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Case Report / Olgu Sunumu

A novel *de novo* mutation at the *ABCC8* gene in a newborn with transient diabetes mellitus

Geçici diabetes mellituslu yenidoğanda *ABCC8* geninde yeni bir *de novo* mutasyon

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The known about this topic

Neonatal diabetes mellitus (NDM) is a monogenic disease which can present within the first six months of life. NDM can be transient or permanent.

Contribution of the study

Activating mutations at *ABCC8* gene can cause transient NDM. Patients with this mutations can respond to sulfonylurea therapy.

Abstract

Neonatal diabetes mellitus is a monogenic disease that can present with hyperglycemia, dehydration, failure to thrive, and ketoacidosis within the first six months of life. Neonatal diabetes mellitus can be transient or permanent. Here, we describe a 10-week-old infant with transient neonatal diabetes mellitus who presented with diabetic ketoacidosis and was found to have heterozygous a *de novo* mutation, p.Thr1381Asn in the *ABCC8* gene, which encodes the SUR1 protein. There was no family history of diabetes mellitus and the parents were negative for the mutation at *ABCC8*. The patient started on insulin therapy and remission of diabetes occurred at 4 months of age. The patient remained euglycemic over a 2-year follow-up period without necessitating any medicine.

Keywords: *ABCC8* gene, neonatal diabetes mellitus, sulfonylurea, transient

Öz

Neonatal diabetes mellitus, yaşamın ilk altı ayında hiperglisemi, dehidrasyon, gelişme geriliği ve ketoasidoz ile ortaya çıkabilen monojenik bir hastalıktır. Neonatal diabetes mellitus geçici ya da kalıcı olabilir. Burada, diyabetik ketoasidoz ile başvuran ve SUR1 proteinini kodlayan *ABCC8* geninde heterozigot *de novo* mutasyonu olan (p.Thr1381Asn), geçici neonatal diabetes mellituslu 10 haftalık bir olguyu sunuyoruz. Ailede diyabet öyküsü yoktu ve ebeveynler *ABCC8*'deki mutasyon için negatifti. Hastaya insülin tedavisi başlandı ve dört aylıkken diyabet remisyonu gerçekleşti. Hasta iki yıllık takipte herhangi bir ilaç gereksinimi olmadan öglisemik kaldı.

Anahtar sözcükler: *ABCC8* geni, geçici, neonatal diabetes mellitus, sülfonilüre

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Introduction

Neonatal diabetes mellitus (NDM) is a rare monogenic disease characterized by hyperglycemia requiring insulin therapy within the first six months of life (1). The estimated incidence of NDM is 1/90.000–215.000 live births (2, 3). The incidence of NDM is higher in countries with high rates of consanguineous marriages, such as Saudi Arabia and Turkey (4, 5). Neonatal diabetes mellitus can be transient or permanent; the transient form constitutes about half of all NDM cases. Chromosomal anomalies at the 6q24 region are responsible for 70% of transient NDM cases. The second most common mutations for transient NDM are related with KCNJ11 and ABCC8 genes encoding for SUR1 and Kir6.2 subunit proteins of the adenosine triphosphate (ATP)- sensitive potassium channel (K-ATP) (6). Here, we report a case of 10-week-old-infant who diagnosed as having transient NDM and found to have de novo heterozygous mutation, p.Thr1381Asn, in the ABCC8 gene.

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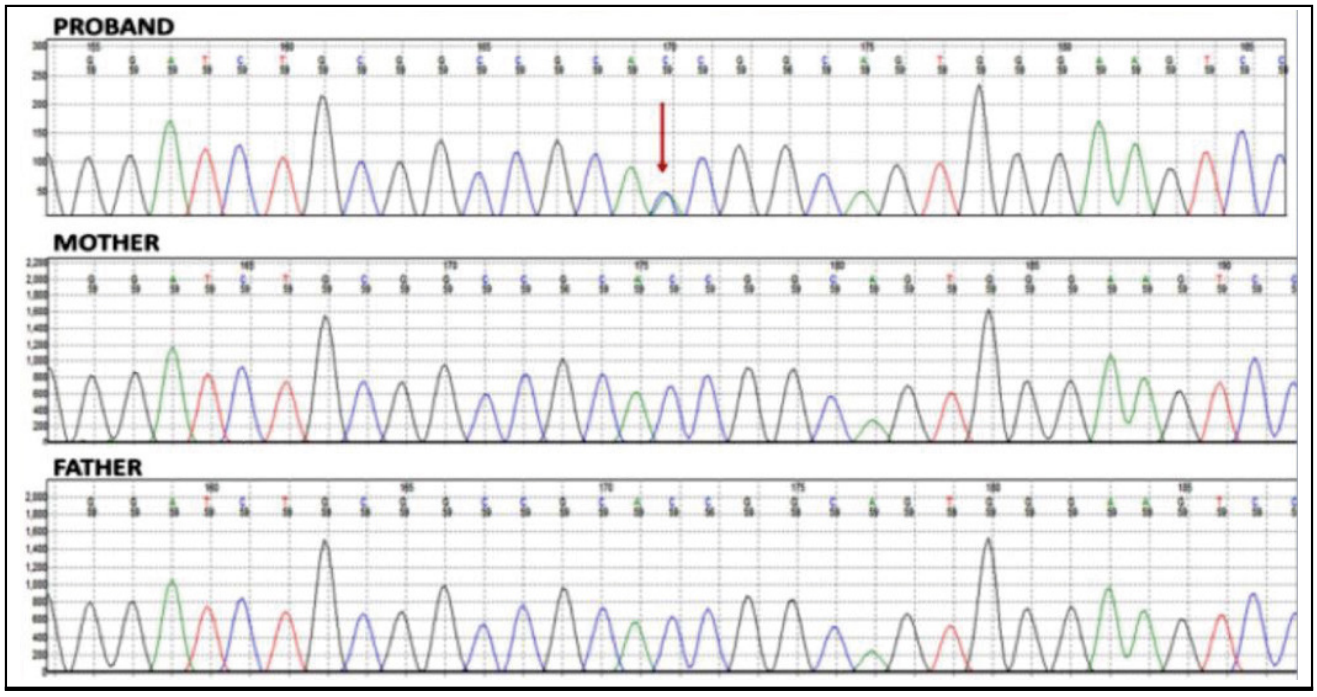

Figure 1. Identification of sequence variation in *ABCC8*. Partial sequence of PCR product. Patient has heterozygous for a novel *ABCC8* missense mutation, p.Thr1381Asn. The threonine residue at codon 1381 is moderately conserved across species and mutation testing in patient's parents has shown that the p.Thr1381Asn mutation has arisen de *novo*

Case

A 10-week-old male born at 38 weeks' gestation with a birthweight of 2200 g presented to the emergency department of our university hospital with cough and wheezing. A physical exam was remarkable for tachypnea and poor newborn reflexes. The patient weight was 6.6 kg (25–50 percentile), length was 61.5 cm (10–25 percentile), and head circumference was 40 cm (3–10 percentile). Initial laboratory findings were significant for very high serum glucose, 800 mg/dL, with capillary blood gas pH of 7.21 (7.35–7.45), pCO2 of 37.7 mm Hg (normal range: 35–45 mm Hg), HCO3 of 13.8 mmol/L (normal range: 22–26 mmol/L) and urine ketone 2+. He had no previous history of hospitalization or medication use. The parents were not related and the family history was clear for diabetes mellitus. He was given a normal saline bolus and admitted to the pediatric intensive care unit (PICU) for further management of diabetic ketoacidosis. In the PICU, an intravenous insulin infusion (0.05 IU/kg/h) was started, and we were able to switch to subcutaneous neutral protamine Hagedorn (NPH) on the second day of the PICU stay. Serum basal insulin was 1.83 mIU/mL (normal range: 2.6–27 mIU/mL), C-peptide was 0.583 ng/mL (normal range: 0.9–4 ng/mL) and glycated hemoglobin (HbA1c) was 7.1% (normal range: 4.27–6.07%). Serum anti-insulin, anti-islet cell, and anti-glutamic acid decarboxylase antibodies were negative. His blood glucose remained under control with NPH and he was discharged after completing diabetes education on the 21st day of admission. Informed consent was obtained from the parents of the patients and the genomic DNA was extracted from the leukocytes in peripheral blood.

Mutational Analysis

Coding genes of ABCC8, KCNJ11, INS, and EIF2AK3 and the surrounding introns were sequenced using Sanger sequencing. A novel missense heterozygote mutation in the ABCC8 gene was detected (p.Thr1381Asn) (Fig. 1). Molecular analysis data revealed that the patient was heterozygous for a C to A transition at position 4142 of the coding sequence c.4142C>A, which led to change from threonine to asparagine in the amino acid at position 1381 (p.T1381N). This is a novel missense variant in the coding region in exon 34 of the ABCC8 gene, which is related with clinical NDM according to the Mutation Taster, PolyPhen-2 and SIFT bioinformatics programs. The parents were negative for the mutation at the sequenced region (Fig. 1).

On his follow-up one month later on NPH, the serum glucose level was in the range of 150 to 250 mg/dL, and the C-peptide level was 0.6 ng/mL (normal range: 0.4–2.2 ng/mL). Therefore, we switched NPH therapy (0.2 IU/kg/day) to an oral sulfonylurea, 0.05 mg/kg/day glibenclamide, in two divided doses. We decreased the dose of

glibenclamide to half on the first week of therapy and completely discontinued by day 10 because he had an hypoglycemic episode. The serum HbA1c level was 6.2 g/dL (normal range: 4.27–6.07 g/dL) and fructosamine was 235.8 µmol/L (normal range: 118–282 g/dL) at the end of therapy.

Discussion

Neonatal diabetes mellitus is a rare monogenic disorder, presenting with hyperglycemia, failure to thrive, and, in some cases, dehydration and ketoacidosis within the first 6 months of life (1). Patients can be found to have hyperglycemia when they are investigated for dehydration, failure to thrive, and polyuria. Although ketonuria is usually absent, and delayed diagnosis can lead to diabetic ketoacidosis, similar to our case.

Although transient NDM disappears within three months after the diagnosis, recurrences can be seen during adolescence or adulthood. Permanent NDM presents in the late fetal or early postnatal life and diabetes does not resolve (7). Activating mutations in the ABCC8 gene can cause both transient and permanent NDM (8). Paternal disomy, paternal duplication, and methylation defects in 6q24 chromosomal anomalies cause about 70% of transient NDM cases (9). Activating mutations in the ABCC8 gene are responsible for about 15% of transient NDM cases (10). Remission of diabetes occurred within six weeks after diagnosis in our case. Currently, the patient is aged 29 months, euglycemic, and not taking any insulin or oral hypoglycemic agents.

Transfer to sulfonylurea from insulin therapy has been reported in patients with mutations in the K-ATP channel with encoding genes such as KCNJ11 and ABCC8. It has been shown that sulfonylurea therapy is more effective in the regulation of blood glucose compared with insulin therapy in NDM with K-ATP channel mutations (7).

In this paper, we presented our experience of an infant with transient NDM with a missense de novo mutation in the ABCC8 gene. As NDM is a monogenic form of diabetes and can respond to sulfonylurea therapy, molecular genetic analysis is necessary in patients with NDM even without a family history of diabetes.

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