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Case Report

Transient neonatal diabetes mellitus due to de novo mutation in KCNJ11 gene

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ABSTRACT

Neonatal diabetes mellitus (NDM) is a rare monogenic diabetes that usually presents in first 6 months of life. Activating mutations in KCNJ11 gene encoding Kir6.2 subunit of ATP-sensitive potassium (KATP) channel cause either transient NDM (TNDM) or permanent NDM (PNDM). A month-old male presenting with diabetic ketoacidosis was managed initially with intravenous (IV) fluids and IV insulin administration and subsequently started on subcutaneous insulin therapy on resolution of ketoacidosis. C-peptide level at diagnosis was 0.51 ng/ml and sanger sequencing analysis of the ABCC8, KCNJ11, INS and EIF2AK3 genes identified a heterozygous missense mutation p.R50Q in KCNJ11 gene. Successful transition to oral sulfonylurea therapy was made with maintenance of euglycemia and remission of NDM was witnessed at 5 months of age. A diagnosis of TNDM due to mutation in Kir6.2 subunit of K-ATP channel was made, supervised discontinuation of sulfonylurea therapy performed and the 50 percent risk of relapse of DM during adolescence or adulthood was explained to the family.

Keywords: NDM, TNDM, KCNJ11, Monogenic diabetes

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a rare monogenic diabetes that usually presents in first 6 months of life and occasionally between 6 months to 1 year of age.[1] The underlying pathology may be a malformation of the pancreas with altered development of insulin-secreting cells or abnormal function of the existing pancreatic β cell. The most frequent genetic lesions leading to neonatal diabetes mellitus with abnormal β cell function are abnormalities of the 6q24 locus and mutations of the ABCC8 or KCNJ11 genes coding for the potassium channel in the pancreatic β cell. Activating mutations in KCNJ11 gene encoding Kir6.2 subunit of ATP-sensitive potassium (KATP) channel cause either transient NDM (TNDM) or permanent NDM (PNDM). About 2 out of 5 infants with NDM are sulphonylurea responsive. We present a case report of one such infant who presented with NDM requiring insulin in the initial period followed by transition to suphonylurea and remission at 5 months of age.

CASE REPORT

A month-old male with birth weight 2.2 kg (< -2 SD on WHO growth charts) was admitted with hyperglycaemia (blood glucose 684 mg/dl) and severe ketoacidosis (pH: 6.94, HCO_3: 5 mmol/l) and was managed initially with intravenous (IV) fluids and IV insulin administration. The c-peptide at presentation was 0.51 ng/ml.

A diagnosis of NDM was considered and with resolution of ketoacidosis, subcutaneous insulin therapy was begun in once daily dose of 0.2 u/kg/day of long-acting insulin glargine and insulin lispro in a starting dose of 0.1-0.15 u/kg/dose 3–4 times per day administered before a feed, if

prefeed blood glucose was above 200 mg/dl. All prefeed blood glucose values were checked initially, though insulin was needed usually with every alternate feed (3–4 times per day). A dose of upto 0.5 unit of insulin could be administered without dilution. Smaller doses were administered using dilution of U-100 insulin (100 units of insulin per 1 ml) to up to one-tenth of the original concentration as required with normal saline. Feeding specific amounts of expressed breast milk each time was followed with total volume kept initially at 150 ml/kg/day and subsequently adjusted ad libitum. Initial total daily insulin requirements varied from 0.84 U/kg to 1.1 U/kg/day. Sanger sequencing analysis of ABCC8, KCNJ11, INS and EIF2AK3 genes identified a heterozygous missense mutation p.R50Q in KCNJ11 gene coding for the Kir 6.2 subunit of the K-ATP channel. The mutation had been previously reported (Flanagan et al) in an infant with TNDM. Both parents tested negative for the mutation. Tablet Glibenclamide was initiated in a dose of 0.2 mg/kg/day and administered in the pulverised form in 3 divided doses. The dose of Glibenclamide was increased in measures of 0.2 mg/kg/day every alternate day with concomitant reduction in the dose of insulin being administered. Insulin administration could be discontinued with maintenance of euglycemia at a dose of 0.6 mg/kg/day of tablet Glibenclamide. Periodic monitoring of capillary blood glucose at least 4 times a day was continued and the option of use of continuous glucose monitoring systems albeit with likelihood of exaggerated mean absolute relative difference (MARD) was offered. The infant was followed up in the outpatient initially weekly for the 1st month after discharge and every fortnight subsequently. The dose of Glibenclamide was revised for the existing body weight during each clinical visit. By 4 months of age, the infant seemed to have outgrown the need for revision of the dose of sulfonylurea with the value of c-peptide and concomitant glycosylated haemoglobin now being 2.16 ng/ml and 6.4 respectively. At 5 months of age, euglycemia was maintained with subthreshold doses of sulfonylurea, suggesting the likelihood of remission of DM as anticipated for the genotype. Supervised discontinuation of the sulfonylurea therapy was performed and the family was apprised of a 50% risk of relapse of the DM during adolescence or adulthood with likely therapeutic amenability of the condition to oral sulfonylurea therapy then. On follow up at 7 months, infant was euglycemic (HbA1c 5.4%) without any treatment. Anthropometric and neuro-developmental assessments seemed within permissible thresholds with the weight, length and occipito-frontal circumference between the 25th and 50th centile on the WHO growth chart.

DISCUSSION

NDM is a rare type of monogenic diabetes which usually presents before age of six months though some may present up to 12 months of life. Reported incidence of NDM is variable and is lower in Western countries [Italy: 1 in 90.000 live births, UK: 1 in 400.000] and higher in Eastern countries [1 in 21.000 in Saudi Arabia].[1-3] Clinically, NDM can be classified into transient NDM (TNDM) and permanent NDM (PNDM). TNDM accounts for about half of NDM and hyperglycaemia resolves in infancy (usually by 13–18 weeks of age) though it may recur in adolescence or adulthood. Overexpression of genes on 6q24 locus is the commonest cause (~70 %) of TNDM.[4] The second most common cause of TNDM is mutations in two genes encoding the subunits of the voltage-dependent potassium channels.[6] KCNJ11 encodes for inner subunit (Kir6.2) of KATP channel and ABCC8 encodes for outer subunit (SUR1). Infants with 6q24 abnormalities usually present earlier than those with KCNJ11/ABCC8 mutation.[1] Additionally, infants with 6q24-related NDM may have macroglossia or umbilical hernia, renal and urinary malformations, cardiac malformations, non-autoimmune anaemia, hypothyroid-ism with gland in situ and neurologic disorders. About 50% of infants with PNDM have KATP channel mutations.[4]

More than 30 activating KCNJ11 mutations have been associated with NDM so far.[7] Majority of them reduce KATP channel's sensitivity to ATP inhibition resulting in membrane hyperpolarization and impaired insulin secretion. Mutations within ATP-binding site are known to be associated with milder phenotypes, while those located in areas responsible for channel opening and closure, cause a more severe phenotype. The height of membrane hyperpolarization caused by each mutation elucidates spectrum of phenotypic variation ranging from TNDM to PNDM with neurological complications (developmental delay, epilepsy and neonatal diabetes syndrome).[8,9]

Managing infants with NDM poses challenges arising from, minuscule insulin dose requirements, high risk of hypoglycaemia, paucity of subcutaneous fat for insulin administration and coordination of insulin therapy with frequent and ungovernable feeding schedule of early infancy. Subcutaneous insulin therapy can be delivered via multiple daily injections (MDI) or as continuous subcutaneous insulin infusion (CSII). Initial doses should be conservative to decrease risk of hypoglycaemia. Subcutaneous insulin should be administered when blood glucose values are above 200–250 mg/dl. CSII has been recommended as treatment of choice in initial management of infants with NDM.[10,11] CSII via insulin pump offers advantage of ability to deliver smaller doses of insulin relative to MDI.[12] Sulfonylureas have inactivating effects on KATP channel and after identification of mutations in KCNJ11 or ABCC8 genes, patients can be successfully transferred from subcutaneous insulin to oral sulfonylurea therapy with most of them responding with improved glycaemic control and lesser hypoglycaemic events.[13-15]

Due to the dearth of any identified predictors of relapse as well as high relapse rate in TNDM, HbA1c should be performed atleast once every 2 years throughout childhood and oral glucose tolerance test in addition to HbA1c annually throughout adolescence. A close surveillance

would have to be maintained on education on neurodevelopmental milestones among all TNDM patients with or without diabetes.[16]

CONCLUSION

We report an infant with TNDM due to heterozygous mutation in KCNJII gene. NDM remitted at 5 months of age with an uneventful course. Studies describing genotype-phenotype correlation of NDM mutations can help clinicians stratify and appropriately manage these patients.

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