

Congenital Hyperinsulinism Caused by Mutations in *ABCC8* (*SUR1*) Gene

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Congenital hyperinsulinism is the most frequent cause of severe, persistent hypoglycemia in infancy and childhood. We report a 2.5 year old girl with severe congenital hyperinsulinism. Mutation analysis showed that the child is a compound heterozygote for two missense mutations in the *ABCC8* gene.

Key words: Congenital hyperinsulinism, Hypoglycemia, Octreotide, *ABCC8* gene.

Congenital hyperinsulinism (CHI) is biochemically characterized by the deregulated secretion of insulin from pancreatic β -cells. It is a major cause of hypoglycemia in newborns and infants [1]. The incidence of CHI is estimated to be 1 in 40,000-50,000 in the general population, while it is 1 in 2500 in some isolated communities with high rates of consanguinity [2]. There is a marked heterogeneity in the clinical presentation, molecular mechanisms and histological basis of the disease [3].

CASE REPORT

This girl presented to us at 2.5 years of age. Her mother was pregnant (gestation of 6 weeks), and wanted prenatal diagnosis. The couple did not want recurrence of problem that occurred in the first child (brain damage due to hypoglycemia). She was born at term by spontaneous vaginal delivery; her birthweight was 3.2 kg and there was no history of birth asphyxia. Antenatally there was no history of diabetes mellitus in the mother. The patient became lethargic within hours after birth. Blood glucose was (27 mg/dL) and there was no acidosis, and urinary ketones were normal. She was able to maintain normal blood glucose only with IV glucose solutions and milk fortified with sugar. On day 3 of life, she was transferred to a tertiary care centre for management. In view of the high serum insulin level (13.4 μ IU/mL) at the time of hypoglycemia, she was diagnosed with congenital hyperinsulinism. Serum growth hormone, cortisol, ammonia and lactate were normal. She was discharged after one week on hydrocortisone, octreotide and diazoxide. At 3 months of age her parents discontinued the

treatment, as there was no response. The parents were given the option of pancreatectomy but they did not agree. Since then she is on antiepileptic drugs for seizures and is not receiving any treatment for hyperinsulinism. She developed meningitis at around 8 months of age and a VP-shunt was done following the identification of hydrocephalus on a CT scan. At presentation, she had global developmental delay and was completely bedridden with high seizure frequency.

Molecular diagnosis: Genomic DNA was extracted from peripheral blood from the affected child and both parents. Mutation analysis of *ABCC8* (encoding SUR1) and *KCNJ11* (encoding Kir6.2) genes was undertaken according to the protocol described previously [7]. The child was found to be a compound heterozygote for the missense mutations R74Q and G111R in exons 2 and 3 of the *ABCC8* gene. This result confirmed a diagnosis of autosomal recessive congenital hyperinsulinism. Sequencing analysis of *ABCC8* gene showed that her father was heterozygous for the G111R mutation, while mother was heterozygous for the R74Q mutation. The risk that their next child will be affected by congenital hyperinsulinism was 25%. As the lady was pregnant, prenatal testing was done. This showed the fetus to be affected and parents chose to abort the pregnancy.

DISCUSSION

Congenital hyperinsulinism is the most common cause of persistent neonatal hypoglycemia and should be considered in every infant presenting with unexplained hypoglycemia. High birthweight for gestational age and elevated glucose requirement to prevent hypoglycemia

strongly suggest the diagnosis of hyperinsulinism. Diagnostic biochemical features for congenital hyperinsulinism include glucose infusion rate > 8 mg/kg/minute; and laboratory values - blood glucose <3 mmol/l with detectable serum insulin/ C-peptide, low serum ketone bodies, low serum fatty acids and low branch chain amino acids [2,5]. Our patient had high serum insulin at the time of hypoglycemia. This strongly suggested the diagnosis.

Infants with Beckwith-Wiedemann syndrome may have hyperinsulinemic hypoglycemia. Congenital deficiency of cortisol or growth hormone may first present with hypoglycemia. Growth hormone and cortisol levels were normal in our case. Defects in fatty acid, glucose, and aminoacid metabolism are rare, but they frequently present with hypoglycemia. To exclude other potential causes of hypoglycemia, plasma samples for C-peptide, free fatty acids, beta-hydroxybutyrate, acetoacetate, lactic acid, carnitine, growth hormone, cortisol, and thyroid hormones should be done. Hypoglycemia has been reported in cases of congenital disorders of glycosylation - CDG Ia, CDG-Ib and in a case of CDG-Id, and hence testing is required to exclude these.

Mutations in seven different genes have been described that lead to dysregulated insulin secretion [9]. Mutations in these genes account for about 50% of the known causes of CHI [10]. Congenital hyperinsulinism, caused by mutations in either *ABCC8* or *KCNJ11*, is the most common form. These genes regulate the ATP sensitive potassium channel (K_{ATP}), which is involved in insulin secretion in relation to meals. CHI can be inherited as autosomal recessive or dominant. Our patient had missense mutations in exons 2 and 3 of the *ABCC8* gene. The G>A mutation at nucleotide 221 (c.221G>A) results in the substitution of glutamine for arginine at codon 74 (p.Arg74Gln) and has been reported previously [8]. The G>A mutation at nucleotide 331 (c.331G>A) results in the substitution of arginine for glycine at codon 111

(p.Gly111Arg) and has also been reported previously [9]. Mutation in *ABCC8* and *KCNJ11* gene also cause diabetes mellitus and there has been reports of the mutations in these genes in diabetes from India [10].

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