RABSON MENDENHALL SYNDROME WITH MEDULLARY NEPHROCALCINOSIS - A NOVEL MUTATION REPORTED

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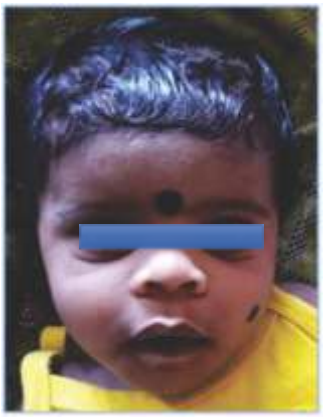
Abstract :

Background : Rabson Mendenhall syndrome is a syndrome of insulin resistance. **Case characteristics:** Clinical features and labs of our patient favoured insulin resistance, genetic analysis done showed a compound heterozygous mutation in the INSR gene which has not been reported earlier; **Outcome:** We report a new mutation causing disease and medullary nephrocalcinosis association which has been reported only once. **Message:** Biguanides are effective in reducing hyperglycemia in Rabson Mendenhall syndrome.

Introduction : Inherited insulin resistance syndromes are Donohue syndrome, Rabson Mendenhall syndrome and Type A insulin resistance . They have defects in carbohydrate metabolism and present with hyperglycemia and acanthosis nigricans. Diagnosis is confirmed by homozygous or compound heterozygous mutation in the INSR gene . In this case report , we present a child with Rabson Mendenhall syndrome confirmed by a novel mutation in the INSR gene and associated with hypercalciuria causing medullary nephrocalcinosis.

Case report : A female neonate born at term to a 30 yr old primigravida by lower segment cesarian section. Parentage was non-consanguineous and there was no family history of diabetes. There was antenatal oligohydramnios, birth weight was 2.25 kg , child had clinical sepsis during newborn period and was treated elsewhere. Brought to our hospital at 3 months of life for breathing difficulty. At admission weight was 4.2kg, length 57cm, OFC 37cm, examination revealed coarse facies, acanthosis nigricans , hirsutism, hyperkeratosis, prominent nipples, sacral dimple, mild tachypnea and there was wheeze on auscultation. Random blood sugar was 281 mg/dl, ionised calcium was 1.36mmol/L, urine sugar was 3+ and ketones were negative. Rest of the electrolytes including phosphorus was normal. On further work-up , fasting insulin levels >300uIU/ml and C-peptide was 11.36 ng/ml which was suggestive of insulin resistance, HbA1c was 5.7%, Further work-up done in view of hypercalcemia revealed normal Vitamin D levels (86.2 ng/ml) and appropriately low PTH levels (5.1 pg/ml). Urine Calcium/Creatinine ratio was 0.57 which suggested hypercalciuria. Lipid profile was within normal limits. USG Abdomen revealed medullary nephrocalcinosis. In view of insulin resistance in the infantile period, a possibility of Rabson Mendenhall syndrome was considered , genetic analysis done showed compound heterozygosity for the pathogenic INSR mutations p.Tyr606Cys (c.1817A>G) and p.Pro13_Ala19del (c.33_53del) confirming a diagnosis of INSR related congenital severe insulin resistance (testing performed on a research basis by the Cambridge Metabolic Research Laboratories). Mother was heterozygous for the pathogenic INSR mutation p.Tyr606Cys , father was heterozygous for the pathogenic INSR mutation p.Pro13_Ala19del , hence both are carrier of congenital insulin resistance gene. Child was managed with Metformin alone, it was started at a dose of 20 mg/kg/day in two divided doses and gradually hiked upto 40 mg/kg/day. HbA1c after 3 months of diagnosis was 6.2 .



At diagnosis (3 mo of age)

Discussion : The insulin receptor gene maps to human chromosome 19. Defects in the insulin receptor gene cause insulin resistance. Clinical diagnosis of insulin resistance is done by quantification of insulin levels in fasting or after oral glucose tolerance testing [(1)], insulin tolerance test (1), estimation of index of insulin sensitivity(Si) by applying minimal model technique to data obtained from the frequently sampled iv glucose tolerance test (FSIVGTT)[(2)], & by euglycemic hyperinsulinemic clamp procedure[(3)]. Fasting insulin levels above 50–70 mU/mL or peak (post-OGTT) insulin levels above 350 mU/mL suggest severe insulin resistance(1) which was seen in our patient.

Inherited insulin resistance syndromes are Donohue syndrome (most severe), Rabson Mendenhall syndrome(intermediate phenotype) and Type A insulin resistance(least severe). Donohue syndrome is characterised by IUGR , failure to thrive , dysmorphic features , distended abdomen , enlarged genitalia, hyperinsulinemia , loss of glucose homeostasis and death by 1 year of age. Type A insulin resistance is seen in adolescent females and features ovarian hyperandrogenism, hirsutism, insulin resistance, diabetes mellitus , polycystic ovaries and survival beyond middle age.

Rabson and Mendenhall in 1956 described 3 sibs who presented with early dentition, a coarse, senile-appearing facies, hirsutism, prognathism, thick fingernails, acanthosis nigricans, abdominal distention, phallic enlargement. They developed insulin-resistant diabetes , and died during childhood due to ketoacidosis and intercurrent infections. At necropsy pineal hyperplasia was found in all[(3)]. Sarita et al[(4)] reported medullary nephrocalcinosis in a child with Rabson mendenhall syndrome as in our child, and we documented hypercalciuria contributing to it. In a study by Liborio et al in acromegaly patients, univariate analysis showed U(Ca) excretion was associated with HOMA-IR . IR mutations (in homozygous or compound heterozygous form) have been found in all patients with Donohue or the Rabson-Mendenhall syndrome[(5,6)].

Treatment of insulin resistance syndromes is not established as the pathogenesis is not well understood, trial with insulin sensitisers like biguanides (Metformin) and thiazolidinediones is given. Cochran et al. (2004)reported that treatment of 2 sibs with pharmacologic doses of human leptin resulted in improvement of fasting hyperglycemia, hyperinsulinemia, basal glucose, and glucose and insulin tolerance[(7)]. Functional activation of a mutant IR, obtained from a patient with the Rabson-Mendenhall syndrome, by a monoclonal antibody in vitro led to improved IR autophosphorylation and glycogen synthesis in vitro, raising hopes that such therapy may benefit patients with severe insulin resistance[(8)].

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