

Neonatal Diabetes Mellitus: Genetic Defect and Management Issues

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Abstract

Neonatal Diabetes Mellitus is a rare disorder characterized by significant hyperglycemia needing exogenous insulin in first 6-8 weeks of life. Two types, Permanent and Transient, have been described in literature based upon the duration of insulin dependency. Recently, various genetic defects like chromosome 6 uniparental disomy and KJN11 gene mutations have been associated with NDM.

INTRODUCTION

Neonatal Diabetes Mellitus is a rare disorder in infants occurring in 1:300,000-400,000 live births, characterized by significant hyperglycemia needing exogenous insulin therapy combined with low level of insulin in first 6-8 weeks of life, and if not diagnosed timely it can be life threatening. Two main types, Permanent Neonatal Diabetes Mellitus (PNDM) and Transient Neonatal Diabetes Mellitus (TNDM), have been described in literature based mainly on clinical course and duration of insulin dependency. We report one such rare case.

CASE REPORT

An 8 weeks old female infant presented to our hospital with frequent urination, frequent demand for feeding and particulate deposits of urine since birth. There was no history of fast breathing, fever, rashes, loose stool, vomiting, drowsiness or convulsions. She was the first (twin A) of the twins born to a couple with 2nd degree consanguineous marriage. She was delivered by lower section caesarean section to a 28-year-old 3rd gravida mother with no live issues. She was full term, breech, and small for gestational age (birth weight 1.5 kg). She was kept in a level one nursery for 9 days because of low birth weight along with the twin B (also a female). Twin B was admitted to a regional hospital at 6 wks of age because of a brief episode of fever, vomiting and lethargy. However, she expired in the hospital with a provisional diagnosis of late onset sepsis. There was also a family history of other two sibling's deaths at the age of 18 months, and 7 wks respectively. Both had a history of failure to thrive, but none of them was diagnosed

with Diabetes Mellitus. There was no history of diabetes mellitus or autoimmune disorders in the family. On initial examination, the child weight was 2.2 Kg, length 45 cms and head circumference 35 cms. There were no signs dehydration and vitals were stable. The initial investigations revealed, Hb 10.8 g/dl, TLC 6240/cmm, Urea 22, Creatinine 0.5 g/dl, Random blood sugar > 600 mg %, Na 145 mEq/L and K 4.5 mEq/l. Urinary sugar was >2 gm% and urine for ketones was negative. On ABG, there was mild compensated metabolic acidosis (pH 7.34, pO₂ 92, pCO₂ 27, HCO₃ 18.6, BE -8). Considering all the history and investigations, we made a presumptive diagnosis of Neonatal Diabetes Mellitus. She was started initially a 4 hourly regular insulin regime. However, the patient had wide fluctuation in her blood glucose levels on this regime and was shifted on 12 hourly NPH after 4 days. Her blood glucose levels finally stabilized on 2.6 U/Kg/day of insulin. On further investigation a sepsis screen was negative, skeletal survey was normal, stool for fat globules was negative and TORCH titers were negative. The patient serum insulin level was 0.50 µIU/ml (normal range 2.0-25 µIU/ml), C Peptide level was 0.025 ng/ml (0.7-1.9 ng/ml) and was negative for anti-islet antibodies. On USG abdomen, pancreas was visible. For genetic analysis, we sent blood samples of both parents and the infant at Robert Debre Hospital, Department of Genetics, Paris, France. A detail genetic analysis was done; however, it was negative for uniparental chromosome 6 disomy (include PCR studies for microsatellites makers covering region ch 6q23-25 and methylation study) and common KCNJ11 mutations. At present, the child is on twice daily NPH regimen and her blood sugar is in the range

of 150–250 mg %.

DISCUSSION

Neonatal Diabetes is a rare disorder comprises of two types PNDM and TNDM. TDMN is more frequent and consists of about 50–65 % cases of NDM. It is a developmental disorder of insulin production that resolves spontaneously in majority of infants within a year but a few have recurrence of type 1 diabetes in late childhood or adulthood as shown by two cohort studies^{1,2}. Most of the neonates are intrauterine growth retardation (IUGR) at birth. They usually present with hyperglycemia, failure to thrive and, in some cases, dehydration leading to ketoacidosis due to inadequate insulin production, requiring exogenous insulin therapy. The exact pathogenesis is still unknown, but absence of anti-islet antibodies (as in our patient) and HLA class II haplotypes conferring susceptibility to type 1 diabetes in most of the reported cases suggests that the condition might not be associated with autoimmune phenomenon³. Majority of TNMD cases are sporadic, most recently, association between paternal chromosome 6 isodisomy and TNDM has been found in about 25–30 % cases and on further genetic evaluation imprinting defects have been implicated involving 6q 23–25 region^{4,5}. We had evaluated the parents of our patient for ch 6 isodisomy, but the results were negative.

Permanent neonatal diabetes mellitus is less common than the transient form. By definition, diabetes develops in the neonatal period and does not go into remission. There are no clinical features or lab parameters that can predict whether a neonate with diabetes will eventually have permanent or transient disease, although cases with the permanent form do not always have IUGR as is universally seen in the transient 6q phenotype and exocrine pancreatic dysfunction has been associated more with PNDM than TNDM. Recently, mutations in KCNJ11 gene, which encodes the Kir6.2 subunit, and mutations in ABCC8, which encodes the SUR1 subunit, of the pancreatic ATP-sensitive potassium channels (K_{ATP}) have been implicated in the genesis of PNDM^{6,7,8}. There is a spectrum of phenotypes associated with activating mutations in Kir6.2 (include R201H, R201C, V59M, G53S, G53R etc) and the most common among these mutations is R201H⁹. In addition to neonatal diabetes, affected neonates can have neurological features like developmental delay and epilepsy, known as Developmental delay epilepsy and neonatal diabetes (DEND) syndrome. Depending upon the severity of neurological phenotype, DEND syndrome can be further classified as Full, Intermediate and Mild type.

Various congenital syndromes are associated with PNDM like Pancreas agenesis, IPEX syndrome, Wolcott-Rallison and Mitochondrial disorders, and should be considered when evaluating a neonate or young infant with PNDM^{10,11,12}. In our case, the genetic analysis for common KCNJ11 mutations was negative.

Insulin therapy, high calorie diet, periodic follow-up, and parent's education and training are the main stay of the management; various regimens, from continuous infusion, periodic regular insulin to once daily isophane insulin, have been tried^{13,14}. However, all pediatricians face numerous difficulties in managing young infants with NDM like route of administration, type of insulin, frequency, coordinated feeding, long term complication and psychosocial issues. We too encountered few difficulties in management of our case. We started with regular insulin, but it was difficult to synchronize feeding with insulin administration, especially in night time, and therefore sugar levels were all over. In our patient, we finally managed to stabilize blood sugar levels with NPH insulin on 2/3rd morning and 1/3rd evening doses and alarm system for mother to provide regular and timely spaced feeding, especially during night hours. Though, insulin administration by infusion pump can be an alternate method for insulin administration as suggested by various other teams, but the major disadvantage is that it needs more stringent supervision under specialists care and home management might be difficult for parents with poor socioeconomic and low education level¹⁵. Various oral hypoglycemic agents, like Sulphonylurea and Glibenclamide, have been considered as an alternative to insulin injections in PNDM, especially in those with Kir 6.2 mutations, because these agents can still able to close ATP insensitive K_{ATP} channels^{16,17}. However, the experience with oral hypoglycemia still very limited and further studies warranted in pediatric population to assess their role in the management of NDM. The Parent's education and training needs special attention before discharging the patient because chances of an episode of severe hypoglycemia leading to permanent long term neuro-developmental sequels are much higher in young infants due to their lack of ability to communicate with the caregiver.

To conclude, NDM is a rare condition, but it should be considered in a sick infant with unexplained hyperglycemia because majority of these cases are of transient type, which can be managed by insulin therapy or oral hypoglycemic agents.

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