

CLINICAL AND GENETIC CHARACTERISTICS AND TREATMENT OF A PATIENT WITH PERMANENT NEONATAL DIABETES DUE TO PDX1 MUTATION: A CASE REPORT

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Introduction

Permanent neonatal diabetes mellitus (PNDM) is a rare form of diabetes defined as hyperglycemia occurring before the age of 6 months that does not resolve over time. The incidence of PNDM ranges from 1:300 000 to 1:400 000 (1). The genetic cause of PNDM has been identified in about 70% of the cases. The course and treatment of PNDM depend on the type of genetic defect. The main causes of PNDM are K_{ATP} channel abnormalities due to heterozygous mutations in KCNJ11 (~30%), ABCC8 (~19%) and insulin gene (~20%). Most patients with PNDM caused by KCNJ11 and ABCC8 mutation are treated with sulphonylurea medications. Patients with INS mutations are, in general, treated with insulin. Exceptionally rare are

Objective. Permanent neonatal diabetes mellitus (PNDM) is a rare form of diabetes. The treatment of PNDM is challenging as it depends predominantly on a genetic diagnosis. Patients with KCNJ11 and ABCC8 mutations are treated with sulphonylurea medications. Patients with INS and other rare mutations (PDX1, PTF11A, EIF2AK3, RFX, etc.) require insulin. **Case report.** We report an extremely rare case of a male newborn with intrauterine growth retardation, hyperglycemia, pancreatic hypoplasia, exogenous pancreas insufficiency and duodenal atresia. PNDM was suspected as the patient had undetectable serum levels of insulin and C-peptide. A homozygous mutation in the PDX1 gene was detected when the boy was 11 months old. The only treatment option for this patient was insulin replacement. **Conclusion.** An insulin pump was better than subcutaneous insulin analogues injections for controlling glycemia for the patient with a homozygous mutation in the PDX1 gene.

patients with PNDM caused by mutations in PDX1, PTF1A, HNF1B, EIF2AK3, RFX6 and GATA6 genes, associated with pancreatic agenesis and hypoplasia (2-7). Achieving acceptable glycaemia in such patients is demanding as they often require low dosages of insulin due to small body weight and sparse subcutaneous tissue (8-10). There are few studies reporting insulin treatment options for children with PNDM and pancreatic involvement. These options are continuous insulin infusion (CII), subcutaneous insulin injections (SII) and insulin pump (IP).

We report an extremely rare case of a male newborn with intrauterine growth retardation, hyperglycemia, pancreatic hypoplasia, exogenous pancreas insufficiency and duodenal atresia.

Case report

At our hospital, no ethical approval for reporting individual cases are needed. We obtained written informed consent from the parents for the inclusion of the patient's information for publication in a medical journal. N.P. was born from the mother's third pregnancy with birth weight of 1800 g (SDS - 3.67) and length of 43 cm (SDS - 3.2) at the 38th week of gestation by elective Caesarean section. The newborn was not dysmorphic. On day 1 of life, he was admitted to the neonatal intensive care unit because of clinical signs of dehydration, hyperglycemia (29.9 mmol/L), and gastrointestinal obstruction and immediately underwent surgery. Gastrojejunostomy and jejunojejunostomy (Braun anastomosis) were performed because of the detected proximal duodenal atresia. The gall bladder was seen during this operation. Hyperglycemia continued after the surgery but no ketoacidosis developed (pH 7.44, HCO₃ 17.7, BE -6.5 mmol/L). Serum insulin (<0.2 µU/ml) and C-peptide (<0.003 nmol/L) levels were extremely low in the face of persistent hyperglycemia without ketonemia and glycosuria. Islet cell autoantibodies, insulin autoantibodies and glutamic acid decarboxylase autoantibodies were negative. Intravenous insulin aspart infusion was started at a dose of 0.0072 IU/kg/h and increased up to 0.4 IU/kg/h (5.64 U/kg/day) to achieve normoglycemia. In addition to PNDM, clinical signs of exocrine pancreatic insufficiency were observed from the first days of life. Steatorrhea and weight loss with low levels of plasma pancreatic enzymes (pancreatic lipase < 9 IU/L, amylase <6 IU/L) were noted. The patient underwent abdominal computed tomography scans and MRI where both showed no body and tail of the pancreas, but only the head of the pancreas as a tiny bud. The diagnosis of pancreatic hypoplasia was made. The patient did not progressed satisfactorily in body weight despite adequate

caloric intake and treatment with insulin, pancreatic enzymes and fat-soluble vitamins in the first three months. In addition, a mild developmental delay was observed from the age of two months. At the chronological age of 3 months and 21 days with a length of 56 cm (SDS - 2.9) and weight of 3700 g (BMI-SDS -5.1), we stopped intravenous insulin infusion (0.045 IU/kg/h or 0.29 U/kg/day) and started SII of insulin analogues into the buttocks and thighs. Insulin detemir was administered at the dose of 1 U in the morning at 08 h and 1 U at 20 h. Insulin aspart was administered before each meal and always in relation to glycemic levels at the dose of 0.05 IU/kg. Blood glucose monitoring was performed at least 10 times per day using test strips. The patient had episodes of mild hypoglycemia regularly. We were afraid of severe hypoglycemia so we ordered an IP via our hospital services. The IP (Paradigm Veo™ Minimed) was applied at the age of 6 months and 17 days when the patient's weight was 4950 g (SDS -4.6), length 62 cm (SDS -2.54) and HbA1c 7.6%. The basal rate was 0.05 IU/h. We had problems with soft cannula length (minimal length on the market of 6 mm). The cannula was too long for the patient's thin abdominal subcutaneous tissue so we placed it in the buttocks. We replaced the insulin infusion set every two days. The infant's feeding pattern was based on eight formula bottles per day, at three hour intervals. Blood glucose monitoring was done at least eight times a day using test strips. No premeal boluses were required. The patient gradually began to gain weight and made rapid neurodevelopmental progress. Cystic fibrosis mutation analysis was negative for 32 mutations. Metabolic, endocrine, ophthalmologic and cardiology evaluations revealed no pathological disorders.

The infant was discharged from the hospital at the age of eight months. The parents were educated to manage the IP. However,

an additional problem for this family is that they live on an island which is not easily connected to the mainland and is long distance from to the closest medical service. Therefore, daily phone contact is needed and outpatient check-ups are scheduled every two months. At the last check-up at the age of 1.31 years, the auxological and neuropsychological development were appropriate. His weight was 7.5 kg (BMI-SDS -3.54) and height 74 cm (SDS -2.10). The levels of HbA1c were taken at each check-up and were stable between 7.5% and 7.6%.

Genetic analysis was undertaken at the molecular genetics laboratory of the University of Exeter Medical School. Our patient is homozygous for a novel PDX1 missense mutation, p.E160K. This mutation affects a highly conserved residue within the home-box domain of PDX1 and current evidence suggests that the mutation is pathogenic. Both parents are heterozygous for the PDX1 mutation and predisposed to develop PDX1-MODY type 4 diabetes. Furthermore, the father had hyperglycemia at zero and 90-th' minute during an oral glucose tolerance test (OGTT) and gliclazide has been suggested at a dose of 30 mg per day. The mother was hyperglycemic in the zero minute in the OGTT test and we suggested weight loss and increasing physical activity.

Discussion

Most patients with PNDM caused by KCNJ11 and ABCC8 mutation will respond to treatment with sulphonylurea medications. Patients with INS mutations are, in general, treated with insulin. Exceptionally rare are patients with PNDM caused by mutations in PDX1, PTF1A, HNF1B, EIF2AK3, RFX6 and GATA6 genes (2-7). For majority of these patients, insulin therapy is mandatory (8-9). Few data are available on the best form of insulin delivery for patients

with PNDM. Wide consent exists that continuous intravenous administration of (short acting or regular) insulin is the therapy of choice for newly diagnosed paediatric patients with persisting hyperglycaemia (10). Reaching satisfactory glycaemia is dependent not only on insulin therapy but also on the correct management of rehydration and metabolic imbalance, as well as the patient's general health condition and comorbidities. As most patients with PNDM are small for gestational age, severely dehydrated and with a sparse amount of subcutaneous tissue, their management requires special considerations. The patients need a very small insulin dosage that is carefully titrated (11). On one hand, the needs are related to patient's weight, insulin absorption capabilities, the frequency and type of feeding and activity status. On the other hand, the insulin needs are related to glycemia levels. Hyperglycemia has to be under control to reduce the risk of late complications in the long run as well as minimising the high risk of hypoglycemia and neurological consequences. It is accepted that the intravenous insulin infusion should be discontinued when the child is clinically stable and ketoacidosis resolved. The best time to switch to SII of insulin analogues or, if available, an IP is not clearly defined. We switched to SII after 3.5 months as IP are not widely used in Croatia for economic reasons. Blood glucose levels were checked at least 10 times per day. Mild hypoglycaemia was detected on a daily base with no severe hypoglycaemia. We noticed that the patient needed higher requirements of insulin (5.64 U/kg/day) to maintain normoglycemia. It is reported that patients with PNDM caused by homozygous inactivating GCJK mutation needed higher dosage of insulin compared to patients with PNDM and other mutations (3). In addition, we struggled with adjustments of the insulin dosages using SII. These adjustments were easily achieved when we applied the IP. This is in accordance with Tubiana-Rufi and co-

authors (12) highlighting that an IP is safer, more physiological and accurate, and easier to manage than SII. In addition, Bharucha et al. (13) described two infants who reached euglycemic goals with an IP but not with SII. The same conclusions were observed by Wintergerst et al. (14) and Beardsall et al. (9) reporting exceptional satisfaction with an IP in the case of neonatal diabetes mellitus and severe growth retardation, necrotizing enterocolitis, and cholestatic jaundice. Ortolani et al. (15) support the use of IP alone as well as sensor-augmented IP as a feasible and safe therapeutic option for neonates and infants with diabetes.

Conclusions

We report an extremely rare case of a homozygous mutation in the PDX1 gene. The IP was better than SII at controlling glycemia in this patient who required a small insulin dosage.

Authors' contributions: IUS and VS contributed to the conception and design of this study as well as drafted manuscript and critically reviewed the manuscript and supervised the whole study process; TK and RS critically reviewed the manuscript.

Conflict of interest: The authors declare that they have no conflict of interest.

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