Case Report

Successful Transition to Sulphonylurea Therapy from Insulin in a Child with Permanent Neonatal Diabetes Due to a *KCNJ11* Gene Mutation

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Abstract

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes mellitus that occurs in the first 6 months of life. It is a rare condition with a prevalence of 1 in 100,000–500,000 live births. We report a 3-month-old girl child with high blood glucose levels. She was diagnosed with diabetes mellitus during the 28th day of life and was on treatment with insulin. She was admitted for the control of high blood glucose levels during which she was started on multiple daily insulin treatment, but the control had been poor. As the age of onset is <6 months of life, genetic analysis has been done. It revealed the presence of a heterozygous mutation p. Gly334Val (p. G334V) in *KCNJ11* gene which confirmed the diagnosis of NDM. The child was successfully shifted from insulin to sulfonylureas, and the blood glucose levels are well maintained.

Keywords: Gene mutation, insulin, neonatal diabetes, sulphonylurea

Introduction

Neonatal diabetes mellitus (NDM) is defined as diabetes diagnosed within the first 6 months of life. This condition can be either permanent, requiring lifelong insulin therapy, or transient where the condition can remit during infancy but mostly relapse later in life. Permanent NDM (PNDM) and transient neonatal diabetes mellitus are rare conditions with an incidence of 1 in 300000 live births.[1,2]

We describe here an infant with PNDM due to a mutation in *KCNJ11* gene that encodes the pore-forming subunit KIR6.2 of the pancreatic ATP-sensitive potassium (K-ATP) channel, who was shifted successfully from insulin injections to oral sulphonylurea (SU).

Case Report

A 3-month-old girl child presented with uncontrolled high blood glucose levels. She was the first born child of a non-consanguineous marriage. She was born by a normal vaginal delivery of preterm gestation with a low birth weight of 2 kg. Antenatal, natal and post-natal periods were uneventful. The baby remained well until an episode of fever on the 28th day of life, during which she was investigated and diagnosed to have diabetes. The mother did not report any previous relevant medical conditions such as gestational diabetes mellitus. At the time of admission to our centre, the baby had a BMI of 13.7 kg/m^2. It was observed that the birth centile of the baby is <3rd centile (http://www.who.int/childgrowth/standards/weight_for_age_field/en) and the Z score was 3. Head circumference of the baby was not available. She was started on multiple daily insulin (MDI) treatment, but glycaemic control remained poor. Investigations showed random blood sugar of 371 mg/dl, serum beta-hydroxybutyrate of 0.08 mmol/L, HbA1c of 7.7%, blood urea of 26 mg/dl and

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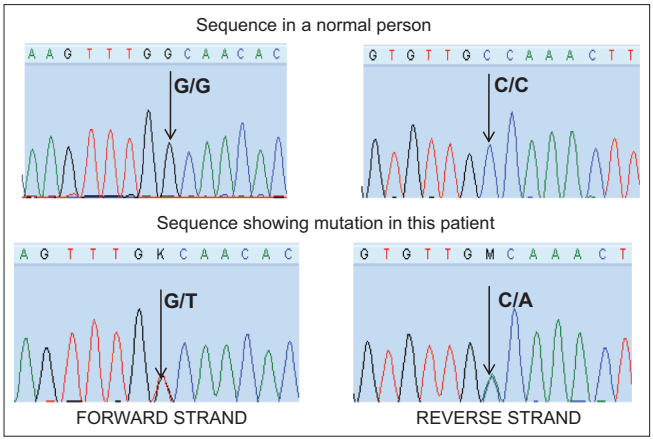

Electropherogram shows the heterozygous mutation of p.Gly334Val (c. 1001G>T)

serum creatinine of 0.3 mg/dl. Haemogram revealed white blood cell count of 11740 cells/mm^3 and haemoglobin of 10.2 gm/dl (normocytic normochromic anaemia). Liver function tests were normal. Ultrasound of abdomen revealed thinned out/hypoplastic pancreas; however, faecal elastase/stool fat estimation was not done. Metabolic encephalopathy also was observed. Serum electrolytes were normal. Thyroid function tests were normal. C-peptide assay showed a stimulated value of 0.6pmol/ml, indicating poor pancreatic beta-cell reserve. Glutamic acid decarboxylase antibody was negative: <1.0 IU/ml. As the age at onset of diabetes was <6 months, we arrived at the diagnosis of neonatal diabetes. Genetic analysis was performed by Sanger sequencing for genes implicated in neonatal diabetes which revealed the presence of a heterozygous mutation p. Gly334Val (p. G334V) in *KCNJ11* gene, which has earlier been shown to be associated with response to SU therapy. The child was started on with glibenclamide a dose of 0.6 mg/kg/day and was increased to 1 mg/kg/day, and the insulin was tapered and eventually stopped. Later, as she was getting hypoglycaemia with glibenclamide, the dose of glibenclamide was reduced to 0.05 mg/kg twice daily.

Discussion

Among the mutations causing PNDM, heterozygous mutations in the potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) and ATP-binding cassette, subfamily C, member 8 (*ABCC8*) genes are the most common causes.[3-5] These mutations impair the ability of the channel to close in response to metabolically generated ATP, thereby preventing glucose-induced insulin secretion from pancreatic beta-cells. SU drugs directly close K_{ATP} channels and facilitate insulin release in response to food. This results in improved glycaemic control.[6]

In this child, the Gly334Val mutation was identified which has been predicted to be deleterious and damaging when bioinformatics tool such as MutationTaster was used. In such cases, SU drugs are the best choice. Oral glibenclamide, a non-selective sulfonylurea, is effective in closing the K + ATP channels in the beta-cells, muscle, and brain. The mutated channels in the nerve muscle and brain are responsible for the neurological symptoms which may be present in some of these cases. The initiation of oral sulfonylurea was done as a rapid inhospital procedure over a period of 1 week. To begin with, sulfonylurea was started with 0.6 mg/kg/day along with a gradual tapering off of insulin before discharging the child. The child now continues to be on SU drug for the past 2 years and is doing well. However, not all patients with mutations in the KCNJ11 or ABCC8 genes are SU sensitive; there has been a report of unsuccessful sulfonylurea therapy in a NDM patient with a different mutation (p. Gly334Asp, c. 1001G >A) in the same amino acid codon[7] [refer supplementary information for protocol of shifting of treatment].

SU treatment is superior to insulin treatment in many PNDM due to mutations in *KCNJ11* gene. Screening of *KCNJ11* and *ABCC8* gene for mutations in patients with PNDM is justified due to the improvement in glycaemic control and the quality of life after switching over to SU from insulin.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Information

Protocol of shifting of treatment

1. Patient to be admitted in the hospital the day before starting to introduce sulfonylureas
2. Regular monitoring of capillary blood glucose and blood or urine testing for ketones to be done.

Day 1:
- Insulin regimen already established should be continued
- 0.6 mg/kg body weight glibenclamide (0.3 mg/kg body weight in the morning and same dose in the evening) to be given.

Day 2:
- If capillary blood glucose >126 mg/dl pre-sulfonylurea (SU), then give 0.35 mg/kg body weight glibenclamide in the morning and same dose in the evening (total dose 0.7 mg/kg/day)
- If capillary blood glucose <126 mg/dl pre-SU, then continue on 0.3 mg/kg body weight in the morning and same dose in the evening (total dose 0.6 mg/kg/day)
- Reduce pre-meal insulin dose by 50%.

Day 3:
- If capillary blood glucose >126 mg/dl pre-SU, then give 0.4 mg/kg body weight glibenclamide in the morning and same dose in the evening (total dose 0.8 mg/kg/day)
- If capillary blood glucose <126 mg/dl pre-SU, then continue on 0.35 mg/kg body weight in the morning and same dose in the evening (total dose 0.7 mg/kg/day)
- Reduce pre-meal insulin dose by another 50%.

Day 4:
- If capillary blood glucose >126 mg/dl pre-SU, then give 0.45 mg/kg body weight glibenclamide in the morning and same dose in the evening (total dose 0.9 mg/kg/day)
- If capillary blood glucose <126 mg/dl pre-SU, then continue on 0.4 mg/kg body weight in the morning and same dose in the evening (total dose 0.8 mg/kg/day)
- Reduce pre-meal insulin dose by another 50%.

Day 5:
- If capillary blood glucose >126 mg/dl pre-SU, then give 0.5 mg/kg body weight glibenclamide in the morning and same dose in the evening (total dose 1.0 mg/kg/day)
- If capillary blood glucose <126 mg/dl pre-SU, then continue on 0.45 mg/kg body weight in the morning and same dose in the evening (total dose 0.9 mg/kg/day)
- Reduce pre-meal insulin dose by another 50%.

Day 6 onwards:
- Maintain dose at 1.0 mg/kg body weight/day of glibenclamide for at least 1 week
- Taper off insulin completely.

Discharge:
- Discharge when no longer requiring insulin treatment and when stable on a glibenclamide (>0.8 mg/kg)
- Patients should continue to monitor capillary blood glucose four times a day and at bedtime, or glibenclamide dose may need to be reduced
- Weekly contact and appropriate titration of glibenclamide until stable.