

Changing the Treatment of Permanent Neonatal Diabetes Mellitus from Insulin to Glibenclamide in a 4-Month-Old Infant with KCNJ11 Activating Mutation

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ABSTRACT

Permanent neonatal diabetes mellitus (PNDM) is a rare type of diabetes and KCNJ11 gene activating mutation is one of its prevalent causes. We introduced a 4-month-old male infant with poor feeding, restlessness, tachypnea, hyperglycemia, metabolic acidosis, and ketonemia. He was discharged with insulin and after 2 months, KCNJ11 gene mutation was found and treatment was switched from subcutaneous insulin to oral glibenclamide. Now, he is 1 year old with desirable glycemic control; therefore, genetic study is recommended for KCNJ11 gene mutation in such patients because if the mutation is found, treatment can be switched from insulin to sulfonylurea.

Keywords: KCNJ11, permanent neonatal diabetes mellitus, sulfonylurea

INTRODUCTION

Neonatal diabetes mellitus is a rare form of diabetes mellitus. Moreover, when hyperglycemia begins before the age of 6 months and lasts for more than 14 days, it is considered as neonatal diabetes. The prevalence of this type of diabetes is about 1 in 500,000 live births.^[1]

Overall, neonatal diabetes is categorized into two groups. In half of the cases; i.e., the transient form, the patients' hyperglycemia is spontaneously improved. In the other type, the patients' hyperglycemia is permanent and is called permanent neonatal diabetes mellitus (PNDM).^[2]

One of the most prevalent causes of PNDM is activating mutations in KCNJ11 and ABCC8 genes, which encode Kir6.2 subunit of the sensitive potassium (K_{ATP}) channel.^[3] Overall, oral hypoglycemic agent sulfonylurea is used in order to treat the PNDM patients with KCNJ11 gene mutation and in fact, the treatment is switched from insulin therapy to sulfonylurea.^[4,5]

In the present study, we introduce a 2-month-old infant who had presented with neonatal diabetes, as well as diabetic ketoacidosis (DKA). After insulin therapy, analysis of KCNJ11 gene was performed for the patient and after diagnosis of the mutation in this gene at the age of 4 months, the treatment was switched from insulin to glibenclamide. After switching the

treatment method to glibenclamide, the patient showed desirable glycemic control during the follow-ups.

CASE REPORT

The case was a 2-month-old male infant who had been referred to Namazee Hospital, Shiraz, Iran 7 days before the admission due to poor feeding, restlessness, and tachypnea. He was born through the cesarean section by a 31-year-old mother with the gestational age of 35 weeks, birth weight of 2450 g, and good APGAR (Appearance, Grimace, Activity, Respiration)¹. The mother had undergone the cesarean section because of hypertension. The parents had non-consanguineous marriage and no history of specific diseases such as diabetes was there in the family.

The patient was hospitalized in Neonatal Intensive Care Unit (NICU)¹ for 5 days with diagnosis of respiratory distress syndrome and then discharged with good general condition. He had desirable health status up to 1 week prior to admission. Then, he presented with poor feeding, restlessness, and respiratory distress and was referred to the hospital.

In the physical examination, the patient seemed dehydrated and lethargic and had kussmaul-respiration. Weight, length, and head circumference of the patient were 4200 g, 50 cm, and 37 cm, respectively and the rest of the physical examinations were normal. Moreover, the patient's laboratory findings revealed BS (Blood Sugar)² = 410 mg/dl, BUN (Blood Urea Nitrogen)¹ = 25 mg/dl, Na = 140 mEq/l, K = 3.9 mEq/l, pH = 7.12, HCO₃ = 8, PCO₂ = 21, and severe ketonemia.

The patient's treatment was started with intravenous fluid followed by insulin. During the hospital stay, he had two episodes of convulsion. After recovery from the acute phase of the disease, since the patient had permanent hyperglycemia, NPH³ insulin was started for him and finally he was discharged with 2.5 units NPH (Neutral Protamine Hagedorn) insulin in the morning and 1 unit in the evening.

Afterwards, blood sample was obtained from the patient and sent to the laboratory of doctors Henrik Thybo Christensen and Klaus Brusgaard in H. O. Andersen Children's Hospital and Department of Clinical Genetics in Denmark. Then, genetic

mutation analysis of KCNJ11 was performed. In the analysis method, deoxyribonucleic acid was extracted and amplified by polymerase chain reaction followed by bi-directional sequencing of the entire coding region. The genetic variation c. 602G > T, p.R201 L was found in a heterozygous form. This genetic variation had been previously described as pathogenic by Codner in 2005.

After 2 months treatment with insulin, the treatment was switched from insulin to glibenclamide. At first, 0.1 mg/kg/day glibenclamide was given to the patient in the morning and at night. Then, based on the blood sugar level, glibenclamide was increased to 0.6 mg/kg/day. After treatment with glibenclamide, the patient's hyperglycemia was successfully controlled and he did not need insulin anymore. Now, the case is a 1-year-old infant with controlled hyperglycemia who only receives glibenclamide.

DISCUSSION

ATP (Adenosine triphosphate)¹ sensitive potassium (K_{ATP}) channels play an important role in insulin secretion from beta cells. The K_{ATP} channel of beta cells has two subunits, inwardly rectifying potassium channel (Kir6.2), and sulfonylurea receptor1 (SUR1).^[1]

The major cause of PNDM mellitus before 6 months of age is a mutation in KCNJ11 or ABCC8 genes that encode Kir6.2 and SUR1 subunits, respectively. Up to now, the activating mutation of the KCNJ11 has been reported to be the most prevalent mutation.^[2]

The treatment of neonatal diabetes with activating mutation of KCNJ11 gene can be switched from insulin injection to oral sulfonylurea.^[3]

The treatment with oral sulfonylurea leads to dramatic improvements in hyperglycemia control and quality of life.^[4]

An important determinant of a possible genetic cause of diabetes is age at the initiation of hyperglycemia. The below 6-month-old diabetic patients have a high likelihood of a monogenic variant of diabetes. Furthermore, some studies have reported that 2% of the diabetic patients between 6 and 12 months old have monogenic diabetes.^[2]

Although PNDM is a rare form of diabetes, it is important because KCNJ11 gene mutation can be identified as a common cause of PNDM in half of such patients. Furthermore, genetic study and finding this mutation is crucial since it helps the

physician to change the patient's treatment from insulin to sulfonylurea.^[4,5]

In the present study, we introduced a PNDM infant who had presented with neonatal diabetes and DKA at the age of 2 months. After 2 months of insulin therapy and diagnosis of KCNJ11 gene activating mutation, the patient's treatment was switched from insulin to glibenclamide. During the follow-up, the patient revealed desirable glycemic control, which was examined by regular checkup of blood sugar and Hemoglobin A1C (HbA1C)¹.

In a study, which was conducted by Stoy *et al.* in the US, KCNJ11 mutation was determined as the most prevalent genetic cause of PNDM in below 6-month-old infants.^[5]

Furthermore, Greeley *et al.* performed a study in the US and concluded that genetic testing in neonatal diabetes had improved the quality of life and was cost-effective as well.^[2] Dupont *et al.* reported the KCNJ11 mutation in a Portuguese family and successful treatment transition from insulin to oral sulfonylurea.^[6]

Besides, Siklar *et al.* reported a successful treatment switch from insulin to glibenclamide in an infant with PNDM mellitus and KCNJ11 mutation.^[7]

In addition, Al-Mahdi *et al.* reported a 3-year-old child suffering from diabetes since the neonatal period and KCNJ11 activating mutation that was treated with sulfonylurea after 3 years.^[8]

Several studies have also reported the successfulness of changing the treatment of PNDM from Insulin to sulfonylurea even years after diagnosis of diabetes.^[9-16] For instance, Vendramini *et al.* conducted a study and showed that long term treatment of PNDM with sulfonylurea was safe and had no side-effects.^[17]

In summary, KCNJ11 activating mutation is a prevalent cause of PNDM, the type of diabetes resulting from this mutation can be treated by sulfonylurea, and the patients show desirable glycemic control by sulfonylurea. Therefore, genetic study is recommended for all PNDM patients; so that in case of finding such mutation, the treatment can be switched from insulin to sulfonylurea.

REFERENCES

1. Nieves-Rivera F, González-Pijem L. Neonatal diabetes mellitus: Description of two Puerto Rican children with

- KCNJ11 activating gene mutation. *PR Health Sci J* 2011;30:87-9.
2. Greeley SA, John PM, Winn AN, Ornelas J, Lipton RB, Philipson LH, *et al.* The cost-effectiveness of personalized genetic medicine: The case of genetic testing in neonatal diabetes. *Diabetes Care* 2011;34:622-7.
3. Gloyn AL, Cummings EA, Edghill EL, Harries LW, Scott R, Costa T, *et al.* Permanent neonatal diabetes due to paternal germline mosaicism for an activating mutation of the KCNJ11 Gene encoding the Kir6.2 subunit of the beta-cell potassium adenosine triphosphate channel. *J Clin Endocrinol Metab* 2004;89:3932-5.
4. Ashcroft FM. New uses for old drugs: Neonatal diabetes and sulphonylureas. *Cell Metab* 2010;11:179-81.
5. Støy J, Greeley SA, Paz VP, Ye H, Pastore AN, Skowron KB, *et al.* Diagnosis and treatment of neonatal diabetes: A United States experience. *Pediatr Diabetes* 2008;9:450-9.
6. Dupont J, Pereira C, Medeira A, Duarte R, Ellard S, Sampaio L. Permanent neonatal diabetes mellitus due to KCNJ11 mutation in a Portuguese family: Transition from insulin to oral sulfonylureas. *J Pediatr Endocrinol Metab* 2012;25:367-70.
7. Siklar Z, Ellard S, Okulu E, Berberoğlu M, Young E, Savaş Erdeve S, *et al.* Transient neonatal diabetes with two novel mutations in the KCNJ11 gene and response to sulfonylurea treatment in a preterm infant. *J Pediatr Endocrinol Metab* 2011;24:1077-80.
8. Al-Mahdi M, Al Mutair A, Al Balwi M, Hussain K. Successful transfer from insulin to oral sulfonylurea in a 3-year-old girl with a mutation in the KCNJ11 gene. *Ann Saudi Med* 2010;30:162-4.
9. Wambach JA, Marshall BA, Koster JC, White NH, Nichols CG. Successful sulfonylurea treatment of an insulin-naïve neonate with diabetes mellitus due to a KCNJ11 mutation. *Pediatr Diabetes* 2010;11:286-8.
10. Ting WH, Huang CY, Lo FS, Lee HC, Lin CL, Guo WL, *et al.* Improved diabetic control during oral sulfonylurea treatment in two children with permanent neonatal diabetes mellitus. *J Pediatr Endocrinol Metab* 2009;22:661-7.
11. Kim MS, Kim SY, Kim GH, Yoo HW, Lee DW, Lee DY. Sulfonylurea therapy in two Korean patients with insulin-treated neonatal diabetes due to heterozygous mutations of the KCNJ11 gene encoding Kir6.2. *J Korean Med Sci* 2007;22:616-20.
12. Chan YM, Laffel LM. Transition from insulin to glyburide in a 4-month-old girl with neonatal diabetes mellitus caused by a mutation in KCNJ11. *Pediatr Diabetes* 2007;8:235-8.
13. Shah B, Breidbart E, Pawelczak M, Lam L, Kessler M, Franklin B. Improved long-term glucose control in neonatal diabetes mellitus after early sulfonylurea allergy.

- J Pediatr Endocrinol Metab 2012;25:353-6.
14. Vaxillaire M, Populaire C, Busiah K, Cavé H, Gloyn AL, Hattersley AT, *et al.* Kir6.2 mutations are a common cause of permanent neonatal diabetes in a large cohort of French patients. *Diabetes* 2004;53:2719-22.
 15. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, *et al.* Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: Patient characteristics and initial response to sulfonylurea therapy. *Diabetes* 2004;53:2713-8.
 16. Klupa T, Skupien J, Mirkiewicz-Sieradzka B, Gach A, Noczynska A, Zubkiewicz-Kucharska A, *et al.* Efficacy and safety of sulfonylurea use in permanent neonatal diabetes due to KCNJ11 gene mutations: 34-month median follow-up. *Diabetes Technol Ther* 2010;12:387-91.
 17. Vendramini MF, Gurgel LC, Moisés RS. Long-term response to sulfonylurea in a patient with diabetes due to mutation in the KCNJ11 gene. *Arq Bras Endocrinol Metabol* 2010;54:682-4.

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