**Permanent Neonatal Diabetes Due to KCNJ11 Gene Mutation**

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**ABSTRACT**

Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of diabetes within the first six months of life and insulin dependence life long. It has been recently discovered that mutation in KCNJ11 gene encoding Kir6.2, the pore forming subunit of ATP sensitive potassium channel (K\textsubscript{ATP}) is the most common cause and such patients may respond better to oral sulphonylurea drugs than insulin. Here is a rare case of permanent neonatal diabetes due to R201C mutation in KCNJ11 gene. [Indian J Pediatr 2007; 74 (10) : 947-949] E-mail : drletha@gmail.com

Key words : Permanent neonatal diabetes; KCNJ11 gene; Kir 6.2; Sulphonylurea; Glibenclamide

Neonatal diabetes mellitus is a rare disease reported to have an incidence of one in 400,000 to 500,000 live births.\(^1\) It can be grouped into two distinct clinical entities; transient and permanent.\(^1,2\) Transient neonatal diabetes mellitus (TNDM) resolves by a median of 12 weeks and is usually associated with abnormalities of chromosome 6, including paternal uniparental disomy and paternal duplications of 6 q 24, with loss of imprinting and increased risk of diabetes later in life.\(^2,3\) Permanent neonatal diabetes can be caused by mutations in the transcription factors; insulin promoter factor (IPF)-1 causing pancreatic agencies, eukaryotic translation initiation factor-2 alpha kinase 3 (EIF2AK3), and forehead box-P3 and in key components of insulin secretion: glucokinase (GCK) and the K\textsubscript{ATP} subunit Kir6.2.\(^3,4\) It has been recently discovered that heterozygous activating mutations in KCNJ11 gene, encoding Kir6.2, the pore forming subunit of the K\textsubscript{ATP} channel causes both transient and almost half of the cases of permanent neonatal diabetes. Here we present the case of a five and a half month old female baby with neonatal diabetes mellitus, who has been detected to be heterozygous for R201C mutation in the KCNJ11 gene. She has been successfully transferred from a regime consisting entirely of high dose insulin to a small dose of oral glibenclamide and successful control of blood sugar values. This is one of the first such cases to be reported from India.

**CASE REPORT**

A two month old baby girl presented with fever of three days duration, cough and fast breathing of one day duration, with an episode of vomiting. She was second born of a nonconsanguinous marriage, born by full term caesarean section; indication being previous caesarean section; her birth weight was 2.3 Kg. Antenatal, natal and postnatal period were uneventful. The baby had remained well since birth till the present illness. She had an elder sibling, a healthy four year old girl. Maternal grandfather had diabetes mellitus diagnosed at the age of 60. On examination, she was severely dehydrated. Her heart rate was 130/minute, respiratory rate was 80/minute, and the capillary refill time was prolonged. There was grunting respiration and flaring of alae nasi. Breath sounds were heard normally.

Cardiovascular and gastrointestinal systems were within normal limits. Baby was drowsy and there was bilateral hyper reflexia with extensor plantar response.

The investigations revealed Hb 9gm/dl, TLC 12000, blood urea 108 mg/dl, serum creatinine 5mg/dl, sodium 140mEq/L, potassium 5.8mEq/L and random blood sugar 606mg/dl. There was severe metabolic acidosis (ABG-pH 6.9, HCO\textsubscript{3} 1.4mmol/L, PCO\textsubscript{2} 27.6 mm of Hg, PO\textsubscript{2} 139 mm of Hg, BE-29.8). Urine examination showed sugar 2% and ketones 4%. A diagnosis of diabetic ketoacidosis with acute renal failure was made and she was treated with insulin, intravenous fluids, antibiotics and peritoneal dialysis. Her renal function improved rapidly but she had seizures on the third day due to hyponatremia and cerebral edema. Her
seizures were controlled and clinical status improved rapidly after correction of the metabolic defect. An ultrasound examination of abdomen done was normal. Since her blood sugar values remained above 300mg/dl, the dose of plain insulin was stepped up to a maximum of 2units/Kg/day over next few days. Even then there was a wide fluctuation in blood sugar values from 40mg/dl to 546 mg/dl. Other investigations including blood culture and urine culture were normal. Her glycated hemoglobin (HbA1C) level was 13.7% and serum C-peptide level was 0.03ng/L (normal 0.4-4ng/L). The patient’s and her parent’s blood was sent for genetic workup. The patient was growing consistently along the 50-75 percentiles for height, and gaining motor and social skills appropriate for age. At 4 ½ months of age, she was detected to be heterozygous R201C mutation in KCNJ11 gene. The C>T mutation at nucleotide 601 results in substitution of cysteine for arginine at codon 201. The result confirmed a diagnosis of neonatal diabetes due to a mutation in Kir 6.2 subunit of KATP channel. Her parents were tested negative, raising the possibility of a denovo mutation.

The patient was put on a trial of glibenclamide therapy. Glibenclamide, delivered orally as a powder dissolved in water was started on a dose of 0.6mg/Kg/day and was increased over the next four days to 1mg/Kg/day and insulin was concomitantly tapered off. At the end of transfer, the serum c-peptide level was 0.26ng/L, showing an increase of eight fold over the level during insulin therapy alone indicating increased endogenous insulin release. The blood glucose limits were set between 140-220 mg/dl to avoid episodes of hypoglycemia. Since her blood glucose levels did not reach the set limits with glibenclamide alone, insulin therapy was restarted, but at a lower dose of 0.6 units/Kg (previous dose 2 units/Kg). With this, over the next few weeks her blood sugar levels stabilized and reached an average of around 198mg%. The wide variations from normal range also decreased. Insulin was later gradually withdrawn. Patient is now on oral glibenclamide (1mg/Kg/day). She is asymptomatic, gaining weight and on regular neurodevelopmental follow up.

DISCUSSION

Neonatal diabetes mellitus an extremely rare entity, usually diagnosed within first three months of life is usually a single gene disorder associated with altered B-cell number of function.\textsuperscript{2} Till recently the genetic etiology of Permanent neonatal diabetes mellitus (PNDM) was unknown. It has been recently elucidated that heterozygous activating mutations in KCNJ11 gene, encoding Kir6.2 subunit of the pancreatic K\textsubscript{ATP} channel is the most common cause of PNDM.

Physiology

The K\textsubscript{ATP} channel plays a central role in glucose-stimulated insulin secretion from the pancreatic beta cell. The channel consists of two of essential subunits: the pore forming subunit Kir6.2 and the regulatory subunit sulphonyl urea receptor 1 (SUR1). SUR1 is found in pancreas and brain muscle, SUR2A in heart and skeletal muscle, and SUR2B in brain and smooth muscle.\textsuperscript{3}

K\textsubscript{ATP} channels are subject to complex regulation by numerous cytosolic factors, the most important being adenine nucleotides ATP and magnesium ADP (MgADP).

At sub stimulatory glucose concentrations, K+ efflux through open K\textsubscript{ATP} channels maintains the beta cell (\(\beta\)-cell) membrane at a hyperpolarized potential of around –70 mV, which keeps voltage-gated Ca\textsuperscript{2+} channels closed. Increased glucose metabolism leads to elevated cytosolic ATP/ADP, closure of K\textsubscript{ATP} channel at plasma membrane, and membrane depolarization. The resulting activation of voltage-sensitive Ca\textsuperscript{2+} channels causes a rise in [Ca\textsuperscript{2+}], which serves as a stimulus for insulin vesicle exocytosis. Under physiological conditions, K\textsubscript{ATP} channel closure is the central step in glucose stimulated insulin release. Sulphonylurea drugs stimulate insulin secretion by binding to and closing K\textsubscript{ATP} channels. Thus, sulphonylureas bypass \(\beta\) cell metabolism but subsequently stimulate the same chain of events as glucose.\textsuperscript{2,6}

There is a spectrum of phenotypes associated with activating mutations in Kir6.2. The mildest phenotype caused by mutation in KCNJ11 gene is Transient neonatal diabetes mellitus (TNDM). In TNDM the babies are born lighter, diagnosed earlier and have blood glucose levels at diagnosis lower (16.5mmol/L) when compared to PNDM cases.

The second phenotype associated is Permanent neonatal diabetes mellitus (PNDM). The mutations associated include R201H, R201C, V59M, G53R, G53S, F35L, F35V etc. The average age at diagnosis is 6 week, and there were no associated neurological findings in most of the cases. The most common among the KCNJ11 mutations is R201H.\textsuperscript{5,7} In most of the studies conducted, the affected patients with a KCNJ11 mutations had their parents unaffected. This is consistent with a denovo mutation in the patient; but the possibility of germ line mosaicism cannot be ruled out.\textsuperscript{5,8} In addition to neonatal diabetes, neurological features, particularly developmental delay, epilepsy are associated with some Kir6.2 mutations. This is known as Developmental delay epilepsy and neonatal diabetes (DEND) syndrome.\textsuperscript{5,5} Those with a very severe neurological phenotype that exhibits all the features are said to have full DEND syndrome. A less severe clinical picture, consisting of neonatal diabetes with developmental delay and/or