Congenital hyperinsulinism presenting with different clinical, biochemical and molecular genetic spectra

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Congenital hyperinsulinism (CHI) is a common cause of hypoglycemia in infants. We report three cases of CHI with differing clinical, biochemical, and molecular genetic spectra. One patient was unresponsive to medical treatment and died after subtotal pancreatectomy because of complications due to the surgery. Two patients have been followed successfully with medical treatment. Early diagnosis and appropriate treatment of CHI are essential to prevent morbidity and mortality.

Key words: congenital hyperinsulinism, clinical spectrum, histopathology, treatment.

Congenital hyperinsulinism (CHI) is a cause of persistent hypoglycemia due to unregulated insulin secretion from pancreatic β-cells and is considered to be the most frequent cause of persistent recurrent hypoglycemia in newborns and infants[1,2]. Despite recent advances, the genetic basis of CHI is still unknown in about 50% of patients. To date, the molecular basis of congenital CHI involves defects in nine key genes (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A* and *UCP2*), the products of which are involved in regulating insulin secretion[3-13]. The clinical presentation and response to pharmacological treatment may vary significantly, depending on the underlying pathology.

Rapid diagnosis and prompt management of the hypoglycemia are essential to prevent complications and irreversible brain damage secondary to repeated episodes of hypoglycemia[14]. The histological differentiation of focal and diffuse CHI is essential for the surgical approach to this disease. Using fluorine-18-L-dihydroxyphenylalanine positron emission tomography (^{18}F-Dopa PET/CT) as an imaging technique in patients with CHI has radically changed the therapeutic approaches[15]. Here, we report three patients with CHI. Two cases were treated with diazoxide (7-12 μg/kg/day), with complete resolution of the hypoglycemia and hypoglycemia-related symptoms. One case was unresponsive to diazoxide treatment and hypoglycemia was cured only by a subtotal pancreatectomy.

Material and Methods

Clinical and biochemical details are summarized in Table I. Transient CHI associated with maternal diabetes mellitus, intrauterine growth retardation, perinatal asphyxia, erythroblastosis fetalis, maternal administration of drugs such as sulphonylureas, and syndromic CHI associated with Beckwith-Wiedemann syndrome and others[16] were excluded.

Case 1 did not respond to diazoxide (20 mg/kg/day) or octreotide (25 mg/kg/day) treatment. Normal blood glucose levels could be achieved only with of high-concentration glucose infusion (20 mg/kg/minute [min]) via a central venous catheter. DNA samples were sent to the United Kingdom (*) for mutation analysis of the β-cell potassium adenosine triphosphate (K_{ATP}) channel genes (*ABCC8* and *KCNJ11*). The patient was followed with high-concentration glucose infusion by a central venous catheter and bottle-feeding for

two months in the neonatal intensive care unit. Recurrent hypoglycemic attacks could not be controlled. Because we did not have the opportunity to image pancreatic tissues by ^{18}F-Dopa PET/CT scanning to differentiate diffuse and focal pancreatic hyperplasia as the etiology of CHI, the patient underwent subtotal pancreatectomy empirically. The distal 75% of the pancreatic tissue was removed. The glucose infusion requirement decreased gradually from 20 mg/kg/min to 8 mg/kg/min, and the diazoxide dose was decreased from 20 mg/kg/day to 15 mg/kg/day over the course of five postoperative days.

Hypoglycemic attacks were provoked by protein-rich feeding in Case 2. A leucine tolerance test was performed at age 2.1 years in this case. The patient was hospitalized for the leucine tolerance test and diazoxide was stopped. Blood glucose was measured every 30 min to detect a possible hypoglycemic attack. One day after stopping the diazoxide, 150 mg/kg L-leucine (Aminoplasmal – Hepa 10%, Braun) was given orally and blood samples were taken at -30, 0, 30, 60, and 120 min for measurements of plasma glucose, insulin, C-peptide, and ammonia. The test was terminated at the 120th min. Blood and urine samples were also taken for the analysis of plasma acylcarnitine and urine organic acids, respectively.

In Case 3, there were no distinctive clinical or laboratory findings, except for hypoglycemia and hyperinsulinemia.

A low-dose short Synacthen test was performed at three months of age in Case 1 and Case 2 because of serum cortisol levels <10 μg/dl (4.2 and 6.9 μg/dl, respectively) during the hypoglycemic attack.

This study was approved by the Ethics Committee of Eskisehir Osmangazi University School of Medicine, and informed consent was obtained from all parents. We complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Clinical Biochemical Measurements

Plasma insulin, C-peptide, cortisol, and growth hormone were measured simultaneously with hypoglycemic plasma glucose (≤2.5 mmol/L or 45 μg/dl). Plasma glucose was measured using a glucose analyzer (Roche Modular Instrument, Mannheim, Germany). Serum C-peptide, insulin, and growth hormone were measured using the Immulite 2000 (Siemens, New York, USA). The lowest limit of detection was 2 mg/dl for glucose, 2.0 μU/ml for insulin, 0.1 ng/ml for C-peptide, 0.018 μg/dl for cortisol, and 0.05 ng/μl for growth hormone.

Genetics*

Blood samples were taken from patients and parents for DNA isolation. DNA was extracted

Table I. Summary of the Clinical and Biochemical Aspects of Patients with Congenital Hyperinsulinemic Hypoglycemia

	Case 1 (Y.A.)	Case 2 (K.Ö.)	Case 3 (M.K.)
Parental consanguinity	No	Yes	No
Gestational age (wk)	38	39	39
Birth weight (kg)	3.51	3.40	3.44
Symptoms of hypoglycemia	Seizures and cyanosis	Seizure, cyanosis, hypotonia	Lethargy and hypotonia
Age of the beginning of symptoms (day)	2	5	10
Maximum glucose infusion rate (mg/kg/min)	20	13	15
Blood glucose (mmol/L)	1.39	1.78	2.1
Insulin (μU/L)	9.01	12	7.6
C-peptide (ng/ml)	5.37	4.92	2.23
Cortisol (μg/dl)	4.16	6.95	22.12
Growth hormone (ng/ml)	28.5	7.9	16
Diazoxide responsive (yes or no) and the maximum dose (mg/kg/day)	No (20)	Yes (12)	Yes (10)

Table II. Leucine Tolerance Test Results in Case 2

Time	-30th min	0 min	30th min	60th min	120th min
Glucose (mmol/L)	4.8	4.4	2.8	2.05 3 ml/kg 10% dextrose was pushed intravenously, and 25 μg/kg glucagon was given s.c.	5.2
C-peptide (nmol/L)	1.89	1.62	3.04	6.41	6.74
Insulin (μU/ml)	12.9	10.51	25.12	41.4	44.2
Ammonia (mg/dl)	41	43	120	90	78

from peripheral leukocytes, and the *KCNJ11*, *ABCC8*, *HADH*, *GLUD1*, and/or *HNF4A* genes were amplified and sequenced as described previously[17-20].

Results

Genetic analysis in Case 1 revealed a heterozygous nonsense mutation, p.E791X (c.2371G→T), in the *ABCC8* gene. Family member testing demonstrated that the patient had inherited this mutation from his unaffected father. To differentiate focal from diffuse CHI, the patient required further study; however, the differential diagnosis of focal or diffuse hyperinsulinism could not be investigated further by ^{18}F-Dopa PET/CT scanning of the pancreas. Currently, there is no opportunity in Turkey to use ^{18}F-Dopa PET/CT scanning as an imaging technique. Blood glucose measurements were hyperglycemic shortly after a subtotal pancreatectomy. The glucose infusion concentration, octreotide, and diazoxide doses were decreased progressively. The histological study of the resected pancreas showed focal islet-cell hyperplasia in the tail of the pancreas (Fig. 1). Unfortunately, a superior vena cava thrombosis developed in the third postoperative day as a central venous catheter complication and the patient died five days after the surgical operation.

Details of the leucine tolerance test in Case 2 are given in Table II. There were no abnormalities in plasma acylcarnitines or urinary organic acids. Genetic analysis of Case 2 revealed a homozygous nonsense mutation, p.R236X (c.706C→T), in the *HADH* gene (reported previously)[17]. Family member testing demonstrated that the parents were both heterozygous for the nonsense mutation and were therefore carriers of CHI.

We did not detect a mutation in the *KCNJ11*, *ABCC8*, *HADH*, or *HNF4A* gene using sequence analysis in Case 3.

A low-dose short Synacthen test confirmed normal cortisol responses in Case 1 and Case 2 (>20 μg/dl); therefore, adrenal insufficiency was ruled out in these two patients. The patients were responsive to diazoxide and have been followed with medical treatment.

Discussion

Based on previous reports[1,2,14-16], the road-map according to priorities in the clinical management of patients with CHI can be summarized as follows:

1) Immediate correction of hypoglycemia by intravenous glucose and the injection of glucagon with the prevention of repeated hypoglycemic episodes,

2) Determine whether the patient will respond to treatment with diazoxide,

3) Based on the ^{18}F-Dopa PET/CT scanning and/or histopathological results, the case should be classified as focal or diffuse CHI. The alternative method for classifying the focal or diffuse disease is genetic study. If the patient is diazoxide-unresponsive and genetic study confirms paternally or autosomal recessive transmission, these findings are suggestive of focal disease. However, at least 50% of CHI patients (50% of diazoxide-responsive and 20% of diazoxide-unresponsive) have no genetic explanation for their disease.

4) Depending on the clinical presentation, the cases should be investigated for one or more of the nine known CHI genes, and finally,

5) A decision should be reached regarding long-term treatment with medication and/or surgery.

Congenital hyperinsulinism (CHI) is

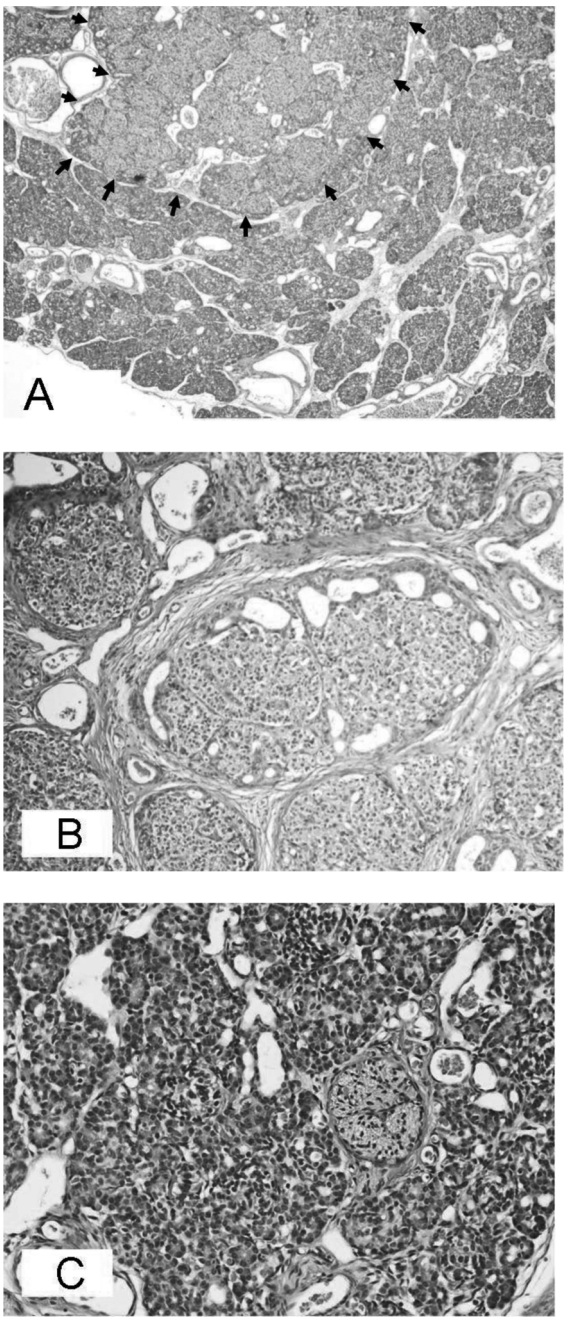

Fig. 1. Microscopic sections of the pancreas from an infant (Case 1) with hyperinsulinemic hypoglycemia. Panel A shows focal islet-cell abnormalities (focal hyperinsulinism, arrows, 6-8 mm in diameter); the exocrine tissue is restricted to the periphery of the pancreatic lobule (hematoxylin and eosin [H&E], x 80). At high magnification (Panel B), the focal lesion is composed of islets containing a heterogeneous population of endocrine cells of various sizes and islet cells have large nuclei and large cytoplasms (H&E, x 400). By contrast, normal islets (Panel C) observed outside the lesion have endocrine cells of usual size without enlarged nuclei (H&E, x 200).

characterized by inappropriate and unregulated secretion of insulin despite low blood glucose levels. Mutations in the β-cell K_{ATP} channel genes *KCNJ11*, which encodes Kir6.2, and *ABCC8*, which encodes SUR1, are the most common causes of CHI[18,19]. Since the discovery of the first mutation, over 174 have now been described in the K_{ATP} channel genes[21-23]. According to the histological classification, focal forms of CHI result from a paternally inherited *ABCC8* or *KCNJ11* gene mutation with loss of the maternal allele in the pancreatic hyperplastic islets, whereas most diffuse forms of CHI show recessive inheritance.

There are two (diffuse and focal) histological subtypes of CHI. The diffuse form affects the entire pancreas, and if medically unresponsive, will require near total (95-98%) pancreatectomy. The focal form affects only a small region of the pancreas and only requires limited pancreatectomy. ^{18}F-Dopa PET/CT scanning differentiates focal and diffuse disease and is 100% accurate in localizing the focal lesion. Recently, Kapoor et al.[11] reported 19 patients with diazoxide-unresponsive CHI with a heterozygous paternal *ABCC8* mutation. Twelve of the 19 patients with a recessively acting paternal mutation had histologically confirmed focal disease that was managed by resection of the focal lesion limited pancreatectomy. In our study, the mutation analysis showed that Case 1 was heterozygous for a paternally inherited *ABCC8* nonsense mutation, in keeping with a diagnosis of focal hyperinsulinism. This case was not responsive to diazoxide or the other medical treatments. Normoglycemic blood glucose levels were only maintained by high-concentration glucose infusion with a central catheter for an extended period in the pediatric intensive care unit. Therefore, surgical treatment was necessary. Unfortunately, we did not have the opportunity to perform ^{18}F-Dopa PET/CT scanning to classify the hyperplasia as focal or diffuse. The patient underwent surgery without imaging of the lesion. Histological examination of the pancreatectomy material confirmed that the lesion was in the tail of the pancreas and was focal (Fig. 1). Subtotal pancreatectomy without imaging of the lesion and long-term follow-up with a central venous catheter were extremely invasive therapeutic approaches in this patient. An important part of the pancreas was removed unnecessarily. Unfortunately, the

patient died in the postoperative period because of complications of surgery and long-term follow-up with the central catheter.

The mode of inheritance depends on the genetic etiology; *GCK*, *GLUD1*, *HNF4A*, and *SLC16A1* mutations are inherited in an autosomal dominant manner, while *HADH* mutations are autosomal recessive[23]. Case 2 presented with postprandial hypoglycemic attacks and convulsions. This clinical presentation was consistent with a *GLUD1* mutation, which is characterized by postprandial hyperinsulinemic hypoglycemia and a mildly elevated plasma ammonia concentration[7]. Activating mutations in the *GLUD1* gene reduce the sensitivity of the enzyme to allosteric inhibition by guanosine triphosphate (GTP) and ATP or, less frequently, cause an increase in basal glutamate dehydrogenase (GDH) activity[24,25]. The loss of inhibition by GTP leads to increased leucine-induced oxidation of glutamate to α-ketoglutarate. Hence, leucine sensitivity is manifested by hyperinsulinemic hypoglycemia and asymptomatic hyperammonemia following protein-rich meals, a classical feature of activating mutations in the *GLUD1* gene[26]. Kapoor et al.[27] recently described severe protein sensitivity in patients with loss-of-function mutations in the *HADH* gene. Sequencing of the *GLUD1* gene in Case 2 failed to detect a change from the normal sequence. However, this case was shown to be homozygous for a nonsense mutation in the *HADH* gene. A number of studies have demonstrated that HADH has a pivotal role in regulating insulin secretion[28,29]. Li et al. [30] examined the mechanism of insulin dysregulation in *HADH*-knockout mice. In this model of HADH-GDH interaction, HADH acts as an inhibitor of GDH. Loss-of-function mutations in the *HADH* gene would hence be associated with loss of GDH inhibition or raised GDH activity, a feature of *GLUD1* mutations. The reported patients with loss-of-function mutations in the *HADH* gene presented with hyperinsulinemic hypoglycemia following protein-rich meals; however, these mutations were not associated with hyperammonemia.

The interesting findings in CHI are typically inadequate counter-regulatory hormone response to severe hypoglycemic attacks. In our three cases, two patients had low cortisol and growth hormone levels during hypoglycemic attacks. In the first case, we began hydrocortisone replacement therapy because of the possibility of adrenal failure. Two weeks later, the dose of hydrocortisone was tapered gradually. In the other case of CHI, serum cortisol and growth hormone levels were also found below low-normal reference limits during the hypoglycemic attacks. At this time, the patient was followed with diazoxide treatment and without hydrocortisone or growth hormone replacement. A low-dose short Synacthen test revealed a normal cortisol response in both cases. More recently, Christesen et al.[31] reported their experiences in cases of CHI. They concluded that recurrent hyperinsulinemic hypoglycemia blunts the autonomic, neuroglycopenic, and glucose counter-regulatory hormonal responses in patients with infant-onset CHI, resulting in clinically silent hypoglycemia.

We did not detect a mutation in the *ABCC8*, *KCNJ11*, *HADH*, or *HNF4A* gene in Case 3 using sequence analysis. However, the patient needed diazoxide treatment at a dose of 10 mg/kg/day for 26 months. About 50% of diazoxide-responsive and 20% of diazoxide-unresponsive patients have no genetic explanation for their disease[16]. Future research should focus on identifying novel genes involved in CHI.

In conclusion, the main cause of death in Case 1 was complications of surgery and long-term follow-up with a central catheter in the intensive care unit. If given the opportunity to perform molecular studies of CHI and ^{18}F-Dopa PET/CT imaging in Turkey, where the incidence of CHI is expected to be higher than in other European countries because of the high incidence of consanguineous marriages, more accurate diagnoses and treatment may be possible soon, and many complications of subtotal pancreatectomy or long-term follow-up in the intensive care unit might be prevented. Early diagnosis and appropriate treatment are the most important factors for reducing the high incidence of morbidity and mortality in CHI. Since loss-of-function mutations in the *HADH* gene are associated with loss of GDH inhibition or raised GDH activity, the *HADH* gene should be analyzed in patients with hyperinsulinemic hypoglycemia following protein-rich meals and in patients in whom *GLUD1* gene mutation screening is negative.

Counter-regulatory hormonal responses, such as cortisol and growth hormone responses, during hypoglycemic attacks in patients with CHI should be interpreted carefully because recurrent hyperinsulinemic hypoglycemia blunts the autonomic, neuroglycopenic and counter-regulator hormonal responses. Some patients with CHI have no genetic explanation for their disease, as illustrated by Case 3.

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