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Case Report

Transient diabetes mellitus presenting with diabetic ketoacidosis: a case report

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ABSTRACT

Neonatal diabetes mellitus (NDM) represents a monogenic form of diabetes mellitus, manifesting with hyperglycemia during the neonatal period. It is relatively a rare condition, affecting an estimated incidence of 1 in every 90,000 live births. Depending on the duration of condition, NDM can be categorized as temporary NDM (TNDM) and permanent NDM (PNDM). We present a case of a 43-day-old infant who presented with diabetic ketoacidosis. Upon evaluation, it was observed that the infant had TNDM, specifically caused by a mutation in the KCNJ11 gene. The infant was initially managed with insulin therapy but was later transitioned to oral sulfonylureas (SU). Initial research suggests that administering SU treatment at an early stage, as opposed to insulin, could enhance neurodevelopmental outcomes in patients who respond well to SU.

Keywords: Neonatal diabetes, Transient, Sulfonylurea, Hyperglycaemia

INTRODUCTION

Neonatal diabetes mellitus (NDM) or congenital diabetes mellitus is a rare genetic disorder predominantly observed in the children before 6 months of age and seldom between 6 months and 1 year, characterized by a minimal incidence of 1 in 90,000 live births, with variations observed across various ethnic groups.[1] Molecular genetics research has demonstrated that the majority of cases of neonatal diabetes are primarily caused by underlying monogenic defects, which originate within a single gene.[2] Mutations affecting proteins that are essential to the healthy operation of pancreatic beta cells are the cause of NDM.[3] The disease is classified into transient and permanent subtypes, and its course exhibits variations based on the mutated genes and proteins.[4] To keep blood glucose levels under control, treatment is needed for the rest of one's life in about half of the cases (PNDM and PNDM). The diabetic state ends in a few weeks or months for the remaining patients (TNDM and TNDM). Diabetes can recur in certain TND patients at any time in their lives, particularly in adolescence.[5]

The most common genetic causes of NDA, characterized by abnormal β cell function, include mutations in the 6q24 locus and abnormalities in the ABCC8 or KCNJ11 genes, which code for the pancreatic β potassium [K]-ATP channel. Variations in these genes can be addressed through the administration of oral SUs, representing approximately 40% of treatment modalities. Initial research suggests that initiation of SU therapy prior to insulin administration may enhance neurodevelopmental outcomes in patients responsive to SU treatment.[6] Early identification of monogenic diabetes is crucial, as it can forecast the progression of the disease, elucidate additional clinical manifestations, and direct suitable management strategies for affected individuals. Here we report a rare case of transient NDM.

CASE REPORT

A 43-day-old boy, who was previously in good health, came to the hospital with vomiting that lasted for 2 days, along with lethargy and a lack of interest in eating for the past 24 hours and fast breathing 2 hours prior to the admission. Infant was first born baby, to third degree consanguineous parents. Mother had uncomplicated antenatal history. The infant was delivered at 37 weeks of pregnancy through a caesarean section. Pregnancy was uncomplicated with normal antenatal scans. Baby cried immediately at birth but soon developed respiratory distress for which baby was admitted in neonatal intensive care unit (NICU) for transient tachypnoea of the newborn (TTNB). The baby did not require any resuscitation. His birth weight was 2125 gm (3rd centile, small for gestational age (GA)), length 44 cm, head circumference 32 cm (18th centile) with Ponderal index of 2.4; with features of intra uterine growth restriction. Baby was exclusively breast fed, and remained in hospital for 72 hours during which blood glucose levels were normal, but had asymptomatic hypocalcaemia, which was treated. He was discharged home on direct breast feeding (DBF).

Upon admission in our hospital, the baby was afebrile with temperature 98.6F. He was in compensated shock with tachycardia, cold clammy peripheries, prolonged capillary refill time, poor peripheral pulses and normal central pulses. Systemic examination revealed no abnormality. The infant was thriving well until this episode: anthropometric parameters at admission were-weight 3.54 kg (weight gain of 32 g/day), length 49 cm (gain of 5 cm in 43 days). Additionally, the head circumference was measured at 35 cm, indicating an increase of 3 cm since birth. There was no evidence of growth restriction or any external malformations. Airway is maintainable with respiratory rate of 70/minute, no retractions and respiratory distress scoring of 3. There is no dysmorphism or syndromic features. Baby had bilateral air entry with no added sounds. Heart sounds were normal. Abdomen is soft with no organomegaly. Neurologically baby was responding to pain. Tone was normal. There were no cranial nerve palsies.

Initial blood gas showed severe metabolic acidosis with high anion gap (pH=6.89, pCO_2 16.6 mm Hg, base deficit of (-20.7) and bicarbonate of 3 meq/l), plasma glucose was 524 mg/dl. Serum electrolytes showed hypernatremia (corrected sodium 147.7 meq/l), hyperkalaemia (6.1 meq/l) and normal chloride levels. Blood urea and serum creatinine were elevated (45 mg/dl and 1.2 mg/dl respectively). Urine ketones were found to be 4+.

Blood picture showed microcytic hypochromic anaemia with thrombocytosis (haemoglobin 6 gm/dl, platelets 6 lakh/cumm and leukocyte count 12,300/cumm). Septic work up including CRP, urine and blood culture were negative. Chest x-ray, ultrasound abdomen and 2D echo were normal.

Following fluid resuscitation, infant was started on insulin infusion as per diabetic ketoacidosis protocol (0.05 units/kg/hr) and blood glucose was monitored serially. Blood glucose reduced at approximate rate of 50 mg/hr for initial 6 hours and then gradually stabilized over next 48 hours. Acidosis resolved 96 hours after insulin infusion which was then changed to subcutaneous insulin. He was started on feeds with expressed breast milk and increased as per tolerance. Further evaluation showed elevated glycosylated haemoglobin of 10.9%, and serum C-peptide was low (0.26 ng/ml). The results of the chest x-ray, ultrasound abdomen, and 2D echocardiogram were all normal, devoid of any abnormalities.

Upon reviewing the patient's clinical presentation, it was deemed necessary to consider a diagnosis of NDM, subsequently leading to further evaluation. Targeted gene sequencing revealed pathogenic variant, a heterozygous missense variation in exon 1 of the KCNJ11 gene (chr11:g.17408672C>G; Depth: 683x) that results in the amino acid substitution of Histidine for Aspartic acid at codon 323 (p.Asp323His; ENST00000339994.4) with a likely inheritance of autosomal dominant.

Post discharge, the baby was on long-acting insulin once a day and subsequently was started on oral Glibenclamide (Sulfonylurea) from 4th month of life at 0.25 mg/kg/day. After 2 weeks, Insulin was stopped and blood glucose was monitored. No hypoglycaemic episodes were noticed. At 5th month of life, he was weaned off Glibenclamide (Sulfonylurea) and currently he is maintaining normal blood sugar with no episodes of hypoglycaemia or hyperglycaemia. Presently, at 7 months age, the infant is thriving well, with weight 7.2 kg length of 67 cm and head circumference 42 cm.

DISCUSSION

NDM is a rare disease that presents as either the TNDM or PNDM form. With advances in molecular genetics, various genetic subtypes have been identified, and treatment varies with the type of disease. Molecular genetic diagnosis is recommended in all patients with NDM and is most likely due to a monogenic defect in 80% cases especially when detected before 6 months of age.[7] Term infants and premature infants born at greater than 32 week's gestational age (GA) are more likely to have a monogenic cause for their diabetes than are very premature infants born at less than 32 weeks of gestational age GA.[8]

The mainstay of the management of NDM in neonatal period is insulin, regardless of the etiology. Patients with NDM were previously believed to require lifelong insulin treatment. The identification of KATP channel mutations has revolutionized the treatment of NDM.[9] Another genetic treatment option is oral sulfonylurea, which is administered based on the diagnosis of KATP channel mutations.[10]

Sulfonylurea binds to the SUR1 subunits of the KATP channel and closes the channel in an ATP-independent manner, causing membrane depolarization and insulin secretion. In the same way, sulfonylurea causes insulin secretion in the mutated KATP channels by binding to the SUR subunits. Of the known genetic subtypes of NDM, only patients with activating KCNJ11 or ABCC8 gene mutations respond to treatment with a sulfonylurea.[11] Sulfonylurea can be started in a patient as soon as the genetic diagnosis is established, and a trial of sulfonylurea in NDM without a genetic diagnosis is not recommended.[12] Preliminary studies indicate that early SU treatment, in contrast to insulin, may improve neuro-developmental outcomes in SU-responsive patients.[13] Our patient was on long-acting insulin once daily during early days and subsequently was started on oral glibenclamide (Sulfonylurea) from 4th month of life given him an improvement.

Marked hyperglycaemia, normal C peptide values, and low birth weight (at or below the 3rd percentile) are common phenotypic features of most cases of PNDM.[14] Early genetic diagnosis is important for predicting clinical outcome. Indications for genetic testing are hyperglycaemia with blood sugar more than 1000 mg/dl, hyperglycaemia persisting for 2-3 weeks in neonatal life and infants presenting with diabetes before 1 year.[15] It is estimated that 70% of TNDM is the result of a loss of imprinting in the chromosome 6q24 region and the subsequent overexpression of both gene products.[16]

Onset of diabetes is usually before 6 months of age. They can present with DKA in 25-75% cases, as happened in our patient.[17] Mutations in KCNJ11 and ABCC8 (affecting the pancreatic beta-cell potassium [KATP channel) account for 50% of cases of NDM.[18] In our patient, we found mutation in KCNJ11 gene. They can lead to TNDM or PNDM. They may be associated with developmental delay, seizures (DEND syndrome) and other neurological features due to the presence of KATP channels in brain.[19]

CONCLUSION

For physicians as well as patient's family, the diagnosis of NDM in the neonatal stage is a very complex condition. Genetic testing is recommended to newborns within the first few days of life to facilitate the early identification and categorization of neonatal diabetes, particularly in infants with a familial history of this condition.

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