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Case report
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Transient neonatal diabetes mellitus caused by a novel mutation in the ABCC8 gene

ABCC8 geninde yeni bir mutasyonun neden olduğu geçici neonatal diyabet

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Abstract

Neonatal diabetes mellitus is a rare monogenic form of diabetes that develops in the first 6 months of life. Neonatal diabetes mellitus is commonly divided in two groups as transient and permanent. Genetic and epigenetic anomalies of chromosome 6q24 locus are responsible for 70% of transient neonatal diabetes mellitus cases. Incidence of macroglossia, umbilical hernia, cardiac and renal anomalies is increased in transient neonatal diabetes mellitus patients. Mutations in the genes (ABCC8 and KCNJ11) encoding two protein subunits (SUR1 and Kir6.2) of ATP-sensitive potassium channels constitute the second common cause of transient neonatal diabetes mellitus. In this article, we present a case with homozygous missense mutation (DNA expression: c1456> T), which was found in the ABCC8 gene in a 3.5-month-old patient with no congenital anomalies, leading to transient neonatal diabetes mellitus.
Keywords: Neonatal diabetes, ATP-sensitive potassium channel, ABCC8 gene

Öz

Neonatal diyabet, yaşamın ilk altı ayında ortaya çıkan ve diyabetin nadir görülen monojenik bir formudur. Genel olarak geçici ve kalıcı diye iki gruba ayrılır. Geçici neonatal diyabetli olguların %70'inden kromozom 6q24 lokusun genetik ve epigenetik anomaliler sorumludur. Bu olgularda makroglossi, umlikal herni, kardiyak ve renal anomali sıklığı artmıştır. ATP duyarlı potasyum kanallarının iki protein alt birimini (SUR1 ve Kir6.2) kodlayan genlerdeki (ABCC8 ve KCNJ11) mutasyonlar geçici neonatal diyabetin ikinci sık nedenini oluşturmaktadır. Bu yazıda konjenital anomalilerin eşlik etmediği, 3.5 aylık bir hastada ABCC8 geninde yeni saptanan ve geçici neonatal diyabete yol açan homozigot missense mutasyonlu (DNA tanımlaması: c1456>T) bir olgu sunulmuştur.
Anahtar kelimeler: Neonatal diabet, ATP duyarlı K kanalı, ABCC8 geni

Introduction

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes often occurring in the first 6 months of life, characterized by severe hyperglycemia. NDM continues for at least 2 weeks and requires insulin treatment for blood glucose regulation [1]. The frequency of NDM has been reported to be 1:100,000-400,000 [2]. While 90% of NDM cases are transient or permanent, the remaining 10% is associated with mutations that effect organs other than the pancreas and hence present syndromes whose spectrum of clinical and radiologic features provide clues to the cause [3]. Transient neonatal diabetes mellitus (TNDM) typically occurs within the first several days or weeks of life and the recovery often occurs within a mean period of 12 weeks. However, TNDM may recur in approximately half of the cases, particularly in adolescent or young adult patients [4].

In this report, we present an infant with TNDM caused by a novel mutation in the ABCC8 gene who recovered at the age of two years.

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Case presentation

The patient was born at 39 weeks gestation with 3200 g birth weight by normal spontaneous vaginal delivery. The parents of the patient were first-degree cousins. An uncle and aunt had been diagnosed with Type 2 diabetes after the age of 40 years, who had previously undergone oral antidiabetic therapy. At the age of 3.5 months, the patient was admitted to another center with the complaints of vomiting and diarrhea and the patient was referred to our hospital due to persistent hyperglycemia. On initial physical examination revealed that weight was 6 kg (33^{rd} percentile), length was 62 cm (60^{th} percentile), dry mouth, and signs of mild dehydration. There was no dysmorphism. All systems examinations were normal. Laboratory investigation revealed that blood glucose 594 mg/dl, glucose-positive and ketone-negative urine, and normal venous blood gas values (pH: 7.38, HCO3: 20.3 mmol/L). Kidney and liver function tests, electrolytes, and complete blood count (CBC) were all normal and anti-GAD antibodies were negative. Glycosylated hemoglobin level (HbA1c) was 11.2%. However, despite the presence of hyperglycemia, C-peptide (0.52 ng/ml, normal range: 1.1-4.4 ng/ml) and the insulin (2.34 mIU/L, normal range: 2.6-24.6 mIU/L) levels were low. Based on these findings, NDM was considered and thus was started on subcutaneous Neutral Protamine Hagedorn (NPH) insulin therapy with a divided dose of 0.5 IU/kg/day. On day 7, the patient was discharged after the stabilization of blood glucose levels and the parents were informed about diabetes.

As the patient had a normal birth weight and no concomitant congenital anomalies, TNDM Type 2 was considered. Subsequently, in the genetic analysis performed in the molecular genetic laboratory, a homozygous missense mutation was detected in the ABCC8 gene (DNA identification: c.1456C>T). The arginine residue at codon 486 is highly conserved across species and current evidence suggests that the p.R486W mutation is pathogenic. This homozygous missense mutation was not found in the Human Gene Mutation Database (HGMD and Locus-specific databases and was interpreted as "disease-causing'' by the Mutation Taster Software (test score: 0.999) (http://www.mutationtaster.org). Both parents were heterozygous carriers for the same mutation. The patient was not brought for regular follow-up examinations. The result of the genetic analysis for the patient was obtained when the patient reached the age of 18 months. After the detection of the ABCC8 gene mutation, sulfonylurea treatment was planned to start at hospital because of the hypoglycemic side effects of the sulfonylureas. However, her parents refused hospitalization; the treatment was continued with insulin. The HbA1c level was 7.6 when the patient was 18 months of age. During this period, it was noticed that the patient needed less insulin. When the patient reached the age of two years, the insulin treatment was terminated. Currently, the patient is four years old with normal blood glucose and HbA1c levels. Depending on this outcome, the patient was considered as having TNDM. Written informed consent was obtained from the patient's family for publication of this case report.

Discussion

Neonatal diabetes mellitus, which leads to hyperglycemia in the neonatal period, usually manifests with severe dehydration attacks in the first weeks of life and is extremely rare compared to other forms of diabetes. The main reason for severe dehydration in affected children is osmotic diuresis. There is poor weight gain despite good nutrition. If diagnosis is delayed without consideration of potential causes, NDM can lead to severe dehydration and life-threatening ketoacidosis [5]. The case presented in this report presented with signs of acute gastroenteritis and mild dehydration and the diagnosis of NDM was established based on the detection of persistent hyperglycemia. In 70% of TDNM cases, the "imprinted" locus of chromosome 6q24 is responsible for the genetic and epigenetic anomalies. These cases are known as TNDM Type 1 (TNDM1) and mostly recover within a mean period of 3 months, which can also be prolonged to up to 48 months [4,5]. Docherty et al. [5] evaluated TDNM1 patients and reported that macroglossia was detected in approximately 50%, umbilical hernia in 25%, cardiac and renal anomalies in 9%, hand anomalies in 8%, and hypothyroidism in 4% of the patients. Remission, when it occurs, is usually around 3 months and about half of these patients will revert to varying degrees of hyperglycemia in the teen years or later.

A second form of TNDM is named TNDM2 which is distinguished from TNDM1 due to the defects in the 6q24 region and includes the mutations in the ATP-regulated potassium channel involving predominantly mutations in ABCC8 (SUR1) and KCNJ11 (Kir6.2), with a small minority being due to recessive insulin gene mutations and mutations in transcription factor HNF1β and SLCA2A, which together account for 30% of TNDM [3,6]. TNDM2 occurs due to the mutations in the genes regulating insulin secretion rather than the expression of imprinted genes. Compared to TNDM1, it has been shown that TNDM2 patients have a greater birth weight, are diagnosed with diabetes mellitus at a later period, remit later and have recurrence earlier [3,7]. In our patient, since the patient had a normal birthweight and did not have congenital anomalies, TNDM Type 2 was considered. Moreover, the genetic analysis indicated homozygous missense mutation in the ABCC8 gene (DNA identification: c.1456C>T). Literature shows that determining ABCC8 or KCNJ11 mutations in NDM is highly important in the management of the treatment process since most mutations in the ATP-associated potassium channels respond to sulfonylurea treatment [7,8]. Therefore, insulin therapy is the initial treatment of choice in patients diagnosed with NDM, which can be followed by sulfonylurea therapy depending on the diagnostic tests performed for molecular examination [7]. In our patient, we also planned sulfonylurea treatment depending on the results of the genetic analysis but we continued the insulin therapy since the parents of the patient refused hospitalization. Therefore, we could not evaluate the response of the ABCC8 gene mutation in our patient to sulfonylurea treatment, which could be accepted as the limitation of our study.

In conclusion, we determined a novel mutation in the ABCC8 gene leading to TNDM. Mutations in the ABCC8 and KCJN11 genes should be considered in the absence of congenital anomalies, such as macroglossia and umbilical hernia, with a

normal birth weight and a later NDM diagnosis. In such cases, the treatment and the long-term follow-up of the patient should be planned based on the mutation detected in molecular examination.

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