The Turkish Journal of Pediatrics 2021; 63: 490-494
https://doi.org/10.24953/turkjped.2021.03.016

Case Report

Neonatal diabetes mellitus due to a new *KCNJ11* mutation - 10 years of the patient's follow-up

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ABSTRACT

Background. Mutations in the *KCNJ11* gene, which encodes the Kir6.2 subunit of the ATP-sensitive potassium channel, often result in neonatal diabetes.

Case. In this report, we describe a 10-year-old girl who is heterozygous for a new missense mutation in the *KCNJ11* gene and whose treatment was successfully switched from insulin to sulfonylurea (glibenclamide) therapy when she was one month old. 10-year data on a low-dose of glibenclamide monotherapy showed excellent glycaemic control with no reports of severe hypoglycaemia and microvascular complications.

Conclusion. An early genetic diagnosis of neonatal diabetes mellitus is highly beneficial because early switch from insulin to sulfonylurea is safe, avoids unnecessary insulin therapy and promotes sustained improvement of glycaemic control on long-term follow-up.

Key words: neonatal diabetes mellitus, new KCNJ11 mutation, sulfonylurea therapy.

Neonatal diabetes mellitus (NDM) is defined as the occurrence of diabetes mellitus within the first 6 months of life. It is a rare disease (1 in 400,000 live births) caused by genetic mutations that can occur spontaneously or be inherited from parents.[1,2] Affected infants frequently present with symptomatic hyperglycaemia and sometimes ketoacidosis.[2] The most common causes of permanent NDM are mutations in the *KCNJ11* and *ABCC8* genes which encode the two protein subunits (Kir6.2 and sulfonylurea receptor 1, SUR1, respectively) of the ATP-sensitive potassium (K_{ATP}) channel on pancreatic β-cells. The identification of the underlying genetic cause has led to improved treatment for patients with mutations in the *KCNJ11* and *ABCC8* genes.[2] Successful switch from insulin to oral sulfonylurea (SU) therapy with excellent initial glycaemic control has been reported in the majority of patients with *KCNJ11* mutations.[3-5] A key question is whether the excellent results in neonatal diabetes will be maintained or whether long-term therapy will cause SU failure or adverse effects. We report the 10-year effect of the switch from insulin to SU (glibenclamide) in a patient carrying the new missense mutation, V252L, in the *KCNJ11* gene.

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Received 26th May 2020, revised 7th September 2020, 24th October 2020, accepted 26th November 2020.

Case Report

A 10-year-old girl presented with marked hyperglycaemia ranging from 10 to 20 mmol/L and glucosuria without ketones on the fourth day of life. This patient had low birth weight (the birth weight of this full-term female neonate was 2780g, on the 5.32th percentile, -1.62 SDS). The patient was born to a 31-year-old mother whose pregnancy was uneventful. The physical examination was normal. There were no other factors (sepsis, infection, dextrose-containing intravenous fluids) that could account for the hyperglycaemia. In addition, there was no family

history of diabetes mellitus or hyperglycaemic disorders. On the fifth day of life, blood glucose was 18 mmol/L and urine contained 1+ glucose without ketones. The patient's C-peptide concentration was 0.18 nmol/L (normal 0.298-2.35) and the serum insulin level was 2.8 μIU/ml (normal 7-24), with a concomitant plasma glucose level of 21 mmol/L.

The initial management of the patient's hyperglycaemia included insulin therapy. At first the patient received infusions of regular insulin at a dose of 0.1-0.2 units/kg/h. On day 8 the infusions were discontinued, and the treatment was switched to a subcutaneous insulin regimen with short-acting human insulin (used to correct hyperglycaemia) and intermediate-acting insulin (administered three times a day to provide basal insulin needs). All in all, she received a daily dose of approximately 2 units/kg/day of insulin. During the neonatal period, genetic analysis was carried out at the Peninsula Medical School, Universities of Exeter & Plymouth. Subsequent testing for mutations associated with PNDM showed that the patient was heterozygous for a new missense mutation, V252L, in the *KCNJ11* gene.[6] The patient's mother was negative for the same mutation and the father was not the patient's biological father.

The patient was one month old when the transition from insulin to oral glibenclamide started at an initial dose of 0.12 mg/kg/day, twice daily. This initial dose was increased over the next 7 days to 0.2 mg/kg/day, while regular insulin was simultaneously tapered off. Her hyperglycaemia resolved completely once her glibenclamide dose was increased to 0.3 mg/kg/day, twice daily, and doses of regular insulin were no longer required. Over the following two weeks the need for glibenclamide slowly decreased and stabilized at 0.2 mg/kg/day and her blood sugar levels reached an average of around 10 mmol/L.

Five months after starting glibenclamide, the patient remained asymptomatic (HbA1c 5.8%); she was gaining weight and showing normal neurodevelopmental progress at follow-up. Her serum C-peptide level was 1.4 nmol/L, showing an eight-fold increase over that seen during insulin treatment alone when C-peptide was 0.18 nmol/L. Oral glucose tolerance test (glucose, 1.75 g/kg) was done one year after the sulfonylurea transition. The results showed the improvement of C-peptide secretory response during treatment. Glucose (0 min-120 min) and C-peptide (0 min-120 min) increased from basal glucose 5.5 mmol/L to 9 mmol/L and from basal C-peptide 0.4 nmol/L to 2.1 nmol/L. Subsequent clinical follow-up visits were at 6 to 12 month intervals. During the follow-up, height and weight were measured, self-monitored blood glucose levels were recorded, HbA1c was measured, and renal and liver function tests were performed.

The patient is now 10 years of age; her height is 140 cm (80th percentile), she weighs 30.5 kg (50th percentile) and shows signs of sexual development (Tanner stage 3). She has normal mental and social skills and strong motivation to learn at school. Recent glibenclamide dose was 0.3 mg/kg per day and her HbA1c was 6.1%. The dosage of glibenclamide was adjusted in accordance with the patient's blood glucose profile and median glibenclamide dose was 0.16 mg/kg/day (0.07-0.3 mg/kg/day) during the ten year of the follow-up period. Under stressful conditions, e.g. while suffering from a mild childhood infection, blood glucose levels remained within the range of 6-10 mmol/L on glibenclamide therapy. Excellent glycaemic control was maintained over the follow-up years and the median of HbA1c was 5.9% (5.6-6.4%; see Fig.1). The median of fasting C-peptide values was 1.8 nmol/L (1.4-2.0 nmol/L) based on 27 measurements over a 9-year period. No reports of severe hypoglycaemia and microvascular complications were recorded. No symptoms leading to suspicion of adverse effects caused by sulfonylurea, including the yellowing of the teeth, gastrointestinal adverse effects, renal and liver dysfunction have been noticed since the switch from insulin to sulfonylurea. A written consent was obtained from the parents for publication purposes.

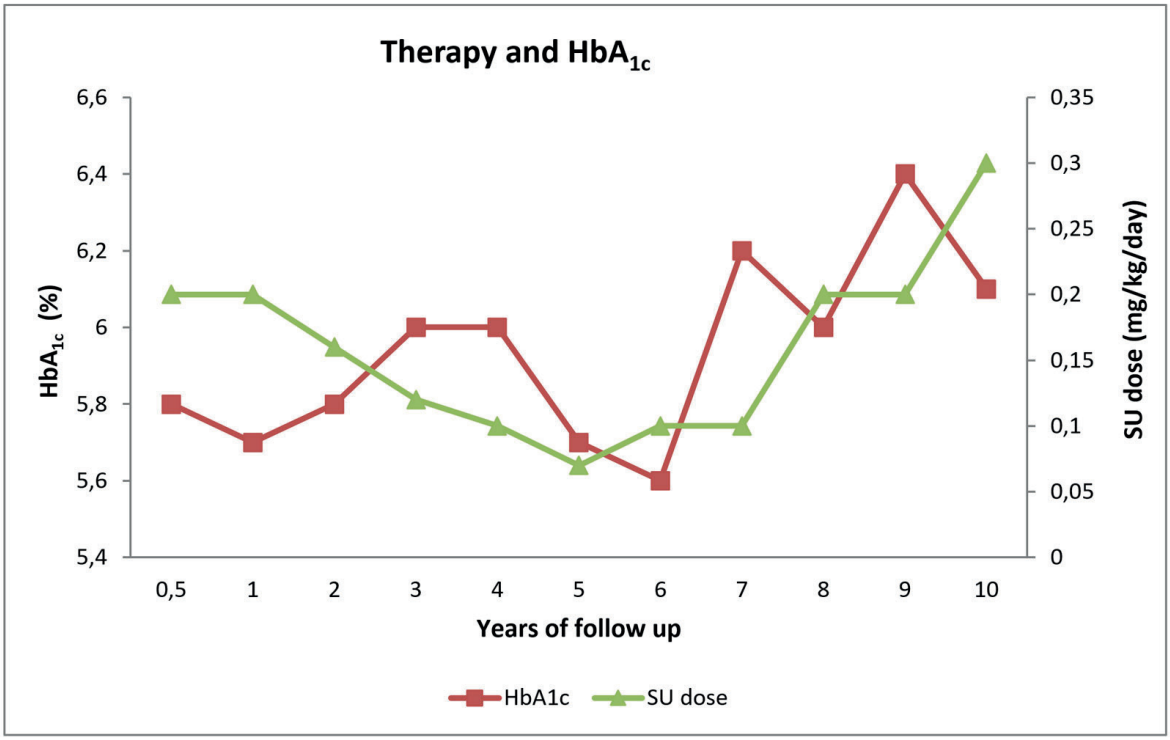

Fig. 1. Overview of the treatment and HbA_{1c} levels during the follow-up of patient with permanent NDM attributable to a V252L in the *KCNJ11* gene. Treatment and HbA_{1c} levels: the point of initial switch from insulin to sulfonylurea is 0 years. Green line with triangles shows sulfonylurea (glibenclamide) dose (mg/kg/day) and red line with squares shows HbA_{1c} levels (%). The dose of sulfonylurea glibenclamide was calculated as the sum of the sulfonylurea doses (in mg) during a day divided by the weight in kg.

Discussion

The number of genes that are found in children with neonatal diabetes continues to increase and there are more than 20 known genetic causes for NDM.[7-10] The various genes are associated with specific inheritance pattern, phenotype, and clinical features.[7] In a large series of 1020 patients diagnosed with NDM before 6 months of age, mutations in the potassium channel genes, *KCNJ11* and *ABCC8*, were found in 38.2% of neonatal diabetes but were identified less frequently in consanguineous families.[7] The clinical presentation varies from incidentally detected asymptomatic hyperglycaemia to severe dehydration and diabetic ketoacidosis (DKA).[11] A genetic diagnosis is crucial, because at least 90% of patients can transfer from insulin injections to oral SU.[12] After transferring to SU treatment, patients have improved glycaemic control at 1 year, without an increase in hypoglycaemia and with less glycaemic variability; however, the key question that remains unanswered is whether the excellent results in NDM will be maintained in the long term.[12-14]

Our patient is one of the youngest patients to commence oral SU therapy for the treatment of NDM because of a new *KCNJ11* mutation, and in a 10-year follow-up SU therapy has been proven safe and effective. The patient maintained excellent glycaemic control without the usual adverse effects of hypoglycaemia. In addition, our result is consistent with the findings of the first study of long-term efficacy and safety of SU that showed that SU failure is not a feature of *KCNJ11* permanent neonatal diabetes.[15] For the 81 patients included in the study which did not include our patient, the median age at diabetes diagnosis was 8.0 weeks, the median age at transfer from insulin to SU was 4.8 years

and 75 (93%) of 81 participants remained on SU therapy alone for the 10-year duration. In these patients, the response dose of SU (0.5 mg/kg/day vs 0.3 mg/kg/day in our patient) and the median maintenance dose of SU (0.23 mg/kg/day vs 0.16 mg/kg/day in our patient) was higher than in our patient whose treatment was successfully switched from insulin to glibenclamide therapy when she was only a month old. Earlier age at the initiation of SU treatment is associated with an improved response to SU therapy and could also lead to a lower maintenance dose which is in contrast with data from a large international cohort study.[15]

A few individuals who initially responded to sulfonylurea (6 of 81 patients) showed worsening glycaemic control on SU monotherapy.[15] The median age at sulfonylurea initiation was 7.4 years and the median age at insulin initiation was 15 years. This fact is important because puberty is associated with increased insulin resistance and suboptimal treatment adherence in diabetes. Patients requiring reintroduction of insulin were on a fairly modest SU dose (median 0.27 mg/kg/day, range 0.19-0.43), suggesting there was capacity to increase the dose further.[15] Taken together, their data suggest that factors other than sulfonylureas having stopped working at the level of the K_{ATP} channel might have contributed to the need for the addition of insulin treatment in these patients. This finding contrasts with the SU monotherapy noted in our 10-year-old patient with signs of puberty (Tanner stage 3). The SU dose was increased at the beginning of puberty from 0.2 to 0.3 mg/kg per day in accordance with the patient's blood glucose profile with satisfactory glycaemic control.

In conclusion, we presented one of the youngest patients to commence oral glibenclamide therapy for the treatment of NDM because of a novel Kir6.2 mutation. An early genetic diagnosis of NDM is important because early switch from insulin to SU is safe, avoids unnecessary insulin therapy, and promotes sustained improvement of glycaemic control on long-term follow-up.

Author contribution

Clinical data and preparation of the manuscript: Maja D Ješić; laboratory analysis: Helena Stock; clinical data: Vera Zdravković, Smiljka Kovačević; statistical analysis: Marko Savić; clinical advisor: Miloš Ješić.

Conflict of interest

The authors declare no conflict of interest.

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