CASE REPORT

Permanent Neonatal Diabetes Mellitus Due to an *ABCC8* Mutation: A Case Report

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ABSTRACT

Context Neonatal diabetes is a rare disorder with an incidence of about 1 in 100,000 live births. It is defined as diabetes diagnosed in the first 6 months of life and it is vital to differentiate this entity from type 1 diabetes to enable accurate diagnosis, prognosis, genetic counseling and treatment. **Case report** We describe a case of permanent neonatal diabetes mellitus due to a novel mutation affecting the *ABCC8* gene that encodes the SUR1 subunit of potassium ATP channel (K_{ATP}). **Conclusion** This genetic diagnosis has therapeutic implications as patients can switch from insulin therapy to sulphonylurea, as described in this case report.

INTRODUCTION

Neonatal diabetes is defined as hyperglycemia occurring within the first few months of life, lasting more than 2 weeks [1]. It is categorized into permanent neonatal diabetes and transient neonatal diabetes. Heterozygous activating mutations in the *KCNJ11* and *ABCC8* genes which encode the Kir 6.2 and SUR1 subunits of the ATP-sensitive potassium (K_{ATP}) channels that control insulin secretion are the commonest causes of permanent neonatal diabetes and a rarer cause of transient neonatal diabetes respectively [2, 3]. Other rare genetic causes of neonatal diabetes include mutations in insulin gene (*INS*), hepatocyte nuclear factor 1B (HNF1B), pancreatic and duodenal homeobox 1(PDX 1), pancreas specific transcription 2 factor, 1a (PTF1A), forkheadbox P3 (FOXP3), eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3), and glucokinase gene [3, 4]. Recently, missense mutations in the genes encoding insulin and its precursors, preproinsulin and proinsulin, have also been reported as causes of permanent neonatal diabetes mellitus [5]. Patients with transient neonatal diabetes due to chromosome 6q24 abnormalities are more likely to have intrauterine growth retardation and less likely to develop ketoacidosis. It is vital to identify K_{ATP} channel mutations as most of these patients do not require insulin and achieve better glycemic control with sulphonylureas.

We hereby report a case of permanent neonatal diabetes, diagnosed to have an *ABCC8* mutation, who has been successfully switched over to sulphonylurea.

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CASE REPORT

A two-month-old female baby, born to non consanguineous parents, was referred to Amrita Institute of Medical Sciences, Cochin, India for diabetic ketoacidosis. Antenatal period was uneventful with no history of gestational diabetes mellitus. Family history was unremarkable except that maternal grandmother had diabetes. The baby was born at full term by normal vaginal delivery with weight of 2.5 kg. Postnatal period was uneventful except for diabetic ketoacidosis.

On examination, the weight was 4.2 kg (25th percentile) and length 55 cm (50th percentile). Her vitals were stable. She had no dysmorphic features. Rest of the systemic examination was normal.

Complete blood counts were normal with no evidence of ketonuria. Fasting blood glucose was 156 mg/dL (reference range: 70-110 mg/dL) and 2-hour postprandial glucose 300 mg/dL (reference range: 100-140 mg/dL) with a glycated hemoglobin of 7.9%. (reference range: 4.0-5.9%). Structural diseases of pancreas were ruled out by ultrasonography of abdomen. Glutamic acid decarboxylase-65 antibody (GAD-65) and insulinoma-associated antibody (IA-2) were negative; the fasting C-peptide was 1 ng/mL, (reference range: 1-3 ng/mL). As the onset was less than 6 months with autoimmune markers being negative, genetic tests for mutation in K_{ATP} channel were carried out. This revealed a heterozygous missense mutation in exon 29 of *ABCC8*. The mutation is a substitution of a T for C at nucleotide 3596, i.e. c.3596C>T which results in the substitution of leucine for proline at amino acid 1199, i.e. P1199L. Testing of the parents showed that the mutation had risen *de novo*. The baby was initially put on neutral Hagedorn (NPH) insulin 2 units daily with bolus of short acting insulin until the results of the genetic analysis were made available, following which she was switched over to glibenclamide.

In our case, the child is on regular follow up and is presently on 3.75 mg/day of glibenclamide with glycated hemoglobin of 6.8% and C-peptide of 2.7 ng/mL, 3 months after starting oral hypoglycemic agent.

DISCUSSION

Activating mutations in Kir 6.2 and SUR1 subunits of the K_{ATP} channels account for one third to one half of cases of permanent neonatal diabetes. Mutations in *ABCC8* gene is thought to account for 10% of all cases of neonatal diabetes [6] and frequently cause transient neonatal diabetes. *ABCC8* mutations may be either dominantly or recessively acting and 40 different mutations have been reported in patients with neonatal diabetes[7, 8].

The K_{ATP} channel is an octamer complex of four regulatory sulphonylurea receptors (SUR) embracing pore forming inwardly rectifying potassium channel (Kir). This channel is normally inhibited by binding of adenine nucleotides to subunit Kir 6.2 which closes the channel and activated by nucleotide binding or hydrolysis on SUR1 which opens the channel. The balance of these opposing action determines the low open channel probability (P_0), which controls excitability of pancreatic beta cells.

It is postulated that activating mutations in these channels reduce the sensitivity to inhibitory actions of ATP and increases sensitivity to stimulatory actions of ADP which causes K_{ATP} channel to remain open, thereby inhibiting insulin release. Sulphonylurea stimulates insulin secretion by binding to SUR1 subunit, thereby closing K_{ATP} channel by ATP independent mechanism.

Babenko *et al*. described seven *ABCC8* mutations with milder phenotypes. Four mutations were familial and showed vertical transmission [6]. L213R and I1424V mutations were associated with permanent neonatal diabetes and other five with transient neonatal diabetes. These patients were diagnosed within first 6 months of life, presented with low birth weight (from less than 3 to 67 percentile) and hyperglycemia with absence of islet cell antibody. Two patients presented with ketoacidosis (H1023Y and I1424V) and four patients with minor neurological symptoms.

Compared to babies with Kir 6.2 mutations, those with SUR1 mutation revealed no significant difference in the prevalence of low birth weight, age at diagnosis or severity of hyperglycemia. However, babies with insulin gene mutations had higher birth weight than those with channel mutations.

The preliminary investigations in our case ruled out type 1 diabetes. Hence, a genetic analysis was done which revealed heterozygous missense mutation (P1199L) in exon 29 of *ABCC8* gene, which results in substitution of leucine for proline. This mutation had arisen *de novo* and is a new mutation not reported so far from India. In our patient, the baby was later switched over to 0.1 mg/kg/day of glibenclamide, which was slowly titrated as per the protocol compiled by Hattersley and Asheroft [2]. A more detailed version of the protocol for transferring patients with diabetes due to Kir 6.2 or SUR1 mutation is available in the www.diabetesgenes.org website. This protocol was for Kir 6.2 mutations, but is also applicable for patients with SUR1 mutations [9]. The sulphonylurea commonly used is glibenclamide at a high dose of 0.5 mg/kg/day which later can be tapered over time.

Rafiq *et al*. followed 27 patients with SUR1 mutation for two months after switching over to OHA and found that 85% could be successfully transferred to OHA without need for insulin [9]. Glycated hemoglobin in them fell from 7.2% to 5.5% (P=0.01). However, long term follow up is needed to see whether improved glycemic trends continue. In seven patients sulphonylureas other than glyburide were tried (i.e., gliclazide, glipizide, tolbutamide). In the study by Rafiq *et al*., four patients could not be successfully switched over to OHA. Two of them had neurological abnormalities and the other two received their molecular genetic diagnosis later in life [9]. Three patients reported side effects due to sulphonylurea. One had transitory diarrhoea, the other had nausea which resolved spontaneously.

One severe hypoglycemic episode was reported, requiring reduction in the dosage of sulphonylurea.

When compared with Kir 6.2 mutations, patients with SUR1 mutation needed lesser dose of sulphonylurea (0.26 *vs*. 0.45 mg/kg/day) and may represent an increased endogenous insulin secretion [9]. Permanent neonatal diabetes due to an insulin gene mutation has been reported earlier from India [10]. To our knowledge, *ABCC8* mutations are rare causes of permanent neonatal diabetes and this is the first case from India. This case has a hitherto undescribed novel mutations.

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Conflict of interest The authors have no potential conflict of interest

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