Original Article

Persistent Hyperinsulinemic Hypoglycemia in Iraqi Pediatric Population: A Single Tertiary Center Experience

Munib Ahmed Al-Zubaidi, Wasnaa Hadi Abdullah[1], Khalid Hatem Kareem[2]

Department of Pediatrics, College of Medicine, University of Baghdad, Baghdad, [1]Department of Pediatrics, College of Medicine, Mustansiriyah University, Baghdad, [2]Department of Pediatrics, Children Welfare Teaching Hospital, Medical City, Baghdad, Iraq

Abstract

Background: Congenital hyperinsulinism (CHI) is an inappropriate insulin secretion by the pancreatic cells. When medical therapies are ineffective, surgical treatment is required. **Objective:** This study aims to evaluate the clinical characteristics of CHI patients and assess the associated factors that may affect their response to treatment. **Materials and Methods:** This is a retrospective study including all patients diagnosed with hyperinsulinemic hypoglycemia who were registered at the Children Welfare Teaching Hospital in Baghdad, Iraq. Patients' data were collected including birth weight, age at presentation, and consanguinity between parents. All patients had a confirmed diagnosis of hyperinsulinism after performing a critical sample. The data of these investigations were collected in addition to the type of medical treatment they received and those who had finally undergone pancreatectomy. **Results:** Among the 44 patients in the study, 38 (86.4%) presented in the first year of life. Of these, 22 (57.9%) were responsive to diazoxide. In addition, 13 (34.2%) of those presenting in the first year required pancreatectomy. Among the remaining six patients who presented after the first year of life, three (50%) responded to diazoxide, while two (33.3%) required pancreatectomy. Patients who did not respond to diazoxide had higher mean insulin and age at presentation with 19.58 ± 17.28 μU/ml and 9.73 ± 28.23 months, respectively. **Conclusion:** While genetic study remains the gold standard for the diagnosis of CHI, clinical characteristics of patients can be the only helpful way to predict further management in countries with limited resources.

Keywords: Diazoxide, hyperinsulinism, hypoglycemia, pancreatectomy

Introduction

Congenital hyperinsulinism (CHI) is an inappropriate insulin secretion by the pancreatic β-cells secondary to various genetic disorders.[1,2] The incidence of hyperinsulinism (HI) is estimated to be 1/50,000 live births (up to 1/2500 in Saudi Arabia due to high consanguinity rate). ABCC8 and KCNJ11 genes mutations are the most common causes of HI, making up 40%–45% of all cases (and accounting for 82% of patients who are not responsive to diazoxide),[3] whereas mutations on six other genes have been found in approximately 5%–10% of the cases, and for the remaining 45%–55% of patients, the underlying genetic cause is still undetermined.[4] Transient HI, which is more common, is frequently linked to prenatal or perinatal conditions such maternal gestational diabetes, birth asphyxia, or low birth weight.[5] In addition, syndromic genetic conditions such as Beckwith–Wiedemann syndrome might have HI in their manifestations.[6] During the neonatal period, seizures occur in 50% of patients with severe hypoglycemia. The majority of the affected babies are macrosomic at birth, with about 30% necessitating cesarean delivery. It can require as much as 17 mg/kg/min of intravenous glucose, on average, to keep plasma glucose levels above 3 mmol/L.[1,7]

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Address for correspondence: Dr. Wasnaa Hadi Abdullah, Department of Pediatrics, College of Medicine, Mustansiriyah University, Baghdad, Iraq..
E-mail: Wasnaa.hadi@uomustansiriyah.edu.iq

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Hypoglycemias throughout infancy and childhood may be identified in half of the patients between 1 and 12 months of age, or even later in life, occasionally due to a delayed diagnosis. Seizures or drowsiness bouts are the symptoms that first appear before the age of 1 year. The signs of hypoglycemia after 1 year include pallor, fainting, sweating, and convulsions. The characteristics of hypoglycemia are parallel, although lower rates of intravenous glucose (12–13 mg/kg/min) are required to maintain normal plasma glucose levels during infancy and childhood.[7] A diagnosis of HI must meet certain criteria, including hypoketotic hypoglycemia, inappropriate plasma insulin and C-peptide levels in conjunction with hypoglycemia (insulin levels should be undetectable at the time of hypoglycemia), an increase in blood glucose greater than 1.7 mmol/L within 30–40 min of receiving 1 mg of glucagon intramuscularly or intravenously (IV), and inappropriately low ketone bodies in urine and plasma and low free fatty acids in plasma.[8] Diffuse and focal histological lesions of HI are clinically indistinguishable from one another. The diagnosis of the two forms is aided by genetics and ^{18}F-fluoro-L-DOPA positron emission tomography (PET). To avoid serious and irreparable brain damage, hypoglycemia must be treated quickly and aggressively. This includes correcting hypoglycemia at the time of its occurrence with a glucose load and/or glucagon injection. Then, an approach to treatment must be determined to prevent hypoglycemia from happening again. This may involve frequent feedings with added glucose, diazoxide, and octreotide. When medical therapies are ineffective, surgical treatment is required. When the entire lesion is removed during the partial pancreatectomy, focal HI may be permanently healed. Conversely, the long-term prognosis of diffuse HI following subtotal pancreatectomy is marked by a significant chance of developing diabetes, but the timing of this is barely foreseeable.[1] Managing patients with severe HI is difficult and necessitates a multidisciplinary team, including: clinicians, surgeons, geneticists, and pathologists. Additionally, due to a paucity of information regarding the long-term neurological and glycemic outcomes of patients according to the type of management (surgical or intense medical treatment), treatment strategies vary significantly among teams worldwide.[1] This study aims to evaluate the clinical characteristics of CHI patients and assess the associated factors that may affect their response to treatment.

Materials and Methods

This is a retrospective study including all patients with HI hypoglycemia who were registered in the endocrine clinic or admitted to the ward of the Children Welfare Teaching Hospital/Medical City Complex in Baghdad, Iraq over a period of 5 months from January 1, 2023 to June 1, 2023. The data were collected from patients' records and some from the parents themselves. With some differences based on the timing of referral to a tertiary center and the availability of drugs, the cases were handled in accordance with the generally accepted international guidelines for treating CHI. Patients' clinical data were collected, including name, sex, gestational age, date of birth, birth weight, mode of delivery, symptoms at presentation (such as fit and lethargy), age at presentation, age at onset of hypoglycemia, consanguinity between parents, and family history of hypoglycemia or diagnosed CHI. Physical examinations (both general and systemic) were done for all patients to exclude any systemic illness that may cause hypoglycemia, including any dysmorphic features or any developmental delay to exclude syndromes. All the patients included in this study had a confirmed diagnosis of HI after undergoing a critical sample inpatient. The following investigations for the critical sample were done when random blood sugar levels fell below 50 mg/dL: C-peptide, insulin levels, cortisol, adrenocorticotropic hormone, growth hormone, and ketone in urine. This is followed by glucagon stimulation test. The diagnosis of hyperinsulinemic hypoglycemia was established when the patient had normal or high levels of insulin (>2 μU/mL), C-peptide (≥0.5 ng/dL), and an inappropriate response to glucagon injection (>30 mg increment in glucose level after 40 min) with absence of ketonuria.[9] Ultrasound of abdomen was done for all patient to exclude any organomegaly or pancreatic mass or cyst. Magnetic resonance imaging of the abdomen done for all patients prior to pancreatectomy. The treatment of hypoglycemia includes glucose water IV infusion in different concentrations to correct hypoglycemia, together with diazoxide when available, and octreotide subcutaneously in multiple doses. Those who responded to diazoxide were maintained on it, while those who did not respond were kept on octreotide injection, especially those whose families refused pancreatectomy.

Statistical analysis

Data were entered using Microsoft® Excel® 365, and the statistics were analyzed using IBM SPSS statistical software version 26 (IBM Corporation, Armonk, New York). Data are expressed as mean ± standard deviation and as groups. In this study, Pearson's correlation coefficient (r) was performed to examine the correlation between multiple parameters. Chi-square test was used to check for the independence of specific variables, and one-way analysis of variance (ANOVA) was used to analyze dependent variables. A P value of <0.05 was considered significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The data were collected from patients' records and some directly from the parents after obtaining

Table 1: Patients' characteristics according to the age of presentation

Variable		Total	<1 Year	>1 Year	*P*-value
		No. (%)	No. (%)	No. (%)	
Sex	Total	44 (100)	38 (86.4)	6 (13.6)	0.318
	Male	23 (52.3)	21 (55.3)	2 (33.3)	
	Female	21 (47.7)	17 (44.7)	4 (66.7)	
Mode of presentation	Total	44 (100)	38 (86.4)	6 (13.6)	0.153
	Fit	34 (77.3)	28 (73.7)	6 (100)	
	Lethargy	10 (22.7)	10 (26.3)	0 (0)	
Weight at birth	Total	41 (100)	36 (87.8)	5 (12.2)	0.125
	LGA	12 (29.3)	12 (33.3)	0 (0)	
	Normal	29 (70.7)	24 (66.7)	5 (100)	
Mode of delivery	Total	41 (100)	36 (87.8)	5 (12.2)	0.305
	C/S	25 (61)	23 (63.9)	2 (40)	
	NVD	16 (39)	13 (36.1)	3 (60)	
Family history	Total	43 (100)	37 (86)	6 (14)	0.782
	Negative	34 (79.1)	29 (78.4)	5 (83.3)	
	Positive	9 (20.9)	8 (21.6)	1 (16.7)	
Consanguinity	Total	43 (100)	37 (86)	6 (14)	0.738
	Negative	17 (39.5)	15 (40.5)	2 (33.3)	
	Positive	26 (60.5)	22 (59.5)	4 (66.7)	
Response to diazoxide	Total	44 (100)	38 (86.4)	6 (13.6)	0.717
	Negative	19 (43.2)	16 (42.1)	3 (50)	
	Positive	25 (56.8)	22 (57.9)	3 (50)	
Pancreatectomy	Total	44 (100)	38 (86.4)	6 (13.6)	0.966
	Negative	29 (65.9)	25 (65.8)	4 (66.7)	
	Positive	15 (34.1)	13 (34.2)	2 (33.3)	
Seconnd pancreatectomy	Total	44 (100)	38 (86.4)	6 (13.6)	0.565
	Negative	42 (95.5)	36 (94.7)	6 (100)	
	Positive	2 (4.5)	2 (5.3)	0 (0)	

Chi-square test (any value below 0.05 is considered significant)

LGA: large for gestational age, C/S: cesarean section, NVD: normal vaginal delivery

ethical approval from the hospital's ethical committee (ethical approval number: 60, dated September 1, 2022). Additionally, data were collected from parents during their visits to the endocrine clinic, ensuring the confidentiality of the personal information and its use solely for thesis purposes.

Results

Among the 44 patients included in the study, 86.4% presented in the first year of life. Males were the dominant sex among patients presented in the first year of life, with 21 cases, while females were the dominant sex after the first year of life. According to mode of presentation, fit was the dominant presentation in the first year and after the first year of life. According to weight at birth, 33.3% of 36 patients who presented in the first year of life were large for gestational age (LGA) at birth, and all patients born with LGA presented in the first year of life. However, weight at birth did not influence the age of presentation with no statistical significance, with a *P* value of 0.125. According to family history of hypoglycemia or CHI, only 21.6% of patients presented in the first year, and 16.7% of patients presented after the first year had a positive family history. Regarding diazoxide response, 57.9% of patients presented in the first year and 50% of patients presented after first year of life were responsive to diazoxide. Of the patients presented in the first year, 34.2% patients required pancreatectomy, while 33.3% of those presented after the first year required the same procedure. Only two patients required a second operation, all of whom were presented in the first year of life, as shown in Table 1.

Females had higher mean insulin, C-peptide, and age at presentation with 16.79 ± 16.72 μU/mL, 4.16 ± 2.4 ng/mL, and 9.34 ± 26.89 months consequently, while males had higher mean birth with weight [Table 2]. Patients who did not respond to diazoxide had higher mean insulin, C-peptide, and age at presentation than the responders. However, only the insulin level showed a statistically significant difference between responders and non-responders, with a *P* value of 0.009 [Table 2].

Patients presented with fit had higher mean insulin, birth weight, and age at presentation. Patients born to consanguineous marriage had higher insulin, C-peptide,

Table 2: Mean birth weight, insulin, C-peptide, and age at presentation according to multiple variables

Variable		Insulin level (μU/mL)	C-peptide (ng/dL)	Birth weight (kg)	Age at presentation (months)
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Total		13.59 ± 13.11	3.74 ± 2.08	3.38 ± 0.73	7.87 ± 23.83
Sex	Male	10.52 ± 7.59	3.33 ± 1.66	3.49 ± 0.86	6.53 ± 21.19
	Female	16.79 ± 16.72	4.16 ± 2.4	3.27 ± 0.57	9.34 ± 26.89
	P value	0.118	0.197	0.340	0.701
Response to diazoxide	Responsive	9.27 ± 6.55	3.33 ± 1.72	3.4 ± 0.64	6.45 ± 20.37
	Non-responsive	19.58 ± 17.28	4.35 ± 2.45	3.37 ± 0.85	9.73 ± 28.23
	P value	0.009	0.119	0.901	0.657
Mode of presentation	Fit	14.02 ± 14.41	3.68 ± 2.23	3.44 ± 0.72	9.96 ± 26.82
	Lethargy	12.16 ± 7.84	3.95 ± 1.6	3.2 ± 0.77	0.77 ± 1.86
	P value	0.700	0.731	0.369	0.289
Consanguinity	Positive	15.61 ± 15.63	3.84 ± 2.29	3.43 ± 0.71	10.1 ± 29.54
	Negative	10.93 ± 8.31	3.62 ± 1.86	3.31 ± 0.79	4.92 ± 11.91
	P value	0.266	0.754	0.613	0.497
Family history	Positive	14.57 ± 10.21	3.56 ± 1.66	3.14 ± 0.52	2.45 ± 4.11
	Negative	13.52 ± 13.99	3.8 ± 2.22	3.43 ± 0.78	9.53 ± 26.9
	P value	0.842	0.772	0.357	0.439
Pancreatectomy	Yes	15.05 ± 8.27	3.89 ± 1.51	3.62 ± 0.84	3.91 ± 9.52
	No	12.88 ± 14.99	3.67 ± 2.34	3.26 ± 0.65	9.92 ± 28.54
	P value	0.617	0.757	0.134	0.434
Mode of delivery	C/S	13.54 ± 9.53	3.76 ± 1.79	3.53 ± 0.8	4.88 ± 19.41
	NVD	14.42 ± 18.1	3.67 ± 2.6	3.18 ± 0.6	13.15 ± 31.19
	P value	0.839	0.897	0.141	0.300

One-way ANOVA (any value < 0.05 is considered significant)

C/S: cesarean section, NVD: normal vaginal delivery

birth weight, and age at presentation. Patients with positive family history for HI had higher mean insulin level and lower C-peptide, birth weight, and age of presentation. Patients presented before the first year of life had higher mean birth weight, while they had lower mean insulin and C-peptide. Insulin level had statistically significant difference between the two groups, with a *P* value of 0.04. Patients who required pancreatectomy had higher mean insulin, C-peptide, and birth weight [Table 2].

Early age of presentation before the first year of life was the most sensitive factor for diazoxide response, with 88%, yet it had high negative predictive factor with 50% [Figure 1]. Later age of presentation after the first year of life was the most specific factor (84%) for diazoxide response, yet it had the lowest sensitivity with 12% [Figure 2]. High weight at birth had the highest positive predictive value for diazoxide response with 67%.

There was a statistically significant positive correlation between insulin and age at presentation (*P* value < 0.001). However, there was a negative correlation between weight at birth and age at presentation, although it was not statistically significant, with a *P* value of 0.387. Insulin and C-peptide levels were positively correlated with birth weight, but these correlations were not statistically significant, with *P* values of 0.959 and 0.939, respectively.

Discussion

In this study, 86.4% of patients presented in the first year of life, while 13.6% presented after the first year of life. These results are consistent with previous studies, which have shown that hypoglycemia presents in the majority of cases (60%–70%) during the first year of life,[1,10] with around 10% of patients presenting and being diagnosed after the first year of age.[1,10]

Males were the dominant among patients presented in the first year of life, while females were the dominant after the first year of life. However, previous studies did not identify sex as a risk factor for developing hypoglycemia.[11] In contrast, female infants were found to have a three-times higher risk of developing hypoglycemia in the study by Ahel *et al*.[12] It is possible that an undetected confounding factor led to our results, especially that the aforementioned study was conducted in premature babies.

According to the mode of presentation during infancy and childhood, seizures are the first sign of hypoglycemia in half of individuals.[1] However, in this study, fits were dominant both in the first year and after, accounting for 28 (73.7%) and 6 (100%) cases, respectively. This may be explained by delayed diagnosis of condition.

Newborns with HI may be macrosomic due to intrauterine hyperinsulinemia; however, the absence of macrosomia

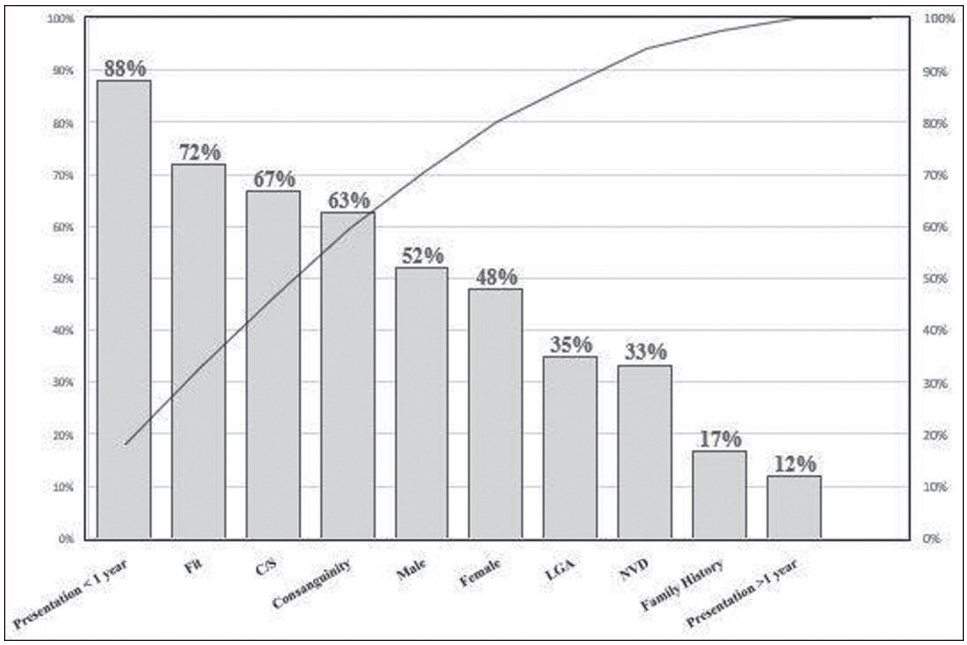

Figure 1: Sensitivity to Diaxoxide response according to specific parameters

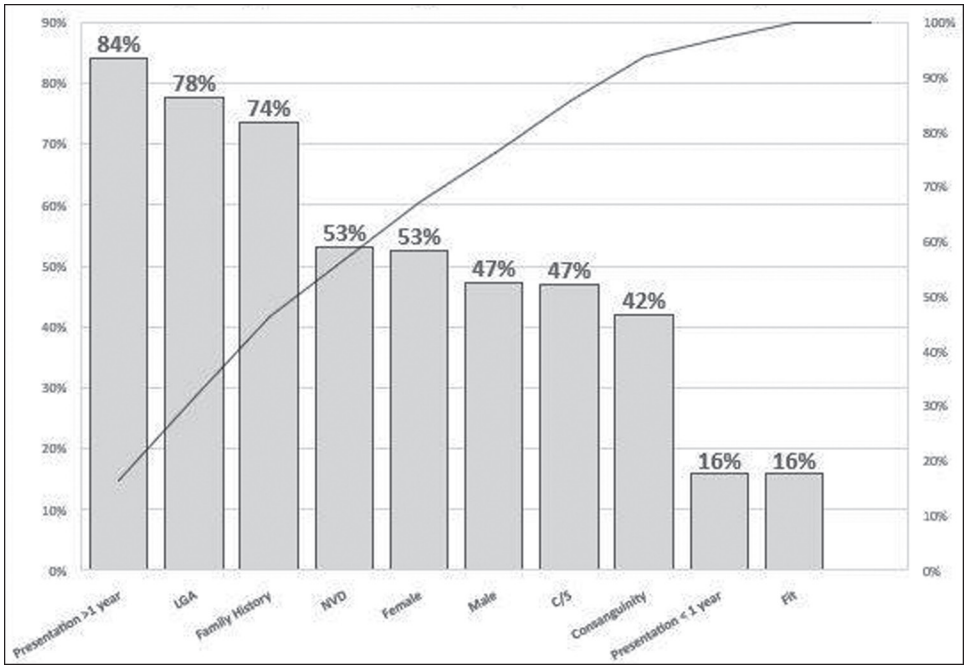

Figure 2: Variable specificity for Diaxoxide response

does not rule out CHI.[13] In our study, we noticed that 12 out of 36 patients (33.3%) who presented before the first year of life were LGA at birth, while all patients who presented after the first year of life were born with normal birth weight.

Regarding diazoxide responsiveness, 57.9% patients presented in the first year and 50% of patients presented after first year of life were responsive to diazoxide. For the purpose of directing genetic testing in CHI patients, birth weight and responsiveness to diazoxide treatment can be used. A study by Hewat *et al*,[14] showed that simple clinical characteristics, such as birth weight and diazoxide responsiveness, were highly predictive for identifying individuals with K_{ATP} CHI from those with CHI of undetermined etiology. More than 80% of cases born LGA or average birth weight who were unresponsive to diazoxide had K_{ATP} channel mutations. Hence, it is imperative that every attempt be made to prioritize genetic testing in these individuals, as finding a K_{ATP} mutation can guide clinical management.[15] This offers vital evidence

in this respect, which is especially pertinent for resource-poor nations with restricted access to genetic testing.

Regarding the consanguinity, more than two thirds of our patients had a consanguineous parents. This can be explained by the inheritance pattern in CHI, in which the autosomal recessive inheritance is more common, but less frequently autosomal dominant inheritance can also be seen.[16] Our study result is higher than that of Laimon *et al.*'s study[17] in Egypt, in which positive consanguinity was found in 45.2% of patients. This difference may be attributed to different sociocultural factors between the two countries.

Two histological types of CHI, focal and diffuse forms, have been identified based on the pathogenesis process. These two types cannot be differentiated based on clinical or biochemical characteristics.[16] During the two-decade study period from 1998 to 2018 at the Children's Hospital of Philadelphia,[18] 500 neonates and children underwent pancreatectomy. The age when the operation was done ranged from 1 week to 26 months. In our study, nearly one third of patients required pancreatectomy. Only 2 (4.5%) out of 42 patients required a second operation, all of whom presented in the first year of life. Our study result is lower than that of Laimon *et al.*'s study[17] in Egypt, in which 50% of patients were resistant to medical therapies and needed pancreatic surgery. This may be explained by differences in medical treatment response between the two samples of children, in addition to differences in the causative genes. It is worth noting that although diffuse disease cannot be cured by surgery, it can reduce the risk of severe hypoglycemia and brain damage.[18]

This study showed that females had higher mean insulin, C-peptide, and age at presentation. However, there is no literature available to support sex-related genetic differences in CHI,[17] thus it is most likely just coincidence.

In this study, patients presented with fit had a higher mean insulin level. However, previous studies showed that there is no correlation between the serum insulin level and the severity of hypoglycemia. Even a "normal" insulin level is usually inappropriate in the presence of hypoglycemia.[2]

Consanguineous families frequently play a role in the detection of novel genes, particularly in pediatric endocrinology. In children with endocrine disorders, specifically CHI, from consanguineous families, there is a higher likelihood that a single-gene disorder with autosomal recessive inheritance is causative.[19] In our study, patients born to consanguineous marriages had higher levels of insulin, C-peptide, and birth weight. This can be explained by recessive homozygous mutations, which usually cause severe forms of diazoxide-unresponsive CHI, although unfortunately, our limited resources hindered genetic profiling studies. In another way, in our study, both groups of patients—those who did not respond to diazoxide and those born to consanguineous marriages—had higher mean insulin and C-peptide. This supports the conclusion of Raicevic *et al.*'s study in Serbia,[20] which suggests that the majority of CHI patients in countries with low consanguinity rates are diazoxide responsive.

In this study, high weight at birth had the highest positive predictive value for diazoxide response with 67%. Conversely, according to the study conducted by Hewat *et al.*,[14] higher birth weight intensely predicts the possibility of CHI due to mutations in ABCC8 or KCNJ11 genes, with most of these patients not responding to diazoxide treatment. Additionally, 86% of infants born large for gestation age who did not respond to diazoxide treatment were diagnosed with K_{ATP}-HI. In contrast, none of the patients born small for their gestational age responded to diazoxide.

Small for gestational age infants had significantly lower body fat at birth compared to LGA infants, which made them more susceptible for hypoglycemia.[21] Body fat is now recognized not only as a source of energy but also as a highly active secreting organ.[22]

It is known from the study of food biochemistry that additional energy sources can be employed in place of glucose and can even provide the brain with the energy it needs.[23] However, insulin promotes lipogenesis, prevents the release of free fatty acids and their beta-oxidation, which prevents the creation of ketone bodies. This explains the hypoketotic state, which reduces the amount of substitute fuels that the brain may use for metabolism. Neonates are more susceptible to hypoglycemic brain damage because their brains consume more glucose than those of adult subjects.[24]

The management strategy for our study's patients was influenced by a number of aspects. First, extremely expensive ^{18}F-fluoro-L-DOPA PET for patients families. Second, while octreotide and diazoxide are both considered first-line treatments for CHI, they are not always readily available or cost-effective for all patients. In addition, genetic testing for CHI is not accessible in Iraq, necessitating the sending of samples abroad. This can lead to delays in receiving results, as well as being expensive and out of reach for most families.

Conclusions

Most of the patients with CHI presented in the first year of life. Fit was the dominant symptom in first year and after the first year of life. Early age of presentation before the first year of life was the most sensitive factor for diazoxide response. High weight at birth had the highest positive predictive value for diazoxide response. Despite genetic studies being the gold standard for diagnosing CHI, clinical characteristics of patients can serve as the primary means to predict response to medical treatment

and guide further management in countries with limited resources.

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Conflicts of interest

There are no conflicts of interest.

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