Monogenic Diabetes –A Case Series

Monogenic diabetes is uncommon, accounting for approximately 1-6% of pediatric diabetes patients [1]. They are rare forms of diabetes resulting from mutations in single gene as against type 1 and type 2 diabetes, which are polygenic. Neonatal diabetes (NDM) and maturity onset diabetes of young (MODY) are the two main forms of monogenic diabetes. NDM occurs in newborns and young infants, while MODY occurs in adolescence or early adulthood. It is important to distinguish monogenic diabetes from type 1 and type 2 diabetes.

For this case we reviewed 295 children diagnosed as diabetes as per ISPAD criteria [2] and admitted in a tertiary care center in Chennai between January, 2014 and December, 2018. Ethics clearance was obtained from institutional ethics committee. Out of these, monogenic diabetes was considered in 10 patients who were diagnosed with diabetes in first 6 months of life, two of those who were diagnosed between 6-12 months and were negative for auto-antibodies and three children diagnosed beyond 12 months who had a sibling with diabetes or clinical features consistent with known genetic syndromes [1]. The GAD-positivity among newly diagnosed children with type 1 diabetes in our center was found to be 79%. One of the patients in whom the diagnosis of monogenic diabetes was considered, died during the course of illness before genetic evaluation, and remaining 14 children underwent genetic analysis. Clinical data including age of presentation, gender, birth weight, associated clinical features and history of consanguinity were collected for all children. Three milliliters of whole blood in EDTA vial of the children and both parents was sent to Royal Devon and Exeter NHS Foundation Trust Laboratory, Exeter, UK for genetic analysis. The samples were first tested for most common causes of NDM (*ABCC8, KCNJ11* and *INS* genes) by Sanger sequencing. If a causative mutation was not identified in first test, the patient's sample was tested for mutation of all known NDM genes using targeted next generation sequencing assay [3]. Genetic diagnosis was confirmed in 11 (3.7%) children, whereas no genetic mutation was identified in three children subjected to genetic analysis. Out of 11 children, 5 were males. Seven children presented with diabetic ketoacidosis, while three children were noted to have developmental delay. Third degree consanguinity was noted in all three children with Thiamine Responsive Megaloblastic Anemia and the child with Wolcott Rallison syndrome. Three children with permanent NDM, the child with Wolfram syndrome, and the child with Rabson Mendenhall syndrome were born with low birth weight.

Genetic analysis confirmed permanent neonatal diabetes mellitus (PNDM) in five children. Two children had *ABCC8, 1 KCNJ11, 1 INS* and 1 *GCK* mutations. Three children were detected to have *SLC19A2* mutation characteristic of Thiamine responsive megaloblastic anemia (TRMA). One child had *WFS* mutation suggestive of Wolfram syndrome, one *EIF2AK3* mutation typical of Wolcott Rallison syndrome and one *INSR* mutation typical of Rabson Mendenhall syndrome. Children with *ABCC8* and *KCNJ11* were switched over to oral sulfonylurea as per standard protocol. All three children with TRMA were started on oral benfothiamine along with insulin, which resulted in better glycemic control and improvement of anemia. The child with Wolfram syndrome had buphthalmos and overlapping toes which are not described in literature. The child with Wolcott Rallison syndrome developed two episodes of acute liver failure from which she recovered. This child did not have any skeletal manifestations, which are considered essential component of the syndrome. The child diagnosed with Rabson Mendenhall syndrome had a poor glycemic control with high doses of insulin prior to genetic diagnosis, and was switched over to oral metformin after genetic diagnosis. The glycemic control continued to be poor in that child and eventually the child died. The remaining 10 children are on follow-up with good glycemic control. All of them except the child with Wolfram syndrome are thriving well.

This series describes children diabetes reporting to a tertiary care center catering exclusively to children less than 12 years of age. Hence, the spectrum described includes mainly neonatal diabetes and the genetic forms of diabetes presenting in early childhood. Prevalence of neonatal diabetes is 4% in our series as against 8% reported in a previous study done in the same center [4], and 7% reported from another center [5]. The number of children who presented with diabetic ketoacidosis and developmental delay was similar to that reported in previous studies [4].

Mutations in genes coding for K_{ATP} channels are common and the detection of these mutations has a therapeutic implication as these children can be successfully switched over from insulin to oral sulfonylurea therapy [6]. The child with Rabson Mendenhall syndrome was difficult to treat and had poor glycemic control as described in literature. Genetic diagnosis guided in switching over this child to oral metformin. Genetic diagnosis guides us to anticipate future complications and initiate swift and appropriate action, as in the child with Wolcott Rallison syndrome. Genetic counseling, and prenatal and postnatal testing were offered to mothers who conceived subsequently. Though molecular testing is expensive and not easily available, it is essential to establish a genetic diagnosis so that we can offer appropriate therapy, prognosticate and offer genetic counseling in future pregnancies.

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SRIDEVI A NAARAAYAN,* RAGHAVAN V DHAKSHAYANI, REMA CHANDRAMOHAN

*Diabetes clinic, Institute of Child Health and Hospital for Children, Egmore, Chennai,Tamil Nadu. *childdoctorsri@yahoo.co.in*

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Excessive Weight Loss in a Neonate - Novel Mutation Causing Primary Hypoaldosteronism

Excess weight loss in a term neonate is a worrying symptom. We report a full-term male neonate who presented with jaundice and was noted to have progressive weight loss. This prompted us to evaluate further, uncovering an underlying endocrine disorder.

A 9-day-old male baby, born at 39 weeks, presented to the outpatient department with jaundice. As serum bilirubin was at treatment threshold (17.7 mg/dL), the neonate was admitted for phototherapy. The neonate had excess weight loss (admission weight- 3.45 kg, birth weight- 3.82 kg, weight loss- 9.7%). With phototherapy, the jaundice subsided in next 36 hours, but the child continued to lose weight over next two days (3.37 kg by day 11). The baby was born to a 30-year-old third gravida mother, with one previous first trimester abortion and a healthy male child. Antenatal scans showed mild left hydronephrosis. Her blood sugars were deranged at 36 weeks and late onset polyhydramnios was noted at 38 weeks (amniotic fluid index-17.5). It was a vaginal birth with smooth perinatal transition. There were no evident physical anomalies/dysmorphism. Baby had jaundice on day 2 of life, for which phototherapy was given for 24 hours and discharged on day 4 of life. At discharge, the child weighed 3.52 kg, breast feeding was well established, and there was adequate urine output. At home, the mother had adequate lactation with signs of good attachment and milk output. Since the continued weight loss was worrisome, the child was evaluated with serum electrolytes, venous blood gas, urine specific gravity, urine culture and sepsis screen. Hyponatremia (124 mEq/L) and hyperkalemia (6.9 mEq/L) were uncovered. C-reactive protein, white blood cell count, blood gas and urine examination were normal. Urine culture revealed growth of *Escherichia coli*. Genitalia, skin pigmentation, blood pressure, urine output and blood sugar were normal. The possibilities considered were salt wasting congenital adrenal hyperplasia, adrenal hypoplasia/hemorrhage, and type 4 renal tubular acidosis.

The child was initiated on liberal fluids, sodium supplements and anti-hyperkalemic measures. However, serial investigations revealed persistence of hyponatremia, worsening of hyperkalemia, new onset normal anion gap metabolic acidosis, and natriuresis (fractional excretion of sodium- 5.8%), fitting into the picture of type IV renal tubular acidosis. On further evaluation, ultrasound of adrenals, expanded newborn screening, 17-hydroxy progesterone, testosterone, dehydroepiandrosterone and cortisol levels were normal, and an appropriate response was noted with ACTH stimulation test, ruling out the possibility of congenital adrenal hyperplasia (CAH) and other structural adrenal pathologies. Trans-tubular potassium gradient was low (0.5) and urinary pH was elevated (6.5) suggesting decreased aldosterone activity. Aldosterone level was low (4.05 ng/dL; normal: 5-90 ng/dL) and plasma renin activity was high (>120 ng/mL/h; normal range: 2-35 ng/mL/h), indicating a possibility of primary hypoaldosteronism. The child was continued on sodium and bicarbonate supplements, and fludrocortisone was initiated. Following this, the child started gaining weight, with normalization of electrolytes and was discharged on day 28 of life.

Whole exome sequencing revealed a novel heterozygous contiguous deletion of 3 kb involving exons 5-9 of *CYP11B2* (ENST00000323110.2) gene at chr8: g.(142913452_142914263)_(142917844_142910557), that results in corticosterone methyl oxidase type I (Type 1) and II (Type 2) deficiency, conclusive of aldosterone synthase deficiency (ASD) (primary hypoaldosteronism). 18-hydroxycorticosterone levels would have differentiated these subtypes, but they were unavailable. Parents were counseled regarding risk of recurrence and the need for antenatal diagnosis in future. At last follow-up, at 3½ months of age, child was on fludrocortisone and sodium supplements, with good weight gain (5.4 kg), and normal serum electrolytes (Na-131 mEq/L and K-5.1 mEq/L).

Excess weight loss with abnormal electrolytes in neonatal period heralds the presence of an underlying life-threatening disorder. Diagnostic approach primarily rests on ruling out congenital adrenal hyperplasia due to 21-hydroxylase deficiency; while X-linked adrenal hypoplasia congenita, ASD and aldosterone resistance (pseudohypoaldosteronism, PHA) are the other less common causes [1,2]. A normal 17-hydroxy progesterone rules out 21-hydroxylase deficiency and normal cortisol and response to ACTH stimulation rules out adrenal hypoplasia. Normoglycemia, stable hemodynamics, and abnormality in electrolytes, acid-base balance, and weight points