Successful transition from insulin to sulphonylurea in a child with neonatal diabetes mellitus diagnosed beyond six months of age due to C42R mutation in the KCNJ11 gene

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Abstract. Neonatal diabetes mellitus is a rare monogenic condition affecting 1 in 100,000–300,000 live births. Mutations in the subunits of ATP-sensitive potassium (KATP) channels, which are the central gatekeepers of electrical activity, are the common cause of this condition, thereby reducing insulin secretion in the pancreatic beta cells. Most cases are diagnosed before 6 mo of age. The development of this condition in the latter half of the first year of life is rare; hence, testing in older infants is not routinely performed. Here, we describe the case of a patient who presented with neonatal diabetes mellitus and diabetic ketoacidosis at 10 mo of age. All the pancreatic autoantibodies were undetectable, prompting us to pursue genetic testing. At 13 yr of age, a heterozygous missense variant, C42R, was identified in the KCNJ11 gene by exome sequencing. Subsequently, sulfonylurea was initiated, and insulin therapy was discontinued that resulted in improved blood glucose control and increased C-peptide levels. Given the potential benefit of switching to oral medication, genetic testing should be extended to all infants diagnosed with antibody-negative diabetes before 1 yr of age.

Key words: neonatal diabetes mellitus, KCNJ11, sulfonylurea

Highlights

● Neonatal diabetes mellitus (NDM) can develop in the latter half of the first year of life.
● It is essential to consider genetic testing for NDM in young infants with antibody-negative diabetes.
● Initiation of sulfonylurea in NDM due to KCNJ11 variants leads to better glycemic control.
Introduction

Neonatal diabetes mellitus (NDM) is a rare monogenic disease characterized by the onset of diabetes before 6 mo of age. It is a clinically and genetically heterogeneous disease with 22 known genetic causes, each of which defines different subtype of the disease (1, 2). The condition is further classified into permanent neonatal DM, which requires lifelong therapy, and transient neonatal DM. Activating mutations in either KCNJ11 or ABCC8 gene, encoded by the Kir6.2 and SUR1 subunits of the ATP-sensitive potassium (KATP) channel, respectively, is the most common cause, accounting for approximately 40% of NDM cases (1). These mutations cause decreased insulin secretion from beta cells by reducing the sensitivity of the KATP channel to ATP. Thus, beta cells remain hyperpolarized even in the presence of glucose, thereby reducing electrical activity and insulin release (3). Consequently, affected individuals present with diabetic ketoacidosis (DKA) or marked hyperglycemia with low circulating endogenous insulin (4, 5).

While NDM classically presents before 6 mo of age, some infants may present in the latter half of the first year of life (6, 7). Hence, genetic testing for NDM in young infants is essential, especially when pancreatic autoantibodies are absent. Early recognition and diagnosis are crucial, as identifying a mutation in the KATP channel might allow successful transition from insulin to sulfonylurea agents in most cases. Here, we report a patient with NDM who presented with DKA at 10 mo of age. Genetic testing, which was performed only when the patient approached adolescence, detected a mutation in the KCNJ11 gene.

Case Report

Our patient was the first child born to healthy Chinese parents. He was born full term with a normal birth weight and unremarkable perinatal history. The patient had no family history of diabetes mellitus. He thrived along the 50th centile until the age of 10 mo, when he presented with severe DKA after a 4-d history of fever and coryzal symptoms. In retrospect, the mother reported more frequent wet diapers than usual for two weeks. Laboratory investigations showed a serum glucose of 23.6 mmol/L, hemoglobin A1c (HbA1c) of 13.1% and C-peptide of 0.02 nmol/L. The patient started on a basal-bolus insulin regimen. HbA1c ranged between 6.1% and 7.3% while he was on insulin therapy, but he experienced frequent postprandial hyperglycemia and hypoglycemia after exercise. Anti-islet cell antibody, anti-glutamic acid decarboxylase (anti-GAD65) antibody, and anti-tyrosine phosphatase-like insulinoma antigen 2 (anti-IA2) tested negative at 9 yr of age when the test was first performed at our institution. He was diagnosed with attention deficit hyperactivity disorder (ADHD) at 9 yr of age but had normal growth and development. In view of early onset diabetes, exome sequencing was performed and revealed a heterozygous missense variant KCNJ11 (NM_000525.4):c.124T>C leading to amino acid substitution p.(Cys42Arg), which is absent in the control population and predicted to be damaging by multiple in silico predictions. The variant has also been reported in another family with several members affected by monogenic diabetes as well as in patients with NDM (8, 9). The mother of our patient was tested negative for the variant, whereas genetic testing could not be performed on the father as he died when the patient was 10 yr old due to unrelated reasons.

Based on this finding, the patient was transitioned from insulin to sulfonylurea at 13 yr of age. Prior to transitioning, he was on a total of 1 unit/kg/d of insulin with an HbA1c of 7.2% and fasting C-peptide of 0.14 nmol/L. As glibenclamide was not available locally, he was started on gliclazide 80 mg twice daily (3.2 mg/kg/d). All insulin was tapered off in 2 weeks, and his gliclazide requirement stabilized at 240 mg twice daily (9.6 mg/kg/d). Glycemic control improved with reduced glycemic variability (Fig. 1). Three months after starting gliclazide, blood tests showed an HbA1c level of 5.2% and the fasting C-peptide was 1.08 nmol/L. He continued to have excellent blood glucose control with a 91% time-in-range with glucose levels at 3.9–10 mmol/L, 7.9% time-above range, and 0.4% time-below range on a continuous glucose monitoring system. There was no significant nocturnal hypoglycemia, and the lowest glucose level was 3.8 mmol/L overnight. No significant improvement in attention span was observed after initiation of gliclazide therapy, and he continued to cope well in mainstream school and required no special educational assistance.

Discussion

We reported the case of permanent NDM that was presented beyond 6 mo of age, harboring a C42R variant in the KCNJ11 gene. This variant has been previously described in four members of a Japanese family (8). However, none of the patients had permanent NDM, as in the present case. Instead, they had variable presentations with transient NDM, childhood-onset diabetes, gestational diabetes, and adult-onset diabetes, with two cases of adult-onset diabetes being controlled with sulfonylurea. While electrophysiological studies showed a reduction in ATP sensitivity and an increase in the open probability of the mutant KATP channel, this was compensated by a reduction in channel expression at the cell surface, which probably accounted for the relatively mild phenotypes and later onset of diabetes in these patients (8). The same variant had also been reported in a southern Chinese child with NDM, but details on its clinical presentation are unavailable (9). Our patient is the first reported case of permanent NDM due to this variant with a good response to sulfonylurea treatment and he was taken off insulin therapy completely. Further functional analysis in our case might help understand the factors that contribute to the more severe clinical presentation compared to previously reported patients. In
addition to diabetes, our patient also had ADHD. Owing to the expression of KCNJ11 in the brain, neurological manifestations ranging from severe developmental delay and epilepsy to milder neurodevelopmental problems are well-recognized associations with KCNJ11 mutations (1, 10). The lack of improvement in the patient’s ADHD characteristics after sulfonylurea therapy, in contrast to the excellent glycemic response, is consistent with a previous study where the central nervous system phenotypes mostly showed an incomplete response to the treatment (11).

Genetic testing is routinely recommended for all infants diagnosed with diabetes before 6 mo of age (12). The yield of genetic testing is much lower in those in the latter half of the first year of life. Two articles previously evaluated the frequency of K<sub>ATP</sub> channel mutations in this group of older infants. Støy et al. identified no mutations in either KCNJ11 or ABCC8 genes among 45 infants diagnosed with diabetes between 6 and 12 mo, whereas a study by Rubio-Cabezas et al. showed that K<sub>ATP</sub> channel mutations represent 2.1% of diabetic cases diagnosed during this period (6, 13). The oldest reported case of NDM due to KCNJ11 mutation was diagnosed at 11.5 mo, when improvement in glycemic control and behavioral development was observed after initiation of sulfonylurea treatment (7). Our patient, who presented with DKA at 10 mo of age, was treated for type 1 diabetes until 13 yr of age. Apart from pancreatic autoantibodies, measurement of C-peptide also helps differentiate type 1 diabetes from monogenic diabetes (12). As in our case, preserved β-cell function with detectable C-peptide is unusual in long-standing type 1 diabetes. Together with the clinical presentation and absence of pancreatic autoantibodies, this prompted us to further pursue genetic testing for monogenic diabetes despite its presentation at an atypical age. Similar to the oldest reported case, the diagnosis has resulted in more effective treatment and better clinical outcomes, illustrating the importance of extending genetic testing for K<sub>ATP</sub> channel mutations in older infants with antibody-negative diabetes.

**Conclusion**

In conclusion, we described the case of a patient who presented with permanent NDM at 10 mo of age caused by a mutation in the KCNJ11 gene that was detected later in adolescence. The transition from insulin therapy to oral sulfonylurea resulted in a positive impact on glycemic control and improved the quality of life. Given the promising clinical benefits of such therapy, genetic testing for monogenic diabetes should be extended to...
infants diagnosed with diabetes before 12 mo of age.

Conflict of interests: The authors have no conflict of interest to declare.

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