CASE REPORT

Congenital Hyperinsulinism: A Novel Mutation in the KCNJ11 Gene

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ABSTRACT

Introduction Hyperinsulinism is the most common cause of both transient and persistent hypoglycemia in the neonatal period. Hyperinsulinism due to mutations in the ATP-sensitive potassium channel encoded by the *KCNJ11* and *ABCC8* genes cause the most common and severe form of hyperinsulinism. Herein, we present a case of congenital hyperinsulinism in which a novel *KCNJ11* mutation was identified. **Case report** An eight-day-old boy with a birth weight of 4,550 g born to a 32-year-old female with diabetes mellitus was transferred to our clinic with the diagnoses of respiratory distress syndrome, congenital heart disease and hypoglycemia. A diagnosis of congenital hyperinsulinism was made based on the presence of elevated serum insulin levels (109 µIU/mL [2.6-24]) during hypoglycemia. Levels of serum growth hormone, cortisol, ammonium, and lactate were normal. Metabolic screening tests for blood and urine ketones and fatty acid oxidation defects were found to be normal. Glucose infusion (14 mg/kg/min), glucagon infusion, and diazoxide were initiated based on the diagnosis of hyperinsulinemic hypoglycemia; however, glycemic control was only achieved after the addition of octreotide and nifedipine. There were no abnormal findings in sonography and abdominal magnetic resonance imaging. **Molecular diagnosis** *ABCC8* and *KCNJ11* mutation analyses was performed on the genomic DNA extracted from peripheral blood. A novel homozygous missense mutation (*p.E126K*) was detected in *KCNJ11* confirming the diagnosis of congenital hyperinsulinism. **Conclusion** A novel homozygous missense mutation (*p.E126K*) was detected in our case, which resulted in hyperinsulinism.

INTRODUCTİON

Hyperinsulinism is the most frequent cause of both transient and persistent hypoglycemia in the neonatal period [1]. Biochemically, congenital hyperinsulinism is the inappropriate release of insulin from pancreatic β-cells despite hypoglycaemia. Its incidence is estimated to be 1: 40,000 to 50,000 in outbred populations [2]. However, it has an incidence up to 1: 2,500 in some populations where consanguinity is widely practiced [3]. Hyperinsulinism due to mutations in the *KCNJ11* and *ABCC8* genes which encode the pancreatic ATP-sensitive potassium [KATP] channel are the most common cause of hyperinsulinism. Histologically two different forms are recognised, diffuse and focal, with the diffuse form commonly inherited in an autosomal recessive manner. In contrast focal disease is usually sporadic. Patients with KATP channel mutations are often born macrosomic with severe hypoglycemia usually presenting immediately after birth [4, 5].

The diagnosis of congenital hyperinsulinism is made according to the following criteria: hyperinsulinemia (plasma insulin >2µU/mL), plasma free fatty acid level <1.5 mmol/L, hypoketonemia (plasma ß-hydroxi butirate level <2 mmol/L) in blood samples obtained during hypoglycemia (glucose <50 mg/dL), and excessive glycemic response to glucagon (delta glucose >30 mg/dL by 1 mg intravenous glucagon). A lack of ketosis during hypoglycemia can exclude many causes of hypoglycemia including insufficient calorie intake, hypopituitarism, adrenal insufficiency, congenital enzyme defects, galactosemia, and fructosemia [6].

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CASE REPORT

An eight-day old boy with a birth weight of 4,550 g born to a 32-year old female with diabetes mellitus was admitted to our neonatal intensive care unit with respiratory distress syndrome, congenital heart disease and hypoglycemia (glucose 32 mg/dL). His parents were second-degree cousins and there was no known history of disease in the family. Physical examination revealed the following findings: weight: 4,550 g (>97 percentile); height: 50 cm (25 to 50 percentile); and head circumference: 35 cm (25 to 50 percentile). Systemic examination showed that the patient was tachypneic and dyspneic with a respiratory rate of 80/bpm, and heart rate of 160/bpm. There was no abnormal finding other than systolic murmur. Patent ductus arteriosus, atrial septal defect, and focal septal hypertrophy (non-obstructive) were detected on an echocardiogram. Mechanical ventilation was then initiated. In the referral facility, glucose infusion (6 mg/

kg/min) was initiated and was subsequently increased to 10 mg/kg/min due to the persistence of hypoglycemia . A diagnosis of congenital hyperinsulinism was made based on the presence of elevated serum insulin-c-peptide levels (109 µIU/ml [2.6-24] and 12 ng/ml [1-1.5], respectively) during hypoglycemia **(Table 1)**. Levels of serum growth hormone, cortisol, ammonium, and lactate were normal. Metabolic screening tests for blood and urine ketones and fatty acid oxidation defects were also found to be normal. Glucose infusion (14 mg/kg/min), glucagon infusion, and diazoxide (initially 5 mg/kg which increased up to 20 mg/kg) were initiated but glycemic control was only achieved when octreotide and nifedipine were intoduced to the treatment regimen (final doses were 30 µg/kg and 1.5 mg/kg/day, respectively). An 18F-DOPA-PET CT scan was not performed as this is currently not available in our country.

Although nasogastric feeding was initiated, the patient was unable to tolerate total enteral nutrition. He was unable to be extubated and his neuorolgical status deteriorated. There was diffuse edematous cerebral hemispheres in cranial magnetic resonance imaging (MRI). Glycemic control was provided but he was died because of respiratory insufficiency.

Molecular Analysis

ABCC8 and *KCNJ11* mutation analyses were performed on genomic DNA extracted from the peripheral blood. A novel homozygous missense mutation (p.E126K) was detected in the *KCNJ11* gene, confirming the diagnosis of congenital hyperinsulinism (genetic analysis was performed at the University of Exeter Medical School, Molecular Genetics, Exeter, UK). His unaffected parents were both heterozygous carriers of the same mutation.

DİSCUSSİON

Hyperinsulinism is the most common cause of persistent hypoglycemia in the neonatal period and early childhood. It is a heterogeneous disease in terms of the genetic, clinical and histological findings.

Genes in which mutations are known to cause congenital hyperinsulinism include *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1 and HNF4A* [7]. In one study *ABCC8* gene mutations were reported in 45% of the affected individuals, whilst mutations in *KCNJ11* were found in 5% of patients [8]. These two genes encode the sulfonylurea receptor 1 (SUR-1) subunit and the inwardly rectifying potassium channel subunit (Kir6.2) of the pancreatic KATP channel respectively. Loss-of-function mutations in these genes result in hyperinsulinism where insulin is secreted regardless of the plasma glucose level.

In our case, a homozygous *p.E126K* mutation was detected in *KCNJ11*, confirming congenital hyperinsulinism. Although this mutation is present in the database of the center where the genetic studies were performed, having been identified in an unrelated patient with congenital hyperinsulinism, it has not reported in the literature to date.

Table 1. Laboratory values of the patient during hypoglycemia (glucose 32 mg/ dL).

Insülin (2.6-24 µIU/ml)	**109**
C-peptide (1-1.5 ng/ml)	**12**
Plasma free fatty acid (0.2-1.5 mmol/L)	**0.1**
Plasma ß-hydroxi butirate (1-3 mmol/L)	**0.8**
Growth hormone (13.6±5.68 ng/ml)	15
Cortisol (1.7-14 µg/ dL)	11
Ammonium (35-65 µmol/L)	44
Lactate (0.5 - 2.2 mmol/L)	1.2

Hyperinsulinism due to *KCNJ11* and *ABCC8* mutations are the most common cause of hyperinsulinism and result in the most clinically severe phenotype. Hyperinsulinism due to K-ATP channel mutations can result in either diffuse or focal histological disease. The identification of a homozygous *KCNJ11* mutation is in keeping with diffuse disease in our patient. Patients with K-ATP channel mutations are often born macrosomic with severe hypoglycemia diagnosed immediately after birth [4, 5]. Our case with KATP channel hyperinsulinism was also a macrosomic infant with severe hyperglycemia presenting early.

Diazoxide treatment is ineffective in the majority of cases with K-ATP channel mutations as the drug exerts its effects by binding to and opening the KATP channel. However, of two cases reported by Shimomura et al. [9], no response was achieved with diazoxide treatment in one case who had a paternally inherited heterozygous *T294M* mutation in *KCNJ11* whilst another case with the same heterozygous mutation inherited by their unaffected mother responded to treatment. Ilamaran et al. [10] also reported a good response to diazoxide treatment in a case with a *KCNJ11* mutation suggesting that some cases with these mutations are amenable to treatment with diazoxide.

For some patients with K-ATP channel mutations who do not respond to diazoxide introduction of additional therapies such a Octreotide and Nifedipine can result in normoglycaemia [11]. In keeping with this our case who was refractory to diazoxide treatment acheived good glycemic control when treated with a combination of octreotide and nifedipine.

CONCLUSİON

In conclusion, hyperinsulinism is the most common cause of persistent hypoglycemia in the neonatal period. A novel homozygous *KCNJ11* missense mutation (*p.E126K*) was detected in our case, which resulted in hyperinsulinism.

Statement of Human and Animal Rights

This manuscript does not contain any studies with human or animal subjects performed by the any of the authors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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