gradually decreased, and remission was achieved at two years of age, notably longer than the typical 3-18 month remission window. The case underscores the prolonged remission potential, recurrent familial risk, and the importance of vigilant glucose monitoring during illness, given the risk of relapse even post-remission.

Keywords: ZFP57 gene, 6q24 chromosome, Transient neonatal diabetes, Consanguinity, Familial recurrence

INTRODUCTION

Neonatal diabetes mellitus (NDM) is defined as insulin-requiring persistent hyperglycemia occurring in first 6 months of life.[1-3] The clinical presentation is characterized by severe hyperglycemia requiring immediate insulin therapy, often accompanied by intrauterine growth restriction (IUGR) and osmotic symptoms including polyuria, polydipsia, and dehydration.[1,4,5] Affected infants may also exhibit congenital anomalies and neurological impairments, depending on their genetic mutations.[3] Other clinical features include macroglossia, umbilical hernia central nervous system anomalies, renal anomalies, developmental delay, congenital heart diseases, limb anomalies, or hypothyroidism.[6] NDM is a monogenic form of diabetes, with insulinopenia resulting from abnormal pancreatic islet development, decreased B-cell mass, or B-cell dysfunction.[1] It is mostly caused by single-gene mutations, but the diagnosis process can be challenging. According to international guidelines, every child diagnosed with diabetes within the first 12 months of life needs to be genetically tested.[2] NDM is considered a rare disease and is usually estimated to affect one in 300,000 to 400,000 newborns.[1-7] Some studies report broader ranges, from 1 in 20,000 to 1 in 350,000 live births.[2] This reflects differences in diagnostic resources and genetic screening availability across countries. In regions with higher rates of consanguineous marriages, such as Middle East, the incidence can be as high as 1 in 21,000 individuals.[8] Available data on NDM from the Gulf region are sparse, consisting primarily of a few studies focusing on permanent Neonatal diabetes mellitus (PNDM). A cohort study by Deeb et al, estimated the incidence of NDM in Abu Dhabi, United Arab Emirates, at 1 in 29,241 live births.[9] NDM can be classified into two different sub-types: transient NDM (TNDM), which reaches remission

by 18 months of age but may relapse later in life, and permanent NDM (PNDM), which requires lifelong treatment.[1,5,6] PNDM and TNDM each accounting for roughly half of all NDM cases.[3] The diagnosis of TNDM and PNDM is not typically clear initially due to similar presenting symptoms and often requires genetic testing and longitudinal follow-up.[5]

TNDM accounts for 50-60% of all NDM cases, with approximately 70% of TNDM cases caused by methylation abnormalities at chromosome 6q24. These abnormalities include paternal uniparental disomy 40%, paternal duplications 40%), and maternal hypomethylation defects 20%.[1,10,11] This case report describes a female neonate with ZFP57-related TNDM who experienced an unusually prolonged remission period of 2 years, representing the second affected sibling in a consanguineous family. The case highlights the phenotypic variability in ZFP57-related TNDM and provides insights into factors that may influence the duration of remission.

CASE REPORT

The female neonate was born to consanguineous, healthy parents at 37+6 weeks of gestation, with a birth weight of 1400 g (<2nd centile), a length of 44cm (<2nd centile), and a head circumference of 33cm (<2nd centile). The family history was unremarkable, except for a previous sibling diagnosed with TNDM. The mother was a 40-year-old gravida 7, para 6+1 (seven pregnancies, six live births, one miscarriage), who had a regular pattern of antenatal follow-up. Her pregnancy was complicated by gestational diabetes, severe oligohydramnios, and IUGR noted on antenatal screening. Notably, the neonate's four siblings were healthy and one term sibling IUGR 1500 g was diagnosed as transient neonatal diabetes mellitus (TNDM).

After an eventful pregnancy was delivered via emergent caesarean section secondary to placental abruption. And had low Apgar scores of 1,2 and 5 at 1,5 and 10 minutes respectively. The neonate was admitted to our tertiary neonatal intensive care unit immediately after birth in view of Perinatal Asphyxia, Severe Hypoxic Ischemic Encephalopathy (HIE). Hypoplastic lungs with respiratory distress of newborn, right pneumothorax, neonatal anemia, IUGR.

During day 1, the baby was mechanically ventilated with different modalities till reaching the proper respiratory support, with insertion of a right intercostal chest tube. Cardiovascular and hemodynamically, inotropic support and blood transfusion were initiated. She was not qualified for whole-body cooling based on birth weight, cardiovascular instability, and general condition. Cerebral function monitoring showed normal interpretation with no seizure activity. The initial clinical assessment of the newborn was normal with no significant anomalies. The first blood glucose level was measured at 18 mmol/L, and insulin infusion was started (stress response), which resolved on day 2 once vasopressors were stopped and the baby was weaned from ventilation. The baby was started on oral feeds on day 4, and hyperglycemia re-emerged (RBS 13.2-17 mmol/L). NDM was presumptively diagnosed in the absence of other causes for the profound hyperglycemia observed, such as infection, medication-induced glucose dysregulation, or intravenous fluid preparation error, with normal pancreatic ultrasound. Because her brother had TNDM, regular continuous insulin infusion with a sliding scale was started (0.02-0.1 units/kg/hr) along with minimal glucose infusion rate. Subsequently, close monitoring of blood glucose levels was implemented, and the infusion rate was adjusted accordingly to maintain blood glucose levels below 12 mmol/L while continuing full oral feeds.

The initial diagnostic investigations during hyperglycaemia episodes and the extensive glucose metabolism evaluation confirmed the presence of glycosuria (3+) and the absence of ketonuria. It was 0.2 mmol/L. Acidosis was not detected; however, there was a low serum insulin level of 1.9 mIU/L (2-25 mIU/l) and a low serum C-peptide level of 0.06 ng/mL (0.81-3.85 ng/mL), and HbA1c was 6.5% when the serum glucose level was high (19.4 mmol/l). The results of abdominal cranial ultrasound and ECHO were unremarkable, and metabolic screening, TORCH, and sepsis tests returned negative results. Renal and liver functions were normal.

On day 11 of life, the girl gained weight appropriately with a diet based on mixed feeding: breastfeeding and infant formula, averaging 30 to 45 grams per day. Glucose readings were recorded between 7 and 18.7 mmol/l, with total insulin intake of 0.3-0.6 IU/kg/day. A reduction in the relative insulin requirement was observed. After 2 days of stable glycaemic levels, insulin therapy was switched to daily subcutaneous injections of regular insulin at 0.1 IU/kg/dose every 6 hours if RBS was above 14 mmol/l.

As of day 16, with blood glucose levels of 13.9-20 mmol/l, multiple daily subcutaneous insulin injections were initiated. Subcutaneous insulin degludec saline, with a concentration of 1 unit/mL, was started. The prescribed dose was 0.15 units once daily, subcutaneously. Additionally, subcutaneous Novorapid insulin 0.16 IU/kg/dose every 6 hours was administered in accordance with glucose readings greater than 14.6 mmol/l. With documented hypoglycemia (RBS 2.8-8.3 mmol/l), subcutaneous Novorapid insulin was decreased to 0.1 IU/kg/dose every 6 hours.

Throughout the NICU course, insulin dosages were routinely adjusted in accordance with blood glucose readings and feeding schedules. Blood glucose control was challenging initially due to the complexities of preparing small quantities of insulin and the use of a continuous glucose monitoring (CGM) system, which was technically difficult; therefore, glycemic monitoring was mostly performed by capillary sampling.

The patient was discharged from the hospital at the age of 1 month postnatal. She was in good general condition and weighed 2125 g, which was below the 2nd centile, with an HbA1c of 6.9%. The patient was prescribed Tresiba 0.3 units once daily and Novorapid (Aspart) 0.2 units four times a day before feeds. The usual daily total of administered soluble insulin was 1.1 units during the first month of treatment.

At 4 weeks of age, a molecular genetic analysis was carried out to identify the genetic factors responsible for NDM.

The patient underwent a follow-up visit to the pediatric diabetes clinic, where she exhibited steady weight gain. The patient was initially prescribed Tresiba 0.3 units OD and Novorapid (Aspart) 0.2 units QID before feeds to maintain blood sugar levels below 13.9 mmol/L, and the genetic study result by the age of 2 months confirmed the presence of TNDM.

By 4.5 months of age, HbA1c had risen to 10%, indicating poor glucose control, even though the child was clinically well, with glucose fluctuations reaching a maximum of 24.6 mmol/L. Therefore, the long-acting Tresiba dose was increased to 0.4 units OD. By 9 months of age, she was on Tresiba 0.4 units OD and only occasionally required Novorapid injections (one or two doses), with an HbA1c of 8.5%.

By 15 months of age, she required only long-acting insulin, with no short-acting insulin needed to control blood glucose, with a maximum blood glucose of 15.5 mmol/L, except during infections when PRN doses were required. HbA1c was 8%, C-peptide increased to 0.6 ng/mL, and insulin level was 1.94 mIU/L.

By 18 months of age, she remained on long-acting insulin only, with occasional mild elevation of blood sugar once daily. The injection dose was gradually titrated with regular follow-up. At 2 years of age, hyperglycaemia was noted only during periods of illness, and therefore insulin was discontinued. The patient entered remission consistent with TNDM.

The patient is currently 2 years and 6 months of age at her last visit and is still being followed up without treatment. HbA1c was 5%, with normalized serum insulin of 3 mIU/L and C-peptide of 1.2 ng/mL. Her growth and mental and physical development are normal. She weighed 12 kg, and her height was 80 cm; both remained below the 2nd percentile, while her head circumference had normalized.

Regular clinical follow-up was established to monitor the patient's progress, especially glycaemic status during infectious episodes, and with a dietitian to achieve satisfactory weight gain through high-calorie intake.

Table 1: Molecular genetic test analysis.

Gene	Parent	Zygosity	Location : GRCh37(hg19)	HGVS description	Classification
ZFP57	Mother	Heterozygous	CHR6:g.29641082	NM_001109809.2:c.806G>A,p (Arg269Gln)	Pathogenic
	Father	Heterozygous	CHR6:g.29641082	NM_001109809.2:c.806G>A,p (Arg269Gln)	Pathogenic

Genetic testing carried out at the University of Exeter Medical Genomics Laboratory and the local Igenomic laboratory confirmed the initial clinical impression of TNDM The couple were both heterozygous for the ZFP57 missense variant p.(Arg269Gln), which is pathognomonic for transient neonatal diabetes, as shown in Table 1. For the girl, the test results showed loss of methylation at the TNDM region on chromosome 6q24, with homozygosity for the familial ZFP57 variant (c.806G>A, p.Arg269Gln). This was due to maternal hypomethylation at the same locus.

The patient's brother, who is currently 5 years of age, was diagnosed with NDM, which remitted at the age of 5 months.[12] Neither of the patient's parents had symptoms of diabetes. The parents and brother's fasting blood glucose levels were within normal limits.

DISCUSSION

The primary pathophysiology of the disorder is caused by mutations in the genes that govern beta-cell function, and currently genetic testing is the primary diagnostic tool to identify cases of NDM. The most common genetic cause, accounting for around 70% of cases, involves defects leading to the overexpression of paternally expressed genes within the imprinted region of chromosome 6, specifically 6q24, primarily PLAGL1 and HYMAI. ZFP57 mutations, as seen in our present case study, represent a rarer genetic cause of the disease. These mutations result in a unique epigenetic signature leading to widespread DNA hypomethylation, including loss of methylation at the 6q24 locus.[13] The familial occurrence of ZFP57-related TNDM in these siblings underscores several key clinical and genetic considerations, such as recurrence risk, inheritance patterns, and the need for genetic counselling for families with consanguinity.

Autosomal recessive inheritance and familial recurrence

When 6q24 TNDM syndrome is related to mutations in the ZFP57 gene, it is inherited in an autosomal recessive pattern. Therefore, two copies of the ZFP57 mutant gene (one from the father and the other from the mother) are

required to cause the disease, and the chance of having a child with the autosomal recessive disease in each pregnancy is 25%. The parents of a person with an autosomal recessive disease each carry a copy of the mutated gene but usually do not show any signs or symptoms of the disease(Figure 1).[1,14]

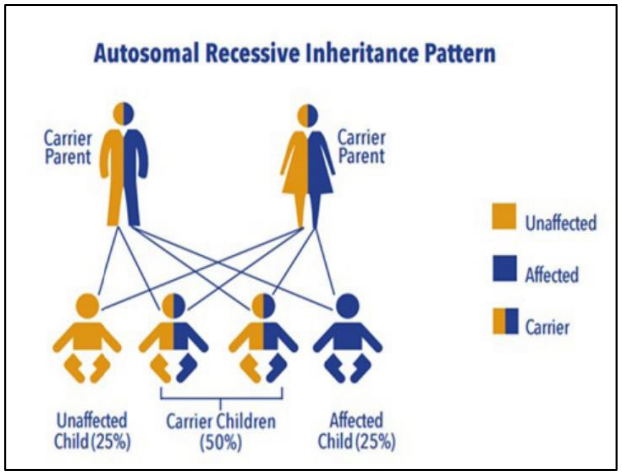

Figure 1: Schematic of the autosomal recessive inherited pattern followed by 6q24-associated neonatal transient diabetes syndrome.[10]

This specific mutation follows Mendelian genetics; when both parents are carriers (heterozygous) with no diabetes, each pregnancy has a 25% chance of producing a homozygous affected child, a 50% chance of producing a heterozygous carrier (unaffected), and a 25% chance of producing a homozygous normal child.

This is particularly relevant in populations with higher rates of consanguinity, where ZFP57-related TNDM is more frequently observed. The familial occurrence in this case, with two affected siblings achieving remission at different time points (5 months versus 2 years), validates the 25% recurrence risk and demonstrates the phenotypic variability within the same family.

Pedigree description and genetic background

This pedigree depicts a consanguineous family (indicated by the double line between parents) in which both parents are heterozygous carriers of the ZFP57 c.806G>A (p.Arg269Gln) variant. The family consists of six offspring: four males (squares) and two females (circles). Two children are affected with TNDM (filled symbols): a 5-year-old son who achieved remission at 5 months of age, and a 2.5-year-old daughter (index case) who achieved remission at 2 years of age.

The remaining four siblings are phenotypically unaffected (clear symbols) but may be carriers or genetically normal individuals. This inheritance pattern demonstrates the 25% recurrence risk characteristic of autosomal recessive conditions, with each pregnancy having an equal probability of producing affected offspring regardless of gender. The consanguineous background increases the likelihood of homozygous recessive conditions, making genetic counselling essential for future family planning decisions.

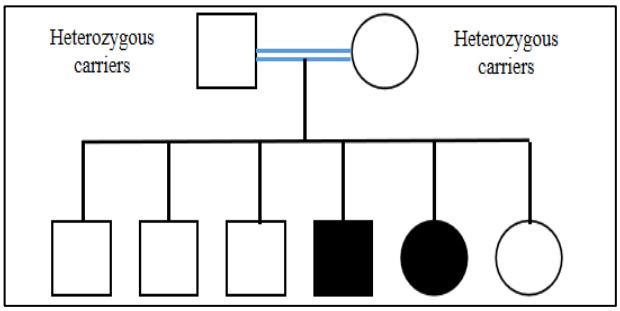

Figure 2: Family pedigree illustrating autosomal recessive inheritance of zfp57-related TNDM.

Prolonged remission: contributing factors

The hallmark feature of TNDM is the spontaneous remission of diabetes that occurs during infancy. This remission typically begins between 3-12 months of age, with most cases achieving complete insulin independence by 18 months.[6,10,14] Therefore, the 2-year remission period in this case is significantly longer than typical. Several interconnected factors may explain the prolonged remission time.

Individual genetic variation in ZFP57-related cases shows high phenotypic variability. The clinical phenotype can range from normal health to severe developmental complications, indicating significant individual variation in disease expression, and this may correlate with prolonged remission periods.[15] Additionally, low birth weight (1400g) and severe IUGR suggest significant β-cell dysfunction, potentially extending recovery time.[16] IUGR is associated with smaller islets, reduced β-cell mass, and impaired insulin secretion, which may delay pancreatic recovery.[16]

Complications during the neonatal period, such as hypoxic-ischemic encephalopathy (HIE) and respiratory distress, may also delay pancreatic recovery.[15] HIE is associated with multi-organ dysfunction, including metabolic disturbances that can affect glucose homeostasis and pancreatic function.[17] All these factors may explain the prolonged remission time.

Infection related hyperglycemia during remission

Even after apparent remission, these patients have a reduced β-cell mass and impaired insulin secretion capacity. During infections or physiological stress, pro-inflammatory cytokines and counter-regulatory hormones (such as cortisol and catecholamines) increase insulin requirements beyond the limited β-cell capacity, causing transient hyperglycemic episodes.[18,19] This necessitates

continuous glucose monitoring during febrile or infectious episodes to detect and prevent severe hyperglycemia. Early detection allows prompt reinstitution of insulin or temporary adjustment of dietary intake, thereby preventing severe hyperglycemia and its acute complications (e.g., dehydration, ketoacidosis). Healthcare providers and families must understand that "remission" is relative rather than absolute, with patients remaining vulnerable to metabolic decompensation during periods of stress.

CONCLUSION

This familial case of ZFP57-related TNDM demonstrates several clinically significant aspects, including prolonged remission of 2 years compared to the typical 3-18 months, autosomal recessive inheritance with a 25% recurrence risk in consanguineous families, and the relative nature of "remission," which requires continued vigilance during infections. The extended remission period likely reflects the combined effects of severe IUGR, perinatal complications including HIE, and individual genetic variability affecting pancreatic recovery. This case reinforces the importance of early genetic testing for appropriate family counseling and management decisions, while emphasizing that patients remain vulnerable to hyperglycemic episodes during physiological stress, necessitating long-term follow-up and monitoring for potential diabetes relapse later in life.

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