

A Case Series: Congenital Hyperinsulinism

Mohammad Reza Alaei,¹ Susan Akbaroghli,^{2,*} Mohammad Keramatipour,³ and Ali Alaei⁴

¹Department of Pediatric Endocrinology, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

²Genetic Counseling Division, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

³Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

⁴School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Susan Akbaroghli, Mofid Children's Hospital, Tehran, IR Iran. Tel: +98-2122227033, Fax: +98-2122227033, E-mail: susanakbaroghli@yahoo.com

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Abstract

Introduction: Congenital hyperinsulinism is a rare inherited disease caused by mutations in genes responsible for β -cell's function in glucose hemostasis leading to profound and recurrent hypoglycemia. The incidence of the disease is about 1 in 50000 newborns. Mutations in at least 8 genes have been reported to cause congenital hyperinsulinism. Mutations in ABCC8 gene are the most common cause of the disease that account for approximately 40% of cases. Less frequently KCNJ11 gene mutations are responsible for the disease. Mutations in other genes such as HADH account for smaller fractions of cases. In nearly half of the cases the cause remains unknown.

Case Presentation: During the period between 2005 and 2010, a total of six patients with persistent hyperinsulinism were investigated at Mofid Children's Hospital. In this study all of the patients had early onset hyperinsulinemia. Five patients had consanguineous parents. After failure of medical treatment in three patients, they were undergone pancreatectomy. Two diffuse types and one focal type had been recognized in pathological analysis of intra-operative frozen specimens of pancreas in these patients. Genetic analysis was performed using polymerase chain reaction followed by Sanger sequencing for ABCC8, KCNJ11 and HADH genes. In five patients homozygous mutations in these genes were identified that indicated an autosomal recessive pattern of inheritance. In one patient a heterozygous mutation in ABCC8 was identified, indicating possible autosomal dominant inheritance of the disease.

Conclusions: Congenital hyperinsulinism can have different inheritance pattern. Autosomal recessive inheritance is more common but less frequently autosomal dominant inheritance can be seen. It appears that mutations in ABCC8 gene can show both autosomal recessive and autosomal dominant inheritance of the disease. PCR followed by Sanger sequencing proved to be an efficient method for mutation detection in three investigated genes. Despite early diagnosis, psychomotor retardation was seen in two patients.

Keywords: Congenital Hyperinsulinism, ABCC8, KCNJ11, HADH

1. Introduction

Congenital hyperinsulinism is a rare inherited disease caused by mutations in genes responsible for β -cell's functions in glucose hemostasis and characterized by dysregulation and inappropriate secretion of insulin from abnormal β -cell of pancreatic islets leading to profound and recurrent hypoglycemia (1). The incidence of the disease is around one in 50000 newborns. It is more common in certain populations than others (2-4). The most common form of inheritance is autosomal recessive yet some studies have reported an autosomal dominant pattern. Major clinical manifestation of the disease is hypoglycemia in the absence of ketonemia (1). Many conditions can cause hypoglycemia including: fasting hypoglycemia divided to two subcategories including reduced gluconeogenesis consisting of adrenal insufficiency, glucagon deficiency, catecholamine deficiency, hypothyroidism, ketotic hypo-

glycemia of infancy, multiple endocrine neoplasia, hepatic congestion, renal hypoglycemia, uremia, alcohol and overutilization of glucose consisting of hyperinsulinism, insulin autoimmunity, and endotoxin shock. The other category is postprandial hypoglycemia consisting of initial stages of diabetes, dumping syndrome, galactosemia, leucine sensitivity, and glucose-6-phosphatase deficiency. The other causes are malabsorption, Whipple's disease, gestational diabetic mother (hypoglycemia in infancy), autonomic dystonia and the complication of drugs such as beta blockers, insulin, phenylbutazone, nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates and warfarin.

Certain factors such as infection, prematurity, maternal toxemia, diabetes in mothers, asphyxia and long-time fasting can cause transient hypoglycemia but severe and persistent hypoglycemia in early infancy can be due to abnormalities in pancreatic β -cell and hyperinsulinism is

the most responsible (3, 5). Clinical presentation ranges from life threatening to unidentifiable symptoms that can be difficult to diagnose. The disease can present in various periods of life. Depending on severity of the disorder and patient's tolerance, the age of onset differs between individuals (1). Nevertheless, the majority of neonate patients showed typical symptoms of hypoglycemia including lethargy, hypothermia, seizure, paresthesia, diaphoresis, nausea and vomiting during their first days of life. Insulin is involved in most of the metabolic procedures; aggressive treatment is needed to prevent irreversible neurological damage and death. Some disorders can mimic the symptoms of hypoglycemia and for this reason the diagnosis of hypoglycemia should be confirmed by low level of serum glucose, symptoms of hypoglycemia and relief of symptoms with glucose intake. When diagnosis is established the first line of treatment is to maintain normal blood glucose with adequate exogenous glucose (3). Glucagon may be necessary if euglycemia is not achieved. Diazoxide is the mainstay of medical treatment. Octreotide and nifedipine are the other choices. The mechanism of all drugs is to prevent stimulation of β -cell membrane and subsequently insulin secretion. After failure of medical treatment pancreatectomy is recommended (1, 3). The underlying pathophysiology of hyperinsulinism is mutation in one of at least eight different genes. Mutations in two subunits of the ATP sensitive K channel, kir6.2 and SUR1, can cause a defect of signal transduction pathway, depolarization of membrane and unregulated insulin secretion. Mutations in ABCC8, KCNJ11 encoded SUR1, kir6.2, respectively on chromosome 11p15 are to the most common cause of congenital hyperinsulinism (CHI). The activity of the KATP channel is reduced or totally absent by the inactivating mutations in ABCC8/KCNJ11, leading to unregulated insulin release in spite of severe hypoglycemia. Defect in glutamate dehydrogenase activity is concomitant with hyperammonemia. Hyperinsulinism-hyperammonemia syndrome (HI/HA) is the second most common form of CHI. Missense mutations in the GLUD1 gene causes the defect in the glutamate dehydrogenase (GDH) activity, a mitochondrial matrix enzyme (1, 6).

Based on the pathogenesis process, two histopathological forms of CHI have been recognized: focal and diffuse. There are no distinguishable clinical and biochemical presentations between these two types. The genetic heterogeneity and therapeutic approach are different in these two types. In focal hyperinsulinism, the pancreas contains small discrete areas of adenomatous β -cells, and is effectively curable by selective resection of adenoma. In diffuse form, near-total pancreatectomy is advised and the main complication is iatrogenic diabetes. Radiological studies are less effective in identifying the form of the disease (1, 3,

6, 7).

2. Case Presentation

Retrospectively during the period between 2005 and 2010, a total of six patients with Congenital Hyperinsulinism (CHI) were investigated at Mofid children's hospital. All of them were referred from other pediatric wards. In this study, four patients were girls and two were boy. Age at the time of research ranged from 1.5 to 5 years (mean: 3.2 years), and all of them had early onset of hyperinsulinemia. All patients except one were full-term at birth. Five out of six patients had consanguineous parents. History of gestational diabetes mellitus in mothers was documented in one case. The diagnostic criteria were: recurrent low level of plasma glucose (< 2.7 mmol/L or < 50 mg/dL), hyperinsulinemia (more than 10 mU/L), increased insulin/glucose ratio (more than 0.4) and high rates of intravenous glucose infusions to maintain plasma glucose in the normal range.

Half of the patients revealed the Whipple triad, including hypoglycemia (plasma glucose < 50 mg/dL), manifestations of hypoglycemia and relief of symptoms after taking carbohydrates. Five patients on the first week of life and one of them at the age of 12 weeks showed symptoms of hypoglycemia including: seizure, fatigue, lethargy, confusion and etc. Despite glucose infusion, episodes of seizure occurred in all patients. Other initial clinical findings in the patients are summarized in Table 1.

Plasma glucose, insulin, insulin/glucose ratio, cortisol and growth hormone levels have been measured and presented in Table 1.

Our protocol for management of the patients was as follows: all the patients on the first day of admission and after the establishment of the diagnosis were treated with glucose infusion, such as serum dextrose water 12.5% - 15% with high rate (10 cc/kg/min) as a conservative therapy and the treatment was continued with diazoxide as the first line of therapy to maintain euglycemia. In three patients, octreotide or glucagon were tested to inhibit excessive secretion of Insulin. The failure to achieve acceptable response after using the combination of medical treatments made surgical intervention necessary in three patients.

Patients underwent echocardiography, electroencephalography and different radiological studies. These patients underwent brain-computed tomography (n = 3), abdominal and pelvis ultrasonography (n = 3), chest X-ray (n = 3), echocardiography (n = 1), and electroencephalography (n = 3) with the results summarized in Table 1.

The patients, who did not respond to medical treatment, underwent surgical treatment, depending on either

Table 1. History, Clinical and Paraclinical Findings of Six Patients With Congenital Hyperinsulinism

Patient ID Data	1	2	3	4	5	6
Gender	F	F	F	M	M	F
Family History	N	Yes	No	No	Yes	No
Birth Weight	3750	4550	4500	3800	3500	2850
Gestation	Preterm	Term	Term	Term	Term	Term
Labor	NVD	C/S	C/S	C/S	C/S	NVD
Parents' Consanguinity	Yes	Yes	Yes	No	Yes	Yes
Diabetic Mother	No	Yes	No	No	No	No
Onset of Symptoms	1st week	1st week	1st week	1st week	12th week	1st week
Seizure	Yes	Yes	Yes	Yes	Yes	Yes
Cyanosis	Yes	No	No	No	Yes	Yes
Apnea	No	No	No	No	No	No
Whipple Triad	Yes	Yes	No	No	No	Yes
Macrosomia	No	Yes	Yes	No	No	No
Anomaly	No	No	No	No	No	No
Perinatal Asphyxia	Yes	No	No	No	No	No
Plasma Glucose, mg/dL	20	22	45	30	35	20
Plasma Insulin, mU/L	44	79	34	38	17	22.5
Insulin/Glucose	2.2	3.6	0.75	1.27	0.49	1.1
Cortisol, µg/dL	NL	NL	NL	NL	NL	NL
Growth Hormone	NL	NL	NL	NL	NL	NL
Hyperammonemia	NL	NL	NL	NL	NL	NL
Brain CT	Hypoxic Ischemic Encephalopathy	Brain Atrophy	NP	NL	NP	NP
Ultrasound	NP	NL	NP	NP	NL	NL
EEG	Very rare Scattered Paroxysmal	NP	NP	NL	NL	NP
CXR	Cardiomegaly	Para Cardiac and Right Para Tracheal Opacity, Right lateral Sinus is closed	NP	NP	NP	NL
Echocardiography	NP	Left Ventricular Hypertrophy	NP	NP	NP	NP
Treatment	Diazoxide, Octreotide	Diazoxide, Octreotide	Diazoxide	Diazoxide, Glucagon	Diazoxide	Diazoxide
Duration of Medical Treatment	94 days	34 days	54 days	-	-	-
Histologic Type	Diffuse	Focal	Diffuse	-	-	-
Pancreatectomy	90%	Near Total	Near Total	-	-	-
Mutation	ABCC8	KCNJ11	KCNJ11	ABCC8	HADH	HADH

Abbreviations: C/S, cesarean section; NL, normal; NP, not performed.

focal or diffuse histopathological form, partial or near-total pancreatectomy was respectively recommended. All resected pieces of pancreas were investigated pathologically. The mean medical treatment period for those who underwent surgical treatment was 61 days (range from 34

to 94 days).

Patients and their parents were investigated by DNA analysis. DNA samples were extracted from peripheral blood samples and shipped to the institute of biomedical and clinical science, Peninsula Medical School, University

of Exeter in the UK to be analyzed for possible mutations in ABCC8, KCNJ11 and HADH genes. Polymerase chain reaction (PCR) followed by Sanger sequencing were used for analysis of all exons in these genes. Results were compared with human reference sequence to identify the causative variants (Table 2).

Table 2. The Results of Direct Sequencing Analysis on Patients' DNA Samples

Patient's Number	Gene	Genotype	Sequence Accession Numbers
1	ABCC8 ^a	U63421, L78208	N32K/N32K
	KCNJ11	NM_000525	N/N
2	ABCC8 ^a	U63421, L78208	N/N
	KCNJ11	NM_000525	G40A/G40A
3	ABCC8 ^a	U63421, L78208	N/N
	KCNJ11	NM_000525	[F117del; P340H] / [F117del; P340H]
4	ABCC8 ^a	U63421, L78208	A1153T/N
	KCNJ11	NM_000525	N/N
5	ABCC8 ^a	U63421, L78208	N/N
	KCNJ11	NM_000525	N/N
	HADH ^{b,c}	NM_005327.2	R236X/R236X
6	ABCC8 ^a	U63421, L78208	N/N
	KCNJ11	NM_000525	N/N
	HADH ^{b,c}	NM_005327.2	R236X/R236X

Abbreviation: N, no mutation.

^a Exon 1-39.

^b Exon 1-8.

^c Patients with negative results for ABCC8 and KCNJ11 were investigated for HADH gene mutation.

All patients, except one, showed typical symptoms of hypoglycemia on the first days of life. Almost all of them revealed seizure as the first symptom of hypoglycemia. By routine blood biochemical check, hypoglycemia was detected. Three patients did not respond to medical treatment hence underwent a surgical procedure. At follow up, three patients that were sensitive to diazoxide had no episodes of hypoglycemia, consequently seizure and other annoying symptoms. Mental and physical development was normal in them. They were well treated with diazoxide with no need for octreotide or nifedipine as medical choices. One of the patients that underwent pancreatotomy, showed low level serum glucose and seizure after one month, but the hypoglycemia was less severe and there was no need for long-term medical treatment. Patient number one had diabetes mellitus as the complication of pancreatotomy and underwent insulin therapy. Psychomotor retardation was detected in two patients.

In summary, two diffuse types and one focal type were recognized in pathological analysis of intra-operative frozen section specimens of pancreas. Mutation detection was performed by PCR followed by Sanger sequencing for ABCC8, KCNJ11, and HADH genes in all patients. After detection of possible causative mutation in patient, parental genotyping for the detected variant was performed to show correct segregation of causative alleles. Five out of six investigated patients (patients number 1, 2, 3, 5, and 6) were genotyped homozygous for a mutation in one of the analyzed genes. Heterozygous healthy status was confirmed in parents of all five patients. These finding was consistent with an autosomal recessive pattern of inheritance in these five families. Only one patient (patient number 4) was genotyped heterozygous for a previously reported variant with possible autosomal dominant inheritance, as described below. In patient number 1, a novel homozygous missense variant was detected in exon 1 of ABCC8. This C>G change (c.96C>G) results in the substitution of lysine for asparagine at codon 32 (p.Asn32Lys, N32K). This asparagine residue is conserved across different species. It is therefore very likely that this variant is the causative mutation in this patient. Her parents were genotyped heterozygous for this mutation. This finding is consistent with a diagnosis of autosomal recessive congenital hyperinsulinism. In patient number 2, a previously reported homozygous mutation was found in KCNJ11 gene. This G>C missense mutation at nucleotide 119 (c.119G>C) results in the substitution of alanine for glycine at codon 40 (p.Gly40Ala, G40A). Her parents were confirmed heterozygous for this mutation, that again was consistent with a diagnosis of autosomal recessive congenital hyperinsulinism. Patient number 3 was homozygous for two mutations in KCNJ11 gene. A homozygous deletion of three nucleotide TCT (c.350_352delTCT), was detected which results in deletion of the amino acid phenylalanine at codon 117 (p.Phe117del, F117del). Another A>C mutation was also found in nucleotide 1019 (c.1019A>C). This nucleotide change, results in the substitution of the amino acid histidine for proline at codon 340 (p.Pro340His, P340H). The phenylalanine and proline residues are both conserved across different species. It is therefore very likely that one or both of the F117del and P340H mutations are pathogenic. This result confirms a diagnosis of autosomal recessive congenital hyperinsulinism. Patient number 4 was heterozygous for a missense mutation in ABCC8 gene. This G>A mutation at nucleotide 3457 (c.3457G>A), (in exon 28 of the gene), results in substitution of threonine for alanine at codon 1153 (p.Ala1153Thr, A1153T). This mutation has previously been identified in a large family where it co-segregates with macrosomia and / or neonatal hypoglycemia and later onset diabetes. It is therefore very likely that A1153T change

is pathogenic. This result is consistent with a diagnosis of autosomal dominant congenital hyperinsulinism. In both patients number 5 and 6, a homozygous nonsense mutation was detected in exon 6 of HADH gene. This C>T mutation at nucleotide 706 (c.706C>T) results in a premature termination codon at 236 (p.Arg236X, R236X). This stop gain mutation has been reported previously. Therefore this result confirms diagnosis of autosomal recessive congenital hyperinsulinism in both patients.

3. Discussion

Congenital Hyperinsulinism (CHI) or familial hyperinsulinism is a rare genetic disorder, which causes severe hypoglycaemia secondary to inappropriate secretion of insulin. It is the most common etiology for infantile persistent hypoglycemia and is clinically and genetically heterogeneous (8). In familial hyperinsulinism or persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), hypoglycemia ranges from severe form with neonatal-onset and difficult-to-manage disease to childhood disease with mild symptoms and difficult-to-diagnose characteristics. Manifestations of neonatal-onset type can be seen within the first hours of life till two days after birth while childhood disease presentation can start at the first months or years of life. Seizure, hypotonia, poor feeding and apnea are non-specific symptoms in the newborn. Extremely low serum glucose concentrations can be seen in severe cases, therefore easily recognized, while in milder cases, mild and variable hypoglycemia can be seen and make the diagnosis more difficult.

Hyperinsulinemic hypoglycemia can be seen in other disorders such as in infants of diabetic mothers, transient hyperinsulinemic hypoglycemia of infancy, Beckwith-Wiedemann syndrome, insulin receptor mutations and insulinoma (1).

Three subtypes of CHI based on histology are diffuse, focal and atypical types. Diffuse type is commonly due to recessive mutations in ABCC8/KCNJ11 genes however it can show autosomal dominant inheritance while the focal type is sporadic. In focal CHI, there is a paternally inherited ABCC8/KCNJ11 mutation and inside the focal lesions there is somatic loss of heterozygosity for the 11p allele (6, 8). In the third histological subtype named atypical or mosaic (9, 10), a nonsense mutation in the ABCC8 gene was detected in one study and showed mosaic interstitial segmental paternal isodisomy. This could cause pancreatic-cell nuclear enlargement only in some sections of the pancreas. The Q54X mutation is present in 64 to 74% of affected tissue yet it was heterozygous in unaffected sections of the pancreas. This unique case suggested that some of the "atypical" histolog-

ical diffuse forms of CHI may be due to at least somatic mosaicism (11).

There are eight different detected genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2) responsible for molecular basis of CHI, which dysregulate insulin secretion from β -cells (6). In nearly 40% of patients, the mutations cannot be detected in ABCC8, KCNJ11, GLUD1, HNF4A, GCK, or HADH genes. It is not clear whether these patients have regulatory or intronic mutations. Major deletions and chromosomal rearrangements could have been missed by the sequence analysis method. Also it is possible that novel mutations in other unidentified genes were responsible (1).

In our study, six patients with hyperinsulinism hypoglycemia were investigated. Early diagnosis had the most important role in clinical outcome (1). Despite early diagnosis, psychomotor retardation was present in two patients. Considering hyperinsulinism is a rare disorder, because of irreversible brain damage as a complication, the disease should be ruled out in all patients specially infants with hypoglycemia (1, 12-14).

In our investigation, in patients who underwent pancreatectomy, normoglycemia was achieved yet occasionally episodes of hypoglycemia were seen, which may be due to one of the following reasons: Long-term fasting, remaining of the pancreatic beta cells in the peritoneum, and exocrine insufficiency of the pancreas (7).

Three patients responded well to medical therapy with diazoxide and they might present a mild type of hyperinsulinism. Nevertheless, if medical treatment fails, pancreatectomy is indicated (1).

Diffuse hyperinsulinism is due to recessive mutations in ABCC8 or KCNJ11 (10, 11). The focal type has mutation in the paternal allele of ABCC8 or KCNJ11 (10, 11, 15).

Mutational analysis revealed the presence of two mutant alleles, which support an autosomal recessive pattern of inheritance in all patients except one patient, who was heterozygous for a missense mutation, in exon 28 of the ABCC8 gene. The A1153T mutation is probably pathogenic. This result is consistent with a diagnosis of autosomal dominant congenital hyperinsulinism (16).

Three patients had either an ABCC8 or a KCNJ11 mutation, which was inherited from the parents.

Patient number one was homozygous for a novel missense mutation, N32K in exon1 of the ABCC8 gene. This result is consistent with the diagnosis of autosomal recessive congenital hyperinsulinism. The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. The ABC proteins transport various molecules across extra- and intra-cellular membranes. This protein, as a member of the MRP subfamily, is involved in multi-drug resistance. This protein functions as

a modulator of ATP-sensitive potassium channels and insulin release. Mutations and deficiencies in this protein have been observed in patients with congenital hyperinsulinism as an autosomal recessive disorder with unregulated and high insulin secretion (15).

Patient number two was homozygous for a missense mutation, G40A, in the KCNJ11 gene, which has been reported previously. This result confirms a diagnosis of autosomal recessive congenital hyperinsulinism (17).

Patient number three was homozygous for two mutations, F117 del and P340H, in the KCNJ11 gene. It is therefore likely, although not certain, that one or both of the F117 del and P340H mutations are pathogenic. This result confirms a diagnosis of autosomal recessive congenital hyperinsulinism (18).

Patient number five and six were homozygous for a nonsense mutation, R236X, in exon 6 of the HADH gene. This mutation has been previously reported. This result confirms a diagnosis of autosomal recessive congenital hyperinsulinism (19, 20).

In this study the frequencies of mutation in three genes ABCC8, KCNJ11, and HADH were the same. Each gene was responsible for the disease in one third of the patients. Clearly this figure is different from the data reported in other studies. But on the other hand the number of patients that were investigated in our study is not large enough to elucidate the reliable frequencies for the genes involved in causing congenital hyperinsulinism in Iranian population. Therefore the different frequencies in genes causing the disease in Iranian population cannot be established by this study.

The summary of the results are shown in Table 2.

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Footnote

Authors' Contribution: Study concept and design: Mohammad Reza Alaei; acquisition of data: Mohammad Reza

Alaei, Susan Akbaroghli, and Ali Alaei; analysis and interpretation of data: Mohammad Reza Alaei, Susan Akbaroghli, and Ali Alaei; drafting of the manuscript: Susan Akbaroghli; critical revision of the manuscript for important intellectual content: Susan Akbaroghli, Mohammad Reza Alaei and Mohammad keramatipour; statistical analysis: Susan Akbaroghli, Mohammad Reza Alaei and Mohammad Keramatipour; administrative, technical, and material support: Mohammad Reza Alaei; study supervision: Mohammad Reza Alaei.

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