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CASE REPORT

Congenital Hyperinsulinism in a Neonate Due to a Novel Homozygous Mutation (ABCC8): A case report

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Congenital hyperinsulinism (CHI), a clinically and genetically heterogeneous disease, is the most common cause of persistent hypoglycemia in infancy. It is characterized by the unregulated secretion of insulin from pancreatic β-cells in relation to blood glucose concentration. The most common form of CHI is associated with autosomal recessive mutations in genes ABCC8 and KCNJ11, encoding the two subunits of the pancreatic β-cell ATP sensitive potassium channel (KATP). When the disease presents in the neonatal period, early diagnosis and maintenance of normoglycaemia are essential to prevent adverse neurodevelopmental outcomes. Prenatal diagnosis of CHI with a known mutation is a promising new avenue which will ensure early and appropriate postnatal intervention and improved long term outcome. We report a case of neonatal CHI due to homozygous recessive mutation in the ABCC8 gene. The parents were asymptomatic carriers of ABCC8 gene. A review of literature and update on the genetics of the disease is presented in this article.

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Introduction

Congenital hyperinsulinism (CHI) also referred to as Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), and previously called familial hyperinsulinism or primary islet cell hypertrophy (nesidioblastosis), is the most common of persistent hypoglycemia in infancy. CHI is a clinically and genetically heterogeneous disease. The clinical manifestations range from life-threatening hypoglycemia, presenting on the first day of life to only mildly symptomatic hypoglycemia in a child or adolescent, and may be difficult to identify. The response to medical and surgical therapy also varies. CHI is characterized by the unregulated secretion of insulin from pancreatic β-cells in relation to the blood glucose concentration. It occurs in sporadic and familial forms. The incidence of the sporadic form is 1 in 40,000 live births; while that of the familial form is 1 in 2500 live births. The clinical severity of CHI varies with the age of onset. The most severe form occurs in neonates and has major implications for management, outcome and genetic counseling. Children usually present in the first month of life with hypothermia, hypotonia, seizures and loss of consciousness, with the condition sometimes being detected accidentally. The delay in the diagnosis and management is the major cause of permanent brain damage and neurological deficits.
The most common form of CHI is associated with autosomal recessive mutations in the ABCC8 and KCNJ11 genes encoding the two subunits of the pancreatic β-cell ATP sensitive potassium channel (KATP). Mutations are found in only 50% of cases, while in the remaining 50%, the genetic etiology remains unknown. We present here the case of a newborn with severe CHI due to a novel homozygous recessive mutation in the ABCC8 gene.

Case report

A full term baby girl, birth weight 5.4 kg, was born by normal vaginal delivery to a 32 year-old G6P5 non diabetic mother, who had pregnancy induced hypertension controlled with methyldopa. The baby was in good condition at birth with Apgar scores of 9 & 10 at 1 and 5 minutes respectively. The baby did not have any dysmorphic features or congenital anomalies; her parents were first degree cousins, and their previous five children aged 3.5, 6, 8, 10 and 12 years old were all normal; there was no relevant family history.

Due to being large for date the baby was admitted in the NICU where she developed symptomatic hypoglycemia within 30 minutes of birth (dextrostix 1.1 mmol/L). She was treated with IV glucose and oral feeds, despite which she continued to have persistent hypoglycemia, eventually being given a 30mg/kg/min of intravenous dextrose with intravenous glucagon infusion to maintain normoglycaemia. Her serum insulin levels were persistently elevated (range 22-84 μU/mL) during hypoglycemic episodes (blood glucose range 1.8-2.2 mmol/L), the ultrasound and CT scan of her abdomen were normal as was her metabolic screen (Arterial blood gas, 17Hydroxyprogesterone, Thyroid stimulating hormone, Biotinidase, Galactosemia and PKU) and the serum ammonia level (49 μmol/L). Her insulin/glucose ratio remained between 0.6 and 1.0 (normal <0.3), and urine was negative for ketones. Echocardiography, done at one week of age, showed mild hypertrophic cardiomyopathy.

The patient did not improve with medical treatment. At four weeks of age, near total pancreatectomy was done after intraoperative biopsies from the tail, body, head and the uncinate process of the pancreas confirmed the diffuse nature of the disease. This resulted in marked clinical improvement; IV fluids were discontinued, glucagon stopped and she was gradually weaned to exclusive demand feeding by bottle with starch (Polycose 5 g) added to every 60 mL of feed. Post surgery, she continued to have intermittent episodes of hypoglycemia and her insulin levels ranged between 7μU/mL and 10μU/mL during these hypoglycemic episodes (blood glucose range 1.8-2.4 mmol/L). This was treated with IV stomatostatin infusion, 15 μg/min, which stabilized her blood glucose levels and the infusion was gradually discontinued over a two week-period, being replaced by oral diazoxide 60 mg, 8 hourly. She was managed with high calorie feeds. Unfortunately she continued to have hypoglycaemic episodes, and became symptomatic of persistent hypertrophic cardiomyopathy (respiratory distress including tachypnoea and subcostal recession requiring oxygen by nasal canula) necessitating continued hospitalization. A repeat ECHO at 4 months of age showed mild to moderate hypertrophic cardiomyopathy with mild biventricular outlet tract obstruction. Her weight gain was high (900 grams during the first four weeks of life), reflecting severe persistent hyperinsulinaemia and a very high anabolic state; the weight, which at birth was above the 95th centile, was still at the same centile at four months of age. Both height and head circumference, which were above 95th centile at birth, decreased to the 90th centile at four months of age.

At the age of 7 months, a second surgery was done, during which most of the remaining pancreas was removed. There was no regeneration of the remaining pancreatic tissue and histological evaluation of the pancreas revealed the same histological findings as before. One week after the second surgery, blood sugar (range 3.1 mmol/L- 4.2 mmol/L)
and the insulin levels (3 µU/mL) normalized. She was taken off somatostatin and diazoxide and successfully fed normal infant formula. The general condition of the baby improved and an echocardiogram, at three weeks after second surgery, showed improvement in the cardiomyopathy; the rate of weight gain also started to slow down.

**Pathologic description of the removed pancreas**

*Gross description:* The specimen comprised of a near total pancreatectomy specimen, measuring 3×2×1.5 cm; it had the usual lobulated yellow surface; no discrete mass lesions could be identified and the major duct was unremarkable.

*Microscopic description:* Sections revealed a pancreas with preserved lobular architecture; the lobules showed significant increase in the number of islets of Langerhans (hyperplasia), some lobules showing 7 to 8 islets. In addition, the islets showed significant increase in their size (hypertrophy), most of the islets were 300-500 micrometer in diameter (Fig.1), some reaching up to 900 micrometers. Some islets were seen in intimate relation with exocrine ducts, forming the so called ductulo-insular complex (Fig.2). The cells forming the islets did show mild nuclear pleomorphism but no significant necrosis or mitosis was seen. Immunohistochemistry highlighted the islets using antibodies against chromogranin and neuron specific enolase (NSE). Majority of the cells within the islets were of the B-cell type, with occasional cells staining with other cell types (alpha, delta, PP).

**Genetic analysis of the ABCC8 and KCNJ11 genes**

Blood samples for genetic testing from the baby and both parents were taken in the Great Ormond Street Hospital London UK. The genetic sequencing was done in Exeter UK. Genomic DNA was extracted from peripheral blood leukocytes using standard procedures.
species. Both parents were confirmed carriers of the ABCC8 gene.

**Discussion**

Rapid diagnosis and prompt management of CHI are the cornerstones for preventing brain damage and mental retardation; its diagnosis should be suspected in any patient who has persistent hypoglycaemia associated with a glucose requirement of >8 mg/kg/min to maintain normoglycaemia, since during the newborn period, it is rare for any other condition to cause such severe hypoglycaemia requiring a very high glucose intake. There is no correlation between the serum insulin level and the severity of hypoglycaemia. The serum insulin level may not be significantly elevated but the presence of insulin in the face of hypoglycaemia is a sign of unregulated insulin secretion. Aynsley-Green et al.’s published diagnostic criteria for CHI include an increased glucose requirement >8 mg/kg/min, absence of ketonuria, and a glycemic response to glucagon. Once the diagnosis is suspected, the management needs to be prompt. Since these patients are unable to generate alternative brain fuels (such as ketone bodies), their blood glucose levels should be maintained within the normal range (3.5-5.5 mmol/L). This can be accomplished by giving a combination of concentrated intravenous dextrose infusions and enteral feeds.

Histologically CHI is either diffuse or focal. The diffuse type of CHI is characterized by large β-cells with abnormally large nuclei distributed throughout the whole pancreas, whereas the focal type consists of an adenomatous hyperplasia confined to one region of the pancreas. Preoperative differentiation between focal and diffuse type of CHI is very helpful in the management and should be carried out using positron emission tomography (PET) whenever possible. Focal disease is curable with partial pancreatectomy with a few long term complications. Until recently highly invasive methods such as intrahepatic pancreatic portal venous sampling, the intraarterial calcium stimulation and venous sampling test and insulin response testing to intravenous glucose, calcium, and tolbutamide were used to differentiate between focal and diffuse types of CHI. More recently 18F-DOPA-PET has successfully replaced these techniques. In addition the 18F-DOPA-PET is also useful in locating ectopic pancreatic foci. In our case, none of these tests were done due to their unavailability in the primary hospital.

As 18 F-DOPA-PET scanning technology is not available in all centers, it is now possible to differentiate diffuse disease in some patients from focal by using rapid genetic analysis; these patients will have either homozygous or compound heterozygous mutation in genes ABCC8 or KCNJ11. On the other hand those with focal disease will have a paternal mutation in the ABCC8 or KCNJ11 genes associated with loss of heterozygosity of the maternal 11p allele in the focal lesion. Hence in patients with consanguinity, it is likely that the diffuse disease is associated with homozygous or compound heterozygous mutation in genes ABCC8 or KCNJ11, (as in our patient). Therefore in patients with genetically confirmed diffuse disease, no further imaging is required with 18F-DOPA-PET scan.

The molecular basis of recessive inactivating ABCC8 and KCNJ11 mutations involves multiple defects in KATP channel biogenesis and turnover, in channel trafficking from the endoplasmic reticulum and Golgi apparatus to the plasma membrane and alterations of channels in response to both nucleotide regulation and open-state frequency. KATP channels have a key role in the physiology of many cells, and any defects either in the channel itself or in its regulation can lead to diseases in humans. Functionally KATP channels provide a means of linking the electrical activity of a cell to its metabolic state by sensing changes in the concentration of intracellular nucleotides and in some cases they mediate the actions of hormones and transmitters. The pancreatic KATP channel is a functional complex of the sulfonylurea
receptor 1 (SUR1) and an inward rectifier potassium channel subunit (Kir 6.2) and plays a pivotal role in regulating insulin secretion from the β-cell. The Kir 6.2 forms the pore of the channel and the SUR1 (an ATP Binding Cassette Transporter) acts as a regulatory subunit.

KATP channels are regulated by adenine nucleotides to convert changes in cellular metabolic levels into membrane excitability. Each subunit of the KATP channel is known to be differentially regulated. The Kir 6.2 subunit determines the biophysical properties of the channel complex including K+ selectivity, rectification, inhibition by ATP and activation by acyl-CoAs. The sulfonylurea receptors endow KATP channels with sensitivity to the stimulatory actions of Mg-nucleotides and KATP channel openers (e.g. diazoxide, nicorandil) and the inhibitory effects of sulphonylureas and glinides.

The genetic aetiology of focal CHI is distinct from that of diffuse CHI. Focal adenomatous hyperplasia involves the specific loss of the maternal 11p15 region and a constitutional mutation of a paternally inherited allele of the genes ABCC8/KCNJ11 encoding the KATP channel. The specific loss of the maternal 11p15 region within the focal region results in paternal isodisomy and a paternally inherited mutation in ABCC8/KCNJ11. The reduction to homozygosity of a paternally inherited ABCC8/KCNJ11 mutation within the focal lesion leads to uncontrolled secretion of insulin. Diffuse disease is inherited in an autosomal recessive or dominant manner which is distinct from that of focal disease.

Prenatal diagnosis is also possible when the mutation in the index case is known. William H. Peranteau and colleagues reported, for the first time, a prenatal diagnosis of diffuse CHI in a baby with a known family mutation and sibling affected with CHI.

To conclude, the diagnosis and management of hyperinsulinaemic hypoglycaemia in newborns remains a challenge for neonatologists and endocrinologists. Early diagnosis and maintenance of normoglycaemia is essential, as without adequate glucose control, an adverse neurodevelopmental outcome is very likely. Prenatal diagnosis of CHI with a known mutation is a promising new avenue which will ensure early and appropriate postnatal intervention and improved long term outcome.

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References