CASE REPORT

PDX1 Gene Mutation with Permanent Neonatal Diabetes Mellitus with Annular Pancreas, Duodenal Atresia, Hypoplastic Gall Bladder and Exocrine Pancreatic Insufficiency

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Background: Neonatal diabetes mellitus is a rare condition. **Case characteristics:** A small for gestational age male, presented with neonatal onset diabetes mellitus, duodenal atresia, annular pancreas and gall bladder hypoplasia. **Observation**: A novel homozygous mutation p.K163R (c.488A>G) in the *PDX1* gene was found. Parents were heterozygous for the same. **Message:** This case highlights the importance of establishing the genetic diagnosis in all cases of neonatal diabetes mellitus.

Keywords: *Genetics, Neonatal diabetes, PDX1 mutation.*

Neonatal diabetes mellitus (NDM) has an estimated incidence of 1:300,000 to 1:400,000 live births [1]. Mutations involving the *KCNJ11*, *ABCC8* and *INS* genes accounts for nearly 70% of monogenic causes of permanent neonatal diabetes mellitus [2]. Mutations in the *PDX1* gene is a rare cause of NDM associated with pancreatic agenesis [3]. The authors wish to report a case of permanent NDM due to homozygous novel mutations in the *PDX1* gene and a phenotype.

Case Report

A two-day-old, first by birth order, term, small for gestational age (1.2 kg) male infant born to non-consanguineous parents presented with abdominal distension and recurrent non-bilious vomiting. Antenatally, he was diagnosed to have polyhydramnios and severe intrauterine growth retardation. Imaging studies suggested duodenal atresia with a non-visualized gall bladder. Intra-operatively, duodenal atresia with an annular pancreas, thin intestinal loops and a hypoplastic gall bladder were observed. Post-operatively the infant had persistent hyperglycemia (>200 mg/dL) requiring insulin administration. Concomitant insulin infusion was continued during total parenteral nutrition. In the presence of undetectable levels of plasma C-peptide, a diagnosis of NDM was made. On initiation of feeds, transition to subcutaneous insulin administration with a combination of once a day dose of glargine and intermittent doses of regular insulin was made.

In view of NDM, hypoplastic gall bladder, duodenal atresia and annular pancreas, a probable genetic etiology was suspected. Mother had diabetes mellitus since the age of 18 years and was on insulin therapy. Blood samples of the infant and parents were sent for analysis of genes associated with NDM. Coding regions and conserved splice sites of the *KCNJ11*, *ABCC8* and *INS* genes were analyzed initially followed by analysis of all the known genes, *EIF2AK3, FOXP3, GATA4, GATA6, GCK, GLIS3, HNF1B, IER3IP1, PDX1, PTF1A, NEUROD1, NEUROG3, RFX6, SLC2A2, SLC19A2, WFS1* and *ZFP57* by targeted next generation sequencing (Agilent custom capture V5/ Illumina Hiseq).

A novel homozygous missense mutation DNA description: c.488A>G and protein description: p.Lys163Arg (p.K163R) in the exon 2 of the *PDX1* gene was identified and subsequently confirmed by Sanger sequencing. This mutation affects a highly conserved residue in the homeobox domain. Both parents were found to be heterozygous for the same mutation.

Exocrine pancreatic function screening was planned at 4 months of age in view of the nature of genetic mutation and the presence of frequent, loose, oily, foul smelling stools. The tests revealed increased fecal fat excretion and low fecal chymotrypsin and elastase level. This necessitated pancreatic enzyme and fat-soluble vitamin supplements in addition to the daily multiple doses of subcutaneous insulin. He is currently 2 years old. His length and weight are just below the third centile but

trending parallel to it on serial monitoring, with near normal developmental milestones. He is currently on total daily dose of insulin of 1 IU/kg/day and exocrine pancreatic supplementation with an HbA1C of 8.9.

DISCUSSION

Based on the clinical course, two forms of NDM have been recognized: transient and permanent. Transient neonatal diabetes usually resolves with or by the first year of life with greater risk of developing diabetes later in life. Permanent neonatal diabetes mellitus is characterized by early onset of persistent hyperglycemia requiring lifelong treatment [4]. PNDM due to mutations in the *KCNJ11* and *ABCC8* genes are amenable to treatment with sulphonylureas, emphasizing the need for genetic testing in all cases of neonatal diabetes [1].

PDX1 (IPF-1) gene is located on chromosome 13q12.2. It encodes for pancreas/duodenum homeobox protein 1. The transcription factor insulin promoter factor (IPF-1) is a master regulator of pancreatic development and differentiation of β cells of islet. In mature β cells, *PDX1* regulates the expression of critical genes including insulin, glucokinase and glucose transporter [2,5].

Stoffers, *et al*. [6] reported a patient with pancreatic agenesis with single nucleotide deletion within codon 63 of the human *IPF1* (*PDX1*) gene (13q12.1). Schwitzgebel, *et al*. [7] reported two mutations affecting the *IPF* (*PDX1*) gene resulting in pancreatic agenesis. The single largest cohort of five patients with *PDX1* gene mutations was described by De Franco, *et al*. who found bi-allelic mutations in three patients with normal pancreas formation and without exocrine function involvement [3]. Nicolino, *et al*. [8] reported two patients with mutations resulting in E178G substitution in the *PDX1* homeodomain. Both patients had permanent neonatal diabetes with subclinical exocrine insufficiency. Our patient exhibited exocrine insufficiency on screening, justifying the screening of exocrine functions in all such patients.

None of the previously reported cases of *PDX1* gene mutations, mention of duodenal atresia, gall bladder hypoplasia and annular pancreas as an association which is seen in RFX6 mutation (Mitchell-Riley syndrome) [9,10]. Based on our single case experience, it is not possible to explain this association.

Permanent insulin therapy is the mainstay of treatment of patients with *PDX1* mutation. Our case highlights the importance of establishing the genetic diagnosis in all cases of NDM and screening for known co-morbidities. The genetic testing in this case highlights the permanent nature of diabetes mellitus, the insulin dependence, the autosomal mode of inheritance and the need for exocrine pancreatic function screening.

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