CASE REPORT

NEONATAL DIABETES WITH KIR 6.2 MUTATION ON GLIBENCLAMIDE THERAPY

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Abstract

Genetic studies in neonatal diabetes can drastically change the therapy lifelong. An 82 days infant with diabetes mellitus on insulin was diagnosed with mutation of the KCNJ11 gene encoding kir 6.2 and was successfully switched over to oral glibenclamide. Child is maintaining euglycemia and is off insulin therapy.

Key words: Neonatal diabetes mellitus, Kir 6.2 mutation, glibenclamide.

Introduction

Neonatal diabetes is a rare metabolic disorder with an incidence of;1 in 400 000 live births. (1) Until recently genetic studies by and large have been found to be of use in arriving at a definitive diagnosis and predicting the risk for future pregnancies. In a few disorders genetics have played a role in deciding the management. One such metabolic disorder is neonatal diabetes mellitus. Genetic studies in diabetes mellitus may reveal whether it is transient or permanent and in case of the latter may reveal the mutations which may be responsive to oral therapy with sulphonylurea. (2)

Case Report

An 82 days old male infant was admitted with history of breathlessness and poor feeding of 2 days duration. He was lethargic and tachypneic at admission. His blood glucose was 450 mg/dl, blood gases revealed severe metabolic acidosis and urine showed ketonuria. History revealed polyuria and infant demanding frequent feeds since 6 weeks of life. Child was treated as per the hospital protocol for management of Diabetic ketoacidosis (DKA) and was stabilized on twice daily intermediate acting insulin therapy. C peptide levels were 0.1pmol/ml (normal: 0.3-1.4 pmol/ml) suggesting poor pancreatic reserve. Glycosylated hemoglobin (HBA1c) level was 7.97%. Glutamic acid decarboxylase (GAD) was <6.54 IU/ml (Normal<10 IU/ml) and insulin antibodies were 0.5 IU/ml (Normal< 15 IU/ml). Serum lipid profile and thyroid function tests were normal. His skeletal work up was negative for epiphyseal dysgenesis. His liver enzymes were within normal limits. He was the first born child of nonconsanguinous parents, delivered as a term baby of 2.4 kg birth weight. Antenatal and birth history was not contributory. There was no family history of diabetes. At admission, he weighed 3.75kg. Child did not have dysmorphic features. Child was followed up in the diabetic clinic every month, had normal development and optimal weight gain. At 6 months of age child was started on twice daily insulin as a combination of short and intermediate acting insulin. Self monitoring of blood glucose was done at home and HBA1c maintained between 6.9 - 8.9%. Genetic analysis was done at 16 months for Kir 6.2, ABCC 8 and INS. Sequencing analysis revealed the baby to be heterozygous for a missense mutation C42R, in the KCNJ11 gene. This T>C mutation at nucleotide 124 resulted in the substitution of the aminoacid arginine for cysteine at codon 42. The mutation has been previously reported. (3) Both the father and mother were negative for this mutation. Diabetes mellitus due to this mutation has been found to be responsive to oral sulphonylurea therapy. (4)

It was planned to switch over the child from insulin injections to oral sulphonylurea therapy. Child was admitted as inpatient and the baseline C peptide and HBA1c levels were taken. Child weighed 10 kg and was on twice daily combination of short and intermediate acting insulin 10units/day. The oral glibenclamide tablet was powdered into packs of 0.5 mg each and was started at a dose of 0.05mg/kg/dose twice daily in increments of 0.1mg/kg/day up to 1mg/kg/day. Simultaneous reduction of insulin was carried under strict blood glucose monitoring. At the end of six days child was completely off insulin and oral glibenclamide was titrated subsequently to 0.5mg/kg/day at discharge. Blood glucose levels were between 120mg/dl to 150mg/dl during self monitoring at home after discharge. Child did not have any side effects during the transfer process and is off insulin during follow up.

Discussion

Mutations in KCNJ11, ABCC8, GCK, INS and PDX1 have been reported in neonatal diabetes. Mutations of the Kir 6.2 has been found to be he common mutation described in permanent neonatal diabetes mellitus. (5) The prevalence of KCNJ11 mutations ranges between 33-50% of neonatal diabetes. (4,5) The pancreatic cell membrane has potassium (K+) sensitive ATP channel which has two subunits, one is SUR (sulphonylurea receptor), the other is Kir 6.2 (inward rectifying K+ channel). Sulphonylureas trigger the insulin release by reacting with SUR receptor to close K+ ATP channel. This leads to increased intracellular potassium leading to depolarization and opening of the calcium channel. Increased intracellular calcium mediates exocytosis and release of insulin. In mutations of the Kir 6.2 leading to insulin deficiency, oral sulphonylurea is used to facilitate this release of insulin. This is the pharmacogenetics in switching over diabetic neonates from insulin therapy to oral sulphonylurea. Transfer to sulphonylurea therapy is successful for most patients with KCNJ11 mutations resulting in improved glycemic control. (2) The therapy with sulphonylureas have been found to be safe in the short term based on the available literature. (2) The commonly reported side effect with oral sulphonylurea is the occurrence of transient diarrhea and this can be overcome by continued therapy. (6)

Oral glibenclamide has been the frequently used drug in Kir 6.2 mutations. Sulphonylureas have been found to be of use in neonatal diabetes irrespective of the age at transfer i.e. from 3 months of age to adult subjects. (7) It is recommended to do genetic studies for monogenic diabetes in all those with infantile onset diabetes mellitus as the results would change the treatment modality from painful multiple

daily injections to more convenient oral sulfonylurea therapy. (8)

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References

1. Jeha GS, Venkatesh MP, Edelen RC, Kienstra KA, Karaviti L, Fernandes CJ. Neonatal diabetes mellitus: patient reports and review of current knowledge and clinical practice. J Pediatr Endocrinol Metab. 2005; 18: 1095-1102
2. Pearson ER, Flechtner I, Njlstad PR, Malecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006; 355: 467-477
3. Yorifuji T, Nagashima K, Kurokawa K, Kawai M, Oishi M, Akazawa Y, et al. The C42R mutation in the Kir6.2 (KCNJ11) gene as a cause of transient neonatal diabetes, childhood diabetes, or later-onset, apparently type 2 diabetes mellitus. J Clin Endocrinol Metab. 2005; 90: 3174-3178
4. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med. 2004; 350: 1838-1849
5. 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: 2713-2718
6. Codner E, Flanagan S, Ellard S, Garcia H, Hattersley AT. High-dose glibenclamide can replace insulin therapy despite transitory diarrhea in early-onset diabetes caused by a novel R201L Kir6.2 mutation. Diabetes Care. 2005; 28: 758-759.
7. Malecki MT, Skupien J, Klupa T, Wanic K, Mlynarski W, Gach A, et al. Transfer to sulphonylurea therapy in adult subjects with permanent neonatal diabetes due to KCNJ11-activating [corrected] mutations: evidence for improvement in insulin sensitivity. Diabetes Care. 2007; 30: 147-149
8. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pediatr Diabetes. 2010; 11: 203-207

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