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**Case Report**

# Transient neonatal diabetes mellitus with subtype ZFP57 genetic defect in 6q24

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## ABSTRACT

Neonatal diabetes (NDM) is a rare form of diabetes that manifests in the first few months of an infant's life. The condition affects approximately one in 300,000 to 400,000 newborns and is characterized by elevated blood glucose levels. Transient and permanent NDM are the two types of this disease. In most cases of transient neonatal diabetes mellitus (TNDM), the genetic cause has been attributed to the overexpression of chromosome 6q24. Regardless of its underlying cause, the primary treatment for neonatal diabetes is insulin therapy.

**Keywords:** ZFP57 gene, 6q24 chromosome region, Neonatal, Neonatal diabetes

## INTRODUCTION

Neonatal diabetes (NDM) is a monogenic disorder that emerges within the first six months of life. The clinical course of this condition is characterized by hyperglycaemia that necessitates insulin treatment in the initial week after birth, typically accompanied by low birth weight. Other clinical features include macroglossia, umbilical hernia, and, less commonly, cardiac or renal abnormalities. This genetic disorder is caused by mutations in genes that govern beta-cell function or insulin sensitivity. Presently, genetic testing is the primary diagnostic tool for identifying NDM, and early diagnosis and appropriate treatment are essential for improving patient outcomes.[1,2]

In 1852, Kitselle provided the first documented clinical description of an illness that became known as this particular condition in his son.[3] The prevalence of the aforementioned condition is approximately 1 in 300,000 to 400,000 newborns, though this estimate may vary considerably based on geographical location and is largely determined by the extent of familial relatedness.[4,5]

In areas of the world such as Eastern countries and Turkey, where marriages between close relatives are common, the occurrence of genetic disorders is more prevalent. As a result, the incidence rate for such disorders is higher in these regions. Specifically, it was found to be 1 in every 21,000 individuals.[5]

Numerous genetic abnormalities are known to be responsible for the onset of NDM. This medical condition can be further classified into three distinct types: transient neonatal diabetes mellitus (TNDM), persistent neonatal diabetes mellitus (PNDM), and syndromic neonatal diabetes mellitus.[1]

The majority of cases, accounting for 50-60%, are caused by abnormalities on chromosome 6q24 and referred to as TNDM.[4] However, in 40% of cases, the genetic cause of NDM remains unknown.[1] TNDM is a condition that can occur due to various reasons such as over-expression of a specific gene located on chromosome 6q24, hypomethylation of the maternal allele, and paternal-uniparental disomy on chromosome 6. Patients with

TNDM and chromosome 6 abnormalities are often treated with insulin as the first-line therapy.[4]

Recently, there have been reports indicating the effectiveness of sulfonylureas.[7] The case we studied did not respond well to sulfonylurea therapy.

## CASE REPORT

The present case described the birth of a male neonate to consanguineous, healthy parents at 39+2 weeks of gestation. The overall family history was deemed irrelevant. The mother, a gravid woman with a G6P4+1 status, exhibited an irregular pattern of antenatal follow-up. Notably, the neonate's four siblings were healthy.

The neonate in question was delivered via normal vaginal delivery and had Apgar scores of 7 and 8 at 1 and 5 minutes respectively. However, the neonate was admitted to our tertiary neonatal intensive care unit on the first day after birth due to intrauterine growth restriction (IUGR) and other respiratory distress.

The initial clinical assessment of the newborn yielded no significant anomalies, with the exception of tachypnea and low birth weight. The child's growth parameters were documented as follows: birth weight of 1600 g (2nd centile), length of 44 cm (2nd centile), and head circumference of 30 cm (2nd centile). The first postpartum blood glucose level was measured at 5.5 mmol/l.

Feed introduction began gradually and there was no requirement for oxygen support or antibiotics by day 3 of life.

During routine blood glucose monitoring on day seven after reaching full feed, an elevated blood glucose range between 15-18.4 mmol/l was detected. Other potential causes of neonatal hyperglycaemia, such as sepsis and stress, hypoxia, drugs as well as intracranial haemorrhage, were ruled out. Subsequently, the patient was initiated on insulin infusion therapy, following a sliding scale approach, if the RBS exceeded 14 mmol/l. Close monitoring of blood glucose levels was implemented, and the infusion rate was adjusted accordingly to maintain blood glucose levels below 14 mmol/l while continuing full oral feeds.[8]

RBS more than 18 insulin was 0.05 u/kg/hr; RBS 17-18 insulin was 0.04 u/kg/h; RBS 16-17 insulin was 0.03 u/kg/hr; RBS 14-16 insulin was 0.02 u/kg/hr; stop insulin infusion if RBS is less than 12 mmol/l.

The initial diagnostic investigations indicated the presence of glycosuria (3+) and an absence of ketonuria. Acidosis was not detected, however, there was a low serum insulin level (1.1 Uiu/ml (2.6-24.9 Uiu/ml)) and a low serum C-peptide level (0.17 ng/ml (0.81-3.85 ng/l)) when the serum glucose level was high (18.4 mmol/l). An abdominal ultrasound revealed a mild degree of bilateral pelvicalyceal dilation, with a more pronounced dilation observed on the right side. The results of cranial ultrasound and ECHO were unremarkable, and the newborn screening tests returned negative results.

Between days 14 and 24, the newborn's weight increased by an average of 30 to 45 grams per day. Glucose readings were recorded between 7 and 21 mmol/l, and the infant was placed on insulin infusion at a rate of 0.02 to 0.05 U/kg/hour, with a daily total dose of approximately 0.42 U/kg/day. Additionally, a six-day trial of titrated doses of glimepiride, a sulphonylurea, was attempted at a dose of 01.27 mg/kg given twice daily; however, the treatment did not result in a significant reduction of GLU levels.

As of day 29, consequently with presence of subcutaneous fat and glucose readings ranging from 3.2 to 13 mmol/L, the administration of insulin infusion has been discontinued. In lieu of this, multiple daily subcutaneous insulin injections have been initiated. Subcutaneous insulin glargine saline, with a concentration of 1 Unit/ml. The dosages prescribed are 0.5-0.7 units, once daily, subcutaneously. Additionally, subcutaneous Humalog insulin is to be administered, pro re nata, in accordance with glucose readings: RBS 14-16-0.05 U/kg; RBS 16-18-0.07 U/kg; RBS>18-0.1 u/kg.

Glargine (Lantus) was administered twice daily due to persistent hyperglycaemia on day 32 of life, particularly persistent prefeed nocturnal hyperglycaemia (15.3 ~19.9 mmol/l). Before feeds, Novorapid (Aspart) 0.4 units was given thrice daily, replacing Humalog.

Throughout the NICU course, insulin dosages were routinely raised and adjusted in accordance with blood glucose readings and feeding schedules. Blood glucose control proved initially challenging due to the complexities involved in preparing small quantities of insulin, coupled with significant fluctuations in blood glucose concentrations. However, ketosis was not detected during this period. In the case of NOVORAPID, the combination of 4 IU insulin Novorapid and 1 ml of saline yielded a concentration of 0.4 unit/0.1 ml SC. Similarly, LANTUS required the combination of 4 IU insulin glargine and 1 ml of saline to achieve a concentration of 0.4 unit/0.1 ml SC.

The patient was discharged from the hospital at the age of 5 weeks postnatal. They had good general condition and weighed 2.6 kg, which was below the 2nd centile. The patient was prescribed Lantus 0.4 units, twice daily, and Novorapid (Aspart) 0.4 units, thrice daily before feeds.

During the period of hyperglycemia (16.2 mmol/l), blood tests were conducted multiple times and the C-peptide level remained low (0.2 nmol/l). At 6 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 they exhibited steady weight gain. The patient was initially prescribed Lantus 0.4 Units, BID, but due to blood sugar levels exceeding 250 mg in two conditions, the prescription of Novorapid (Aspart) was shifted on an as-needed basis. At the age of two months, a routine clinical examination revealed bilateral lipohypertrophy at the site of injection, and the majority of readings exceeded 250. To address this, the injection sites were changed, and the Novorapid injection was adjusted to 0.1 unit/kg twice if BG>300 mg, with a target RBS<250. The injection was gradually titrated according to blood glucose levels, and by five months of age, insulin was no longer necessary due to the absence of hyperglycemic episodes. A regular clinical follow-up was established to monitor the patient's progress. At seven months of age, the patient exhibited normal anthropometric parameters, with no infectious episodes or hyper- or hypoglycemic events. Investigations revealed normal results, including serum insulin (6.1 Uiu/ml (2.6-24.9 Uiu/ml)), serum C-peptide level (1.15 ng/mL (0.81-3.85 ng/l)), and HBA1C 6.1%. A dietician was consulted to optimize the patient's calorie intake and ensure normal growth. The parents were informed of the need for long-term follow-up given as the lack of clinical, biological, or genetic correlations to predict the non-negligible risk of recurrence. The genetic testing carried out at the University of Exeter Medical School's genomic laboratory confirmed the initial clinical impression of transient diabetes, which demonstrated a reduction in insulin requirements and came to a complete halt by the age of 5 months. The test results showed a loss of methylation at the TNDM region on chromosome 6q24, and this was due to maternal hypomethylation at the same locus. Table 1 provides further details on this matter.

**Table 1: Molecular genetic test analysis.**

| Gene | Parent | Zygosity | Location : GRch37(hg19) | HGVS description | Classification |
|---|---|---|---|---|---|
| **ZFP57** | Mother | Heterozygous | CHr6:g.29641082 | NM_001109809.2:c806G>A,p.(Arg269Gln) | Pathogenic |
| | Father | Heterozygous | CHr6:g.29641082 | NM_001109809.2:c806G>A,p.(Arg269Gln) | Pathogenic |

***Molecular genetic study and interpretation***

The subject of inquiry pertains to a couple, both of whom are heterozygous for the ZFP57 missense variant p. (Arg269Gln), which has been identified as pathognomonic for transient neonatal diabetes. The probability of transient neonatal diabetes impacting the couple's subsequent pregnancy is one in four. Their son, who has presented with low birth weight and was diagnosed with diabetes during the initial week of life, exhibits typical clinical features of 6q24 transient diabetes of the newborn. Methylation and microsatellite analysis confirmed that the son has maternal hypomethylation at the 6q24 locus, which is a fundamental characteristic of transient neonatal diabetes, subtype ZFP57 (PP4_strong) (Table 1).

## DISCUSSION

NDM is a form of diabetes caused by a mutation in a single gene, which leads to the abnormal development of pancreatic islets. This, in turn, can cause the loss of B-cell mass or B-cell dysfunction due to various genetic mechanisms, including loss of methylation, paternal-nonpaternal disomy, and paternal duplication.[9] The monogenic nature of NDM is more prevalent in regions with high degrees of consanguinity.[10]

This case report details the presentation of a male neonate with TNDM due to maternal hypomethylation at the 6q24 locus with heterozygous variants of the ZFP57 gene, which is considered the molecular hallmark of TNDM subtype ZFP57. A study conducted in the south eastern Anatolia region of Turkey by Demirbilek et al found that the annual incidence of NDM was at least once per 30,000 live births. The incidence of TNDM caused by ZFP57 gene mutation was also high in this Turkish cohort, where 2/3 of TNDM cases with chromosome 6q24 methylation abnormalities had ZFP57 gene mutations. The prevalence of ZFP57 gene mutations is higher in consanguineous families, and the risk of recurrence in affected families is 25%, hence TNDM can be suspected.[11] ZFP57 gene mutations are associated with the first inherited global imprinting disorder that is compatible with life described in humans.[12] Mutation following an autosomal recessive pattern with intrinsically variable epigenetic effects and clinical features result in a more severe phenotype of recessive inheritance, which leads to earlier presentation and lower birth weight.[13] The neonate in this case had recessive mutations, which explains the early presentation and low birth weight. It is noteworthy that both parents were carriers of neonatal diabetes.

In the context of pregnancy, diabetes is frequently correlated with low birth weight and intrauterine growth restriction (IUGR) in the third trimester. These characteristics are attributed to the prenatal absence of insulin.[4] Our infant's birth weight registered 1.6 kg with IUGR, which is commensurate with the findings of a French cohort study from 2002. Specifically, the study identified that 74% of cases of TNDM and 36% of cases of PNDM were linked to IUGR.[6]

Patients with TNDM are typically identified prior to 4 months of age, and they often recover before reaching 18 months but may experience a recurrence later on.[4,6] The individual in question was diagnosed within the first

week of life and had achieved remission by the age of 5 months.

Insulin is the primary treatment, regardless of the cause, as per reference.[9] Following insulin treatment, the infant's glucose levels returned to normal. We began administering a continuous intravenous infusion, and after glucose levels stabilized and subcutaneous tissue developed properly, we initiated subcutaneous injections prior to meals, with multi-injection boluses calculated based on pre-meal glucose levels, type of food, and post-meal glycaemia. We aimed to minimize the risk of hypoglycaemia and glycaemic fluctuations.

It's eminent to mention that we applied clinical criteria to diagnose transient diabetes in our case. These criteria involved assessing the birth weight, age of first detection of hyperglycaemia, and the initiation of insulin administration, followed by a gradual reduction and ultimate cessation at 5 months of age. Moreover, the normal neurological feature and absence of other characteristics. Additionally, we obtained genetic confirmatory results at age of 3 months to support the diagnosis of transient neonatal diabetes.

Neonatal diabetes is a multifaceted condition that entails clinical, therapeutic, and genetic complexities. Early diagnosis and prompt intervention are paramount for clinical success; however, there are significant challenges due to the severity of metabolic complications and the difficulty in achieving appropriate weight gain and neurological development in those infants. In cases of transient diabetes, diligent monitoring is highly recommended, particularly during the initial years of life, as infants may encounter symptomatic hypoglycaemia or recurrent hyperglycaemia during frequent infectious episodes.[14]

## CONCLUSION

NDM is a rare medical condition that manifests in two forms, namely TNDM and PNDM. Insulin therapy is an essential modality for managing hyperglycaemia and achieving satisfactory weight and growth. The combination of high clinical suspicion, early and accurate diagnosis, and timely management are pivotal in simplifying diabetes management and improving the quality of life.

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