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Case Report

Successful Transition to Sulfonylurea for Relapsed Monogenic Diabetes Due to Rare 6q23.3 Duplication

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Abstract

Transient neonatal diabetes mellitus (TNDM) due to 6q duplication usually presents in the first 4 months of life, resolves before 18 months of life, and recurs in adolescence or adulthood. Insulin is the first-line treatment for chromosome 6–related neonatal diabetes in infancy. While there is no ideal treatment for patients with relapsed TNDM, residual β-cell function after remission of neonatal diabetes indicates a potential role for insulin secretagogues. Patients with 6q24 duplication have been successfully transitioned from insulin to sulfonylureas (SUs) in adolescence. We present the first report to our knowledge of TNDM secondary to a rare 6q23.3 duplication for which reemergence of diabetes was successfully transitioned from insulin to SU treatment. The successful transition to SU improved glycemic control, cost-effectiveness, and overall quality of life, while decreasing occurrence of hypoglycemia.

Key Words: neonatal diabetes, sulfonylurea, 6q23.3 duplication, 6q24 duplication

Abbreviations: DKA, diabetic ketoacidosis; GAD-65, glutamic acid decarboxylase 65; HbA_{1c}, glycated hemoglobin A_{1c}; HCO_3, bicarbonate; IA2, islet antigen 2; PCR, polymerase chain reaction; SUs, sulfonylureas; TNDM, transient neonatal diabetes mellitus; VUS, variant of unknown significance; WBCS, white blood cells; ZN transporter 8, zinc transporter 8.

Introduction

Neonatal diabetes, a monogenic subtype of diabetes, presents phenotypically as transient, permanent, or as a part of a syndrome. The transient form occurs due to overexpression of the genes in the 6q22 to 24 region, which are normally maternally imprinted [1].

6q24 duplication, the most common cause of transient neonatal diabetes mellitus (TNDM), has an estimated prevalence of 1 in 400 000 [2]. Hyperglycemia usually starts within the first week of life and lasts, on average, for 3 months, though it can last longer, and usually resolves before age 18 months. Subsequently, affected children may develop intermittent episodes of hyperglycemia during illnesses and overt diabetes may reoccur in adolescence or later in adulthood [3, 4]. Insulin is the first-line treatment for TNDM during the neonatal period and is also effective for relapsed TNDM. In contrast, successful transition from insulin to sulfonylurea (SU) has been achieved in 90% to 95% of infants with permanent neonatal diabetes due to mutations in the *KCNJ11* and *ABCC8* genes, which encode critical components of the adenosine triphosphate (ATP)-sensitive potassium channel, closing the K_{ATP} channel by an ATP-independent route [5, 6]. (Fig. 1). However, unique features of TNDM including residual β-cell reserve, intact SU receptors, and decreased sensitivity to glucose, suggest a potential role for SUs in treating patients with relapsed TNDM [7]. (see Fig. 1). Several patients with 6q24 duplication have been successfully transitioned from insulin to SU in adolescence [7].

The 6q23.3 duplication is an extremely rare mutation linked to TNDM, with its prevalence largely unknown due to the scarcity of reported cases [8]. There are limited data on the typical presentation, differences, and similarities between 6q23 and 6q24 duplications, the likelihood of relapse later in life, and the response to SUs. Here we describe a rare case of neonatal diabetes secondary to a 6q23.3 duplication, transitioning to SU during adolescence.

Case Presentation

A 15-year-3-month-old girl with a history of 6q23.3 duplication, global developmental delay, and TNDM presented with a 5-day history of fever, fatigue, vomiting, decreased appetite, polydipsia, polyuria, and recent weight loss.

The patient was born small for gestational age with limited subcutaneous fat. She developed neonatal hyperglycemia, necessitating insulin until age 4 months. She experienced fasting hypoglycemia from 25 months to 3 years, requiring glucose monitoring and dietary changes. Her examination revealed a tall, broad forehead with sparse hair at the temples, hypertelorism, arched eyebrows, hyperopia, esotropia, bilateral ptosis, small, low-set ears, an open-mouth posture, a short philtrum, a thick vermilion border, protruding central incisors, micrognathia, and bilateral dystrophic fifth toenails. As a high school freshman, she functioned at a first-grade level and required educational support.

Diagnostic Assessment

Laboratory studies revealed leukocytosis at 18.9×10^3/μL (18.9×10^9/L) (normal, 4-10.5 $\times 10^3$/μL; 4-10.5 $\times 10^9$/L),

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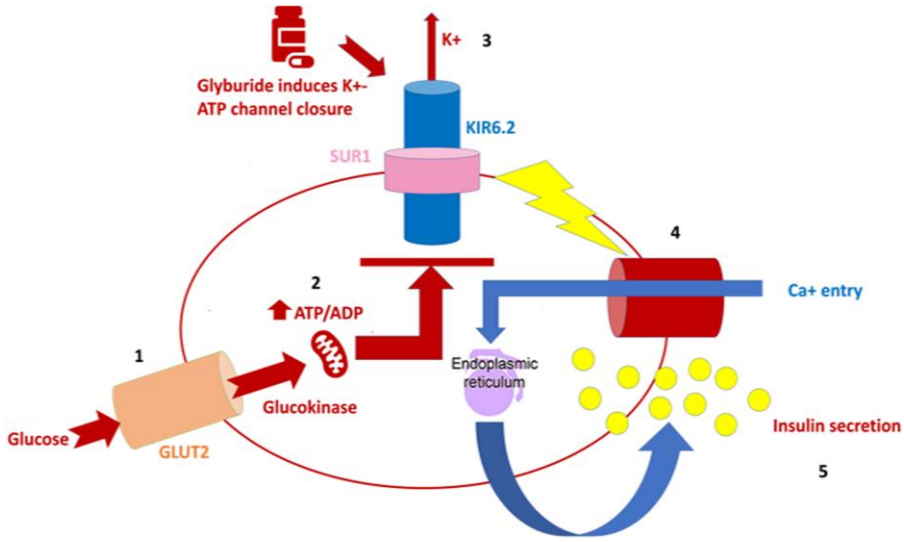

Figure 1. In patients with transient neonatal diabetes mellitus caused by 6q chromosomal abnormalities, β cells are functional but have reduced sensitivity to glucose as a trigger for insulin release. Sulfonylureas can enhance insulin release in response to glucose through an adenosine triphosphate (ATP)-independent mechanism.

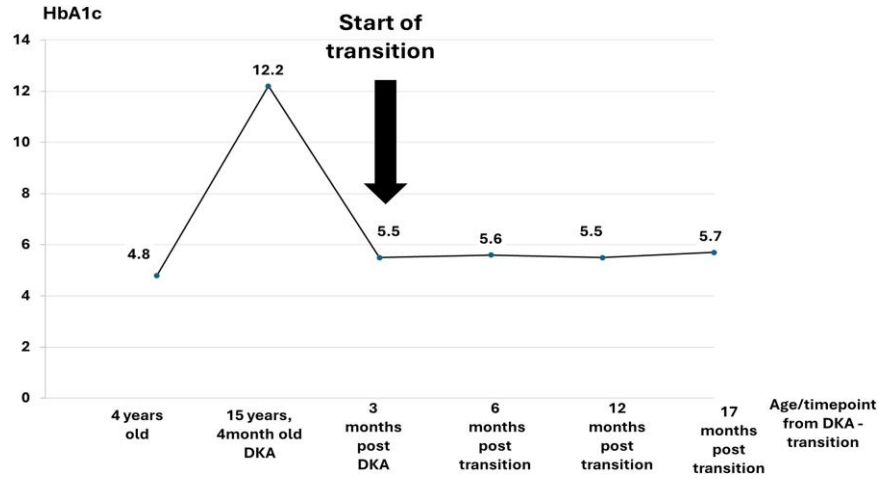

Figure 2. Trend of glycated hemoglobin A_{1c} (HbA_{1c}) over time starting from age 4 years (after resolution of neonatal diabetes and fasting hypoglycemia followed by diabetic ketoacidosis (DKA) presentation, 3-month, 6-month, 12-month, and 17 month follow-up visits post transition).

ketoacidosis with an anion gap of 25 mEq/L (25 mmol/L) (normal, 3-11 mEq/L; 3-11 mmol/L), and HCO3 of 79 mg/dL (13 mmol/L) (normal, 122-170 mg/dL; 20-28 mmol/L). She had hyperglycemia and a glycated hemoglobin A_{1c} (HbA_{1c}) of 12.3% (111 mmol/mol) (normal, 4.0-5.6%; 20-38 mmol/mol) (Fig. 2). The infectious workup, including urinalysis, x-ray, and COVID testing, did not reveal a source for her leukocytosis and fever. Type 1 diabetes antibodies (glutamic acid decarboxylase 65 [GAD-65], islet antigen 2 [IA2], islet cell, zinc transporter 8) were negative (Table 1). Genetic testing revealed a de novo duplication at 6q23.3, with both parental microarray analyses showing a normal 6q23.3 region. This duplication was initially classified as a variant of unknown significance (VUS) in 2007.

Following diabetic ketoacidosis (DKA) presentation, the genetics team sought to obtain an updated analysis, but insurance denied coverage for chromosomal microarray and whole-exome sequencing.

Treatment

The patient was treated appropriately for DKA and transitioned to a basal-bolus insulin regimen at 0.7 units/kg/day, with a decrease in her HbA_{1c} to 5.5% (37 mmol/mol) at 3-month follow-up (see Fig. 2). She was also started on a continuous glucose monitor.

In preparation for transition to glyburide (an SU), her long-acting insulin was reduced by 50% the night before starting glyburide 2.5 mg once daily. The short-acting dose at mealtimes was reduced by 50% if her preprandial glucose was less than 200 mg/dL(<11 mmol/L) (normal reference range, 90-130 mg/dL; 5-7 mmol/L). Long-acting insulin was discontinued on the second day of glyburide, and short-acting insulin was discontinued the third day.

Outcome and Follow-up

Following the transition to glyburide 2.5 mg once daily, blood glucose readings remained within the target range 97% of the

Table 1. Laboratory studies of our patient at presentation in diabetic ketoacidosis

Laboratory parameter	Result	Normal range
Anion gap	**25 mEq/L (25 mmol/L)**	3-11 mEq/L (3-11 mmol/L)
HCO_3	**79 mg/dL (13 mmol/L)**	122-170 mg/dL (20-28 mmol/L)
HbA_{1c}	**12.3% (111 mmol/mol)**	4.0%-5.6% (20-56 mmol/mol)
WBCS	**18.9×10^3/μL (18.9×10^9/L)**	4-10.5×10^3/μL (4-10.5×10^9/L)
Infectious workup: Urinalysis Chest x-ray COVID-19 PCR	Negative	
Type 1 diabetes antibodies (GAD-65, IA2, islet cell, ZN transporter 8)	Negative	

Abnormal values are shown in bold font. Values in parenthesis are International System of Units (SI).

Abbreviations: GAD-65, glutamic acid decarboxylase 65; HbA_{1c}, glycated hemoglobin A_{1c}; HCO_3, bicarbonate; IA2, islet antigen 2; PCR, polymerase chain reaction; WBCS, white blood cells; ZN transporter 8, zinc transporter 8.

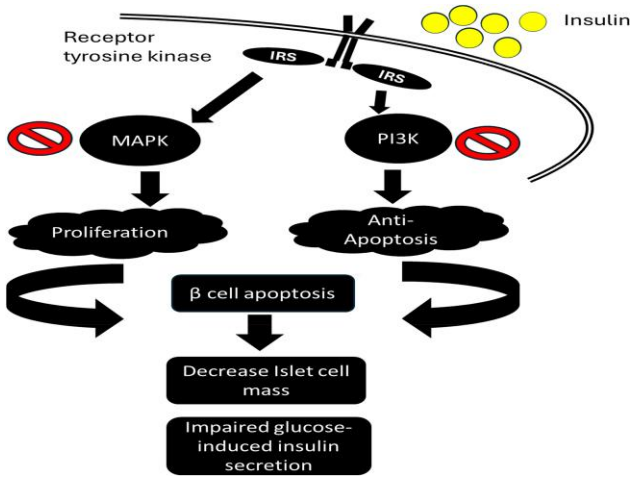

Figure 3. Insulin binds to tyrosine kinase receptors leading to dimerization and phosphorylation of tyrosine residues. Activated tyrosine residues phosphorylate to IRS proteins to activate the PI3K and MAPK signaling pathway. Overexpression of *PLAGL1* leads to 6q-related transient neonatal diabetes mellitus by damaging the MAPK and PI3K pathways in β cells responsible for β-cell proliferation and glucose-induced insulin secretion.

Abbreviation: IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide-3-kinase.

time. Occasional episodes of hypoglycemia occurred 2 hours after a glyburide dose in the morning during the first month of treatment. Proactive snacking around this time prevented further episodes. After 2 months, episodes of overnight hyperglycemia prompted a split in glyburide dose to 1.25 mg twice daily. At 12 months, the patient's dose was reduced to 1.25 mg once daily due to hypoglycemic episodes with physical activity at school, which resolved with this adjustment. HbA_{1c}, 17 months after transition, was 5.7% (38 mmol/mol). (see Fig. 2).

Discussion

We report a rare patient of relapsed TNDM secondary to a de novo 6q23.3 duplication successfully transitioned to SU. While there have been reported patients of TNDM secondary to 6q23.3 duplication [8], to our knowledge our patient is the first to be successfully transitioned from insulin to an SU for relapsed diabetes.

The clinical presentation and severity of 6q duplications vary based on the size, location, and specific genes involved. Patients with smaller duplications, particularly those between bands 6q21 and 6q23, exhibit mild features and minimal developmental delays. In contrast, distal duplications from 6q23 onward are associated with considerable learning difficulties. Reported cases of distal duplications have presented with variable dysmorphisms and developmental outcomes, making it difficult to establish a consistent genotype-phenotype correlation [9]. A child with a 6q21 to q23.3 duplication showed mild learning disabilities, while another child with the same duplication had substantial developmental delays, including delayed toilet training until age 13, similar to those observed in our patient [10].

Patients with 6q24 duplications who relapse later in life have presented without ketoacidosis [11]. Reports of relapse include incidentally detected fasting hyperglycemia, glucosuria, or symptoms such as dental disease [11–13].

Our patient presented with ketoacidosis, likely triggered by an undiagnosed infection and the glucotoxic effects of chronic hyperglycemia, which impaired pancreatic β-cell insulin release [14]. The recovery of insulin secretion is demonstrated by her ability to maintain stable HbA_{1c} levels off insulin for 17 months with only SU therapy, indicating residual β-cell insulin reserve.

Advances in genomics, bioinformatics, and large-scale databases have enabled the reclassification of VUS, which is critical for improving diagnosis, precision therapy, and surveillance [15]. This is relevant for our patient, whose duplication was initially classified as a VUS in 2007 due to technological limitations. Updated microarray and whole-exome sequencing are needed to identify break points and understand the extent of the duplication and the genes involved.

The most confined region of duplication in patients with 6q24-related TNDM resides between 6q23 and 6q24, where the likely gene of interest, *PLAGL1*, is found [16]. Overexpression of *PLAGL1* in rodents was found to reduce β-cell mass at birth and to disrupt the mitogen-activated protein kinase and phosphoinositide-3-kinase pathways in β cells responsible for glucose-induced insulin secretion. (Fig. 3).

The literature reveals few reports of NDM due to 6q23.3 duplication. One infant with TNDM due to duplication at 6q22.33 to q23.3 required insulin until age 3 months, while another with a similar duplication died at birth. Four family members had TNDM related to 6q23.3, but long-term follow-up was not possible [8]. In contrast, a recent systematic review identified 30 patients with 6q24-related TNDM who were transitioned to noninsulin medications. Successful transition to SU occurred in only 9 out of 16 patients during the neonatal period, but among those who relapsed during adolescence or adulthood, the response to SU was more consistent, with 13 out of 14 patients successfully transitioning to SU and discontinuing insulin [17]. The variability in response to SU during infancy is likely due to reduced β-cell function which, over time, gradually improves and leads to remission of TNDM. In contrast, relapse of TNDM during adolescence is associated with preserved β-cell function, which enables a more consistent response to SU [17].

Transgenic mice overexpressing *PLAGL1* showed preserved β-cell mass with a reserve of insulin granules but with a deficiency in insulin secretion. While β-cell islet size normalized with age, suggesting normal function, they exhibited decreased sensitivity to glucose as a trigger for insulin release. Given the ability of SUs to prompt β cells to release insulin in response to glucose, this suggests their potential role in patients with 6q-related TNDM [18] (see Fig. 1).

Insulin is considered the first-line treatment for neonatal diabetes related to 6q duplications, but the ideal treatment for diabetes relapse has not been established due to its rarity. The positive response to SU in 6q24-related TNDM and in our patient suggests that remission of neonatal diabetes associated with 6q23.3 duplication also involves residual β-cell function. This supports the use of insulin secretagogues like SU as a potential treatment strategy for managing diabetes relapse in patients with 6q23 duplications [19].

Hypoglycemia is the primary adverse effect of SU use. However, in reported patients of 6q-related TNDM, therapeutic SU doses have been particularly low compared to those needed for patients with K_{ATP} channel mutations, and hypoglycemia has been effectively managed through dose adjustments [18].

This is exemplified by our patient, currently requiring glyburide 1.25 mg once daily (0.02 mg/kg), similar to a 15-year-old with relapsed TNDM due to 6q24 uniparental disomy of chromosome 6 (UPD6) who maintained good long-term glycemic control with preserved c-peptide secretion on 2 mg of glimepiride daily (0.04 mg/kg) [12]. This contrasts with patients with permanent neonatal diabetes due to *KCNJ11* mutations, in whom a median SU dose of 0.30 mg/kg per day is reported [20]. In *KCNJ11*-mutation patients, high doses of SU are required to sufficiently increase the sensitivity of K_{ATP} channels to inhibition and closure to permit insulin secretion. In patients with 6q duplications without a channelopathy, these high SU dosages are not required for a clinical effect [21].

SU is an exciting potential therapy option for patients with 6q23-related TNDM relapse. A transition from daily insulin injections to oral SU provides significant improvement in quality of life while maintaining excellent glycemic control, lower risk of hypoglycemic events, and greater cost-effectiveness for families.

Learning Points

- TNDM caused by the extremely rare 6q23.3 duplication can relapse later in life, similar to 6q24-related TNDM. The first reported patient case of relapse due to this mutation initially presented with DKA.
- Residual β-cell function with adequate insulin reserve but a defect in insulin secretion could explain the success of insulin secretagogues in relapsed TNDM secondary to 6q23.3 duplication.
- SUs are a safe and effective treatment for relapsed TNDM, even when the cause is not channelopathy.

Contributors

All authors made individual contributions to the work. D.H., D.A., and M.C. were involved in the initial diagnosis and management of the patient. D.H. and M.C. continued to follow up with the patient. All authors contributed to the writing, reviewing, and editing of the manuscript.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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