

Transient Neonatal Diabetes due to *Kcnj11* Mutation

A 2.3 kilogram full-term male infant was born to a 26 year primigravida mother by uncomplicated vaginal delivery. Despite adequate breast feeding, there was slow growth and poor weight gain. At 4 months of age, the child presented to a local hospital with fever, drowsiness and breathing difficulty for 2 days. There was no history of rash, diarrhea, bleeding, vomiting, recurrent infections, developmental delay or seizures. The weight was 3.9 kg. Apart from drowsiness and mild tachypnea, the systemic examination was normal. Investigations revealed a blood sugar of 1245 mg/dL with severe metabolic acidosis (pH:7.108, bicarbonate:5.2mEq/L with base-deficit:-22.3mEq/L). He was managed as diabetic-ketoacidosis (with hydration, insulin therapy, antibiotics and strict electrolyte and cardiorepiratory monitoring) and subsequently started on intermittent subcutaneous regular insulin (at 0.1 Units/kg/dose) 3 times a day. The child continued to have episodes of hyperglycemia documented by blood sugar measurements. While on insulin therapy, the child also had intermittent episodes of jitteriness with documented hypoglycemia requiring intravenous glucose boluses and/or feeding. The child was referred to our institute for further management.

On enquiry, the mother revealed that he had grown increasingly hungry and persistently demanded feeds, especially at night. Furthermore, the diaper used to be relatively heavy since a month, needing frequent changing.

His blood counts, renal and liver function tests were normal. Serum potassium was raised (6.1mEq/L), as was the glycosylated-hemoglobin (14.2%) while insulin levels [2.5 mIU/mL (0.104 microgram/L); normal: 2.6-24.9 mIU/mL] were low. The C-peptide levels were also low (0.26ng/dL, normal range:0.48-5.05ng/dL). Anti-insulin antibodies were negative. Ultrasound abdomen was normal.

In view of age, non-response to insulin, low C-peptide and elevated glycosylated-hemoglobin levels; neonatal diabetes was suspected and genetic analysis for KCNJ11, ABCC8 and INS gene mutations was performed. The patient was heterozygous for the E227K missense-mutation in the KCNJ11 gene. This G>A mutation at nucleotide 679 (c.679G>A), resulting in the substitution of lysine for glutamic acid at codon 227 (p.Glu227Lys), confirmed the diagnosis of transient neonatal diabetes (TND) (OMIM 601410) due to a mutation in the Kir6.2 subunit of the KATP channel(1,2). Parental testing was negative, hence, it was a *de novo* mutation.

He was managed with insulin (intermittent doses of insulin up to 0.2 U/kg/dose) and regular blood sugar monitoring. Thereafter, he was switched over to glibenclamide according to standard protocols(1). Glibenclamide was administered orally as powder dissolved in water. C-peptide started rising on day 2 (1.3-1.42 ng/dL). At 3 months follow-up, the child had normal insulin, C-peptide and blood sugar levels and was on 0.2 mg/kg glibenclamide that was titrated and tapered gradually. Currently, at 6 months of follow-up, the child is off glibenclamide.

Neonatal diabetes is a insulin-requiring hyperglycemia diagnosed within first 3 months of life. It may be transient, resolving within 18 months, or permanent. A proportion of the cases with TND may subsequently relapse and are diagnosed with diabetes in adolescence or early adulthood(1). Recently, TND has been shown to be genetically heretogenous and mutations in KCNJ11 have been shown to be associated with it. To the best of our knowledge, this is the first report from India describing TND due to E227K missense mutation in KCNJ11 gene(3,4).

Patients with TND are at an increased risk of permanent diabetes mellitus and several molecular forms of TND are associated with increased risk to siblings, adverse neurodevelopmental outcome and chanellopathies(1-5).

Glibenclamide can effectively attain euglycemia and obviate the need for insulin in many molecular forms of TND, as observed by us(4,5). The response to sulfonylureas may result from the closing of mutant KATP channels independent of adenosine-triphosphate, thereby augmenting insulin secretion in response to incretins and glucose metabolites(4,6).

Titration of insulin dose in these patients requires serial insulin levels and or blood glucose levels. Obtaining serial insulin levels may often be difficult in a resource limited setting. As used in our patient, C-peptide levels could be used as a surrogate marker of insulin levels and could ease dose adjustment and titration during acute phases as well as during follow up. This could obviate the need for stringent blood glucose/insulin level monitoring during switch over to sulphonylureas from insulin therapy. We emphasize the utility of C-peptide levels in titration of glibenclamide/sulfonylureas and maintenance of euglycemia, which has not been reported earlier in TND(6).

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Urban Poverty and Child Welfare

Dr Vashishtha rightly draws attention to increasing urban poverty as a “blot on our country’s shining armor”(Indian Pediatr 2009; 46:875-876). There, of course, are many other blots! Abysmal living conditions and lack of basic facilities (safe water, health care, education etc) faced by the urban poor are well-recognized, and preventable diseases, abuse and exploitation, and antisocial activities have been on the rise in metropolitan cities. The burgeoning immigration from rural areas of some of the poor states to cities has put intolerable strain on their

infrastructure. Children are the worst sufferers in such adverse conditions. Infants and young children remain abandoned and uncared for while older children are often out of school, employed in various forms of work or on the street.

Whereas IAP can do little about poverty and poor governance, it can help to tackle the problems of children in urban underprivileged communities. Basic health care and education are crucial rights of every child and must be demanded. The parents being illiterate and poor cannot take proper care of their children. That responsibility must be assumed by the community, their elected representatives and the Govt officials, who should have the onus of looking