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Case Report

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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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.

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 (K_{ATP}) 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

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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 (K_{ATP}) 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 K_{ATP} 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 K_{ATP} 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 K_{ATP} 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

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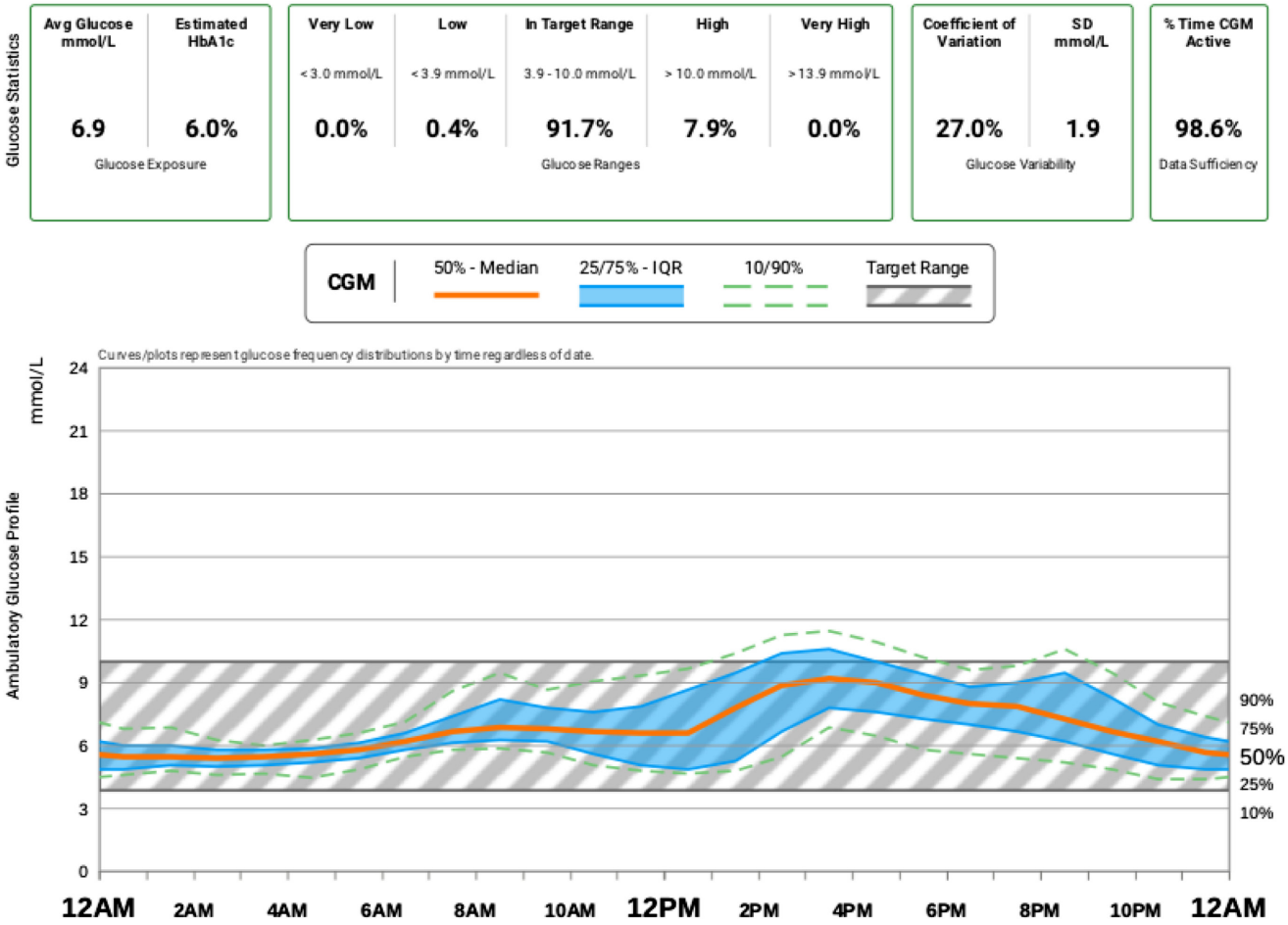

Fig. 1. Ambulatory glucose profile of our patient after switching to sulphonylurea treatment.

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_{ATP} 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_{ATP} 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_{ATP} 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

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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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References

1. De Franco E, Flanagan SE, Houghton JA, Lango Allen H, Mackay DJ, Temple IK, *et al*. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet 2015;386: 957–63. [Medline] [CrossRef]
2. Ellard S, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, Colclough K, *et al*. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. Diabetologia 2013;56: 1958–63. [Medline] [CrossRef]
3. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, *et al*. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350: 1838–49. [Medline] [CrossRef]
4. Letourneau LR, Carmody D, Wroblewski K, Denson AM, Sanyoura M, Naylor RN, *et al*. Diabetes presentation in infancy: high risk of diabetic ketoacidosis. Diabetes Care 2017;40: e147–8. [Medline] [CrossRef]
5. Edghill EL, Flanagan SE, Ellard S. Permanent neonatal diabetes due to activating mutations in ABCC8 and KCNJ11. Rev Endocr Metab Disord 2010;11: 193–8. [Medline] [CrossRef]
6. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr Diabetes 2012;13: 322–5. [Medline] [CrossRef]
7. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pediatr Diabetes 2010;11: 203–7. [Medline] [CrossRef]
8. Yorifuji T, Nagashima K, Kurokawa K, Kawai M, Oishi M, Akazawa Y, *et al*. The C42R mutation in the Kir6.2 (KCNJ11) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. J Clin Endocrinol Metab 2005;90: 3174–8. [Medline] [CrossRef]
9. Lin Y, Sheng H, Ting TH, Xu A, Yin X, Cheng J, *et al*. Molecular and clinical characteristics of monogenic diabetes mellitus in southern Chinese children with onset before 3 years of age. BMJ Open Diabetes Res Care 2020;8: e001345. [Medline] [CrossRef]
10. Gloyn AL, Diatloff-Zito C, Edghill EL, Bellanné-Chantelot C, Nivot S, Coutant R, *et al*. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. Eur J Hum Genet 2006;14: 824–30. [Medline] [CrossRef]
11. Bowman P, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E, *et al*. Neonatal Diabetes International Collaborative Group. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol 2018;6: 637–46. [Medline] [CrossRef]
12. Hattersley AT, Greeley SAW, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, *et al*. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl 27): 47–63. [Medline] [CrossRef]
13. Støy J, Greeley SAW, Paz VP, Ye H, Pastore AN, Skowron KB, *et al*. United States Neonatal Diabetes Working Group. Diagnosis and treatment of neonatal diabetes: a United States experience. Pediatr Diabetes 2008;9: 450–9. [Medline] [CrossRef]

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