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CASE REPORT – OPEN ACCESS

A Rare Duplication in the PLAG1 Gene: A Case of Neonatal Diabetes

Berna Hekimoğlu[1], Şenol Çitli[2]

ABSTRACT

Background: Neonatal diabetes mellitus (NDM) is a rare form of diabetes. It occurs due to several different genetic abnormalities, and two main groups have been recognized, transient and permanent. Although insulin is often used as a first-line treatment for transient types, this mode of therapy is not helpful in some cases.

Case Report: We present a newborn case treated with oral sulfonylurea diagnosed as transient type NDM in the first days of life. The chromosomal microarray analysis detected a rare *de novo* duplication of 3383 kb in the 6q24.1q24.2 region.

Conclusion: An oral sulfonylurea treatment is a useful treatment option in the management of neonatal diabetes cases. This report describes a rare deletion that has not been described in the literature to date. Advanced genetic evaluation is vital for early diagnosis and intervention in patients with chromosome 6q duplication.

Keywords: Transient neonatal diabetes, 6q24, sulfonylurea treatment, duplication

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[1]Division of Neonatology, Department of Pediatrics, University of Health Sciences Turkey, Kanuni Training and Research Hospital, Trabzon, Turkey
[2]Department of Medical Genetics, Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey

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Correspondence
Berna Hekimoğlu, University of Health Sciences Turkey, Kanuni Training and Research Hospital, Department of Pediatrics, Division of Neonatology, Trabzon, Turkey
Phone: +90 462 230 23 00
e-mail: dr.bernasygn@gmail.com

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a genetic disease that occurs in the first 6 months of life and is defined by hyperglycemia (1, 2). It is generally estimated that 1 in 300,000–400,000 newborns have this disease. This can vary widely based on location and is primarily dependent on consanguinity rates (3, 4). For eastern countries and Turkey, where consanguineous marriage is too high, the incidence rate is higher and reached 1 in 21,000 (4).

Several different genetic abnormalities may cause NDM, which is further classified as transient (TNDM), permanent (PNDM), or syndromic (1). TNDM constitutes 50%–60% of all cases (3), and it is usually caused by abnormalities in the 6q24 chromosome. Moreover, mutations in the KCNJ11 and ABCC8 genes encoding the KATP channel can affect NDM (5–7), particularly these mutations may result PNDM. The genetic cause is unknown in 40% of NDM cases (1). The TNDM may result from overexpression of gene located on chromosome 6q24 owing to paternally inherited duplication of 6q24, paternal-uniparental disomy of chromosome 6, and hypomethylation of the maternal allele (5).

Insulin is often used as the first-line treatment in patients of TNDM with chromosome 6 abnormalities (3, 6). However, sulfonylureas have recently been reported to be effective (8, 9). In this article, a case of neonatal diabetes requiring sulfonylurea treatment was presented due to the rarity of the disease and unusual deletion detected in the 6q24 chromosome.

CASE REPORT

A baby girl was admitted to the intensive care unit on her first day of life since her blood glucose level was 300 mg/dL due to "lack of sucking." The baby was born to a 26-year-old healthy mother after an uneventful twin pregnancy at the 35th week of gestational age with a 1470 g (–3.75 SDS) birth weight. Her female twin was unaffected. The patient did not have any family history of diabetes, and they were not relatives. On her physical examination, there was no pathology other than being small for gestational age and having macroglossia (Fig. 1). She had an easily reducible umbilical hernia. When serum blood glucose level was 300 mg/dL, blood ketone was negative, serum insulin level was 1.15 IU/mL, and C-peptide was 0.23 ng/mL. The anti-insulin antibody, islet cell antibody, and anti-glutamic decarboxylase antibody were negative. Metabolic scanning, TORCH, and sepsis examinations were all normal. On her second day of life, and insulin infusion of 0.01 U/kg/hour was started. During follow-up, insulin infusion was given with an increasing dose, and subcutaneous injection was initiated after blood glucose levels were partially controlled. However, a very variable need for insulin was observed in the baby that caused hypo and hyperglycemic attacks throughout the day. When she was 21 days old, oral sulfonylurea therapy was attempted. Glibenclamide was given in two doses with an oral syringe of 0.2 mg/kg/day. There was

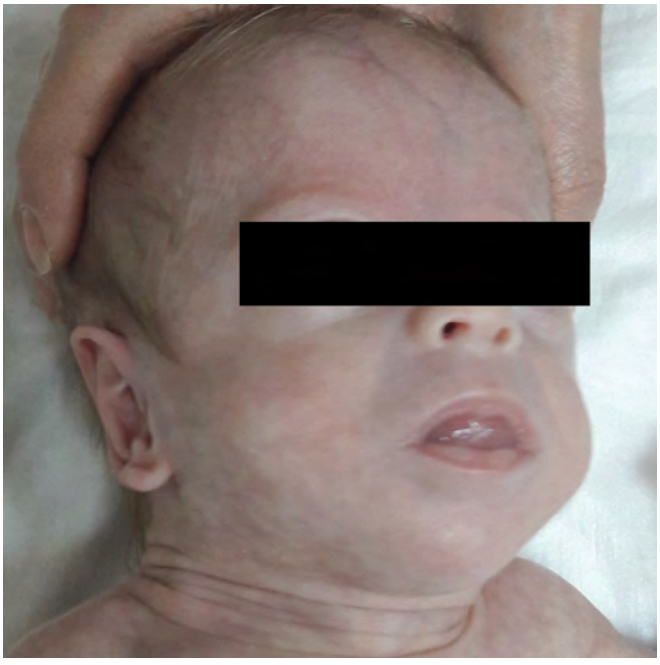

Figure 1. Dysmorphic facial features of the case

no need for any insulin therapy in the baby after the first dose of glibenclamide. Treatment was discontinued when the patient was 5 months old. No side effects were observed during treatment. She was 12 months old on her last visit and is still being followed up without treatment, and HbA1c was 5%. However, she was being followed up due to mental and motor development retardation.

For the etiology of NDM, all gene sequence analysis was examined. No pathogenic variant was detected in the analysis. Subsequent chromosomal microarray analysis revealed *de novo* duplication in the region of 6q24.1q24.2 at a size of 3383 kb (arr [hg19] 6q24.1q24.2 (141,494,387-144,877,906) x3). A detailed analysis revealed that the PLAGL1 gene, a gene responsible for NDM, was located in this region (5). Her parents' microarray analysis was normal.

Written informed consent was obtained from the patient's parents to publish the case report and images.

DISCUSSION

Intrauterine growth restriction (IUGR) in the third trimester of pregnancy and low birth weight are usually associated with diabetes. These features are owing to insulin deficiency in the prenatal period (3). Dysmorphic symptoms are more common in patients with TNDM. Our patient had the most commonly reported dysmorphic symptoms, macroglossia, and umbilical hernia (1). Clinically, the low birth weight of our patient was consistent with severe prenatal insulin deficiency. TNDM patients are often diagnosed before 4 months of age, enter remission before 18 months but relapse later in life (3, 5). Our patient was in remission at the age of 5 months.

Molecular genetic diagnosis is vital for babies with persistent hyperglycemia regarding prognosis and treatment options (1, 2). We also conducted a genetic test analysis and found a rare *de novo* duplication in chromosome 6q24. Two genes located in the region have been considered candidate genes for the disease: Pleomorphic adenoma gene-like 1 (PLAG1) and hydatiform mole-associated and imprinted (HYMAI). PLAG1 is a transcriptional regulator of the type 1 receptor for pituitary adenylate cyclase-activating polypeptide, which regulates insulin secretion (1). This duplication effect may cause TNDM. The function of HYMAI has not been defined yet. In our case, a rare deletion in the PLAG1 region was detected in chromosome 6q24. This duplication was determined to be *de novo* and was believed to have a pathological effect with gene dosage effect.

The pathophysiology of 6q24 related diabetes is unknown. Hyperglycemia in TNDM cases develop because of reduced or absent insulin output during the fetal period, which continues until postnatal life. Genetic origin has been detected in more than 90% of TNDM cases. It has been reported that the deficiency in insulin output may result either from delayed maturation of pancreatic islets and β cells due to altered expression of imprinted genes on chromosome 6 or β-cell secretion dysfunction that impairs insulin secretion (10). It may also develop due to various genetic mechanisms such as methylation loss, paternal-uniparental dysomia, and paternal duplication. These anomalies may trigger overexpression of PLAGL1 gene (10). Sulfonylurea therapy has recently been found to be effective in non-KATP channel genetic mutation-associated NDM (9). Sulfonylurea binds to the SUR 1 subunits of the KATP channel and promotes insulin secretion (11). Glibenclamide is the most widely used sulfonylurea in the treatment (3). The chromosome 6q24 abnormalities do not alter functioning of the KATP channels present in the ß-cells but decrease the sensitivity to glucose and block the event cascade that leads to insulin release. Sulfonylurea can improve insulin release, possibly by augmenting intact KATP channel closure through an ATP-independent mechanism (6). Our patient started empirical sulfonylurea treatment before genetic test results. Her hyperglycemia improved with sulfonylurea treatment, and she was in remission at 5 months of age. Since the cases were related to the 6q chromosome, it may have had serious mental disability (12). Hence, genetic diagnosis is essential for follow-up studies. All patients with TNDM long-term follow-ups should be implemented due to potential neurodevelopmental retardation and relapse diabetes in later life (3, 7). Our patient was being followed up due to mental motor retardation.

In conclusion, our case confirms that sulfonylurea treatment is successful in infants with TNDM resulting from *de novo* duplication identified on the 6q24 chromosome. Our case emphasizes the importance of advanced genetic evaluation for early diagnosis and intervention for patients with chromosome 6q duplications.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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