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Persistent Hyperinsulinemic Hypoglycemia of Infancy, Clinical Presentation and Treatment

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Abstract: Background Persistent hyperinsulinemic hypoglycemia of infancy also known as, congenital hyperinsulinism, is a collection of disorders that lead to persistent hypoglycemia, a result of the congenital excess of insulin secretion, and is not to be mistaken with acquired forms, which include insulinoma, iatrogenic hyperinsulinemia, and dumping syndrome. It is the most likely cause of persistent hypoglycemia in the infants and neonates.

Aims of the study

To study demographic & clinical features of patients with congenital hyperinsulinism & response to treatment.

Patients and methods

Case-series study was carried out on patients with congenital hyperinsulinism, who diagnosed and/or treated at Children Welfare Teaching hospital, Baghdad Medical City started on 1st of January 2013 and ended on 30th of October 2019. In this study out of 35 patients diagnosed as congenital hyperinsulinism, only 27 patients were studied (8 patients were excluded because of lost follow up)

Results

All patients were full term except for one patient was preterm.

All patients had mothers without diabetes mellitus except for one

Patient who had mother with gestational diabetes, 17(62%) patients were male & 10(38%) patients were female.

The birth weights were ranged from 3 to 5.2 kg (median 3.5 kg), with 11(40%) patients were macrosomic.

The age at presentation was ranged from 1 day to 45 months (median 1 day).

The age at diagnosis was ranged from 2 day to 48 months (median 2 months), 13(48%) patients were products of normal vaginal delivery, 14(52%) patients were products of caesarian section, 5(18%) patients had positive family history of affected siblings.

The parent's consanguinity was found in 22 (81%) patients.

The blood glucose level during critical sample was ranged from 8 to 49 mg/dl (median 30 mg/dl).

The insulin level during critical sample was ranged from 2.6 to 182 Mu/ml (median 16.5 Mu/ml)

The insulin to glucose ratio was ranged from 0.06 to 9.57 (median 0.72).

Nine patients were never treated with diazoxide because the drug was not available, the remaining patients (18) were treated with diazoxide, only 4 (22%) patients were diazoxide – responsive.

All 27 patients were treated with octreotide, only 13(48%) patients were responded to octreotide.

Thirteen (48%) patients were underwent subtotal pancreatectomy, with 1 (8%) patient, was underwent 2nd pancreatectomy.

Postoperatively 1(8%) patient developed diabetes mellitus &required insulin therapy, 12(92%) patients were still hypoglycemic & required octreotide &frequent feedings to control their blood glucose level.

We come to the conclusion that the congenital hyperinsulinism is rather widespread in Iraq, and it is associated with the high consanguinity.

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy also called Congenital hyperinsulinism (CHI) is a set of diseases that result in persistent hypoglycemia as a result of excessive secretion of insulin, which is congenital, and is not related to acquired disease, including insulinoma, iatrogenic hyperinsulinemia or dumping syndrome. It is the most widespread cause of continuing hypoglycemia in neonates and infants (1,2), First was referred to as idiopathic hypoglycemia of infancy by MacQuarrieas (3).

The global incidence of congenital hyperinsulinism stands at 1 per 50000 live births with the highest incidence of up to 1 per 2500 in regions with high rate of consanguineous marriages (2).

Inactivated KATP channels mutations that are causing the most common and the most severe type of congenital hyperinsulinism(KATP-hyperinsulinism KATP HI).

KATP HI divided to three subtypes depending on the severity of the molecular defect and the phenotype:

Recessive, diazoxide-unresponsive; (2) dominant, diazoxide-unresponsive; and (3) dominant, diazoxide-responsive. [(4)]

There are few treatment options of diazoxide-unresponsive cases. In most cases, these babies may need pancreatic surgery in their early weeks of birth to control the hypoglycemia. Diazoxide on the other hand is highly efficient in the management of hypoglycemia in cases where KATP HI is dominant diazoxide responsive. Octreotide, a long-acting analog of somatostatin, is a second line medication treatment of infants who do not respond to diazoxide, A nonsurgical intervention in diazoxide-unresponsive hyperinsulinism combining octreotide with either continuous or frequent enteral nutrition is a proposed intervention (5).. It would be difficult to manage such children at home, feeds have to be administered every 2-3 hours per day, glucose levels have to be checked frequently, and oral feeding abilities might be lost.

KATP-hyperinsulinism has two unique histologic types, focal and diffuse hyperinsulinism.

A. Focal KATP-Hyperinsulinism (Focal Adenomatosis). The focal disease is found in approximately 40-60 percent of the cases of KATPHI (that necessitate surgery) (6). Most of the mutations that result in the focal lesions are the ABCC8 gene (7).

B. Diffuse Hyperinsulinism. In diffuse hyperinsulinism, the entire B-cells in the pancreas are involved. It is caused by two recessive mutations in ABCC8 or KCNJ11 or a dominant mutation in the these genes.

The focal and diffuse types of hyperinsulinism are clinically the same in the presentation and in the absence of diazoxide response.

There is a possibility of focal KATP HI) being curable through surgery but diffuse KATP HI cannot. Thus, in preoperative infants with diazoxide-unresponsive hyperinsulinism, the need to diagnose and localize focal lesions is crucial.

The positron emission tomography (PET) scanning of flurorine-18 L-3, 4 dihydroxyphenylalanine (18 F-fluoro-L-DOPA) is the gold standard method of localizing the focal lesions. L-DOPA is uptaken by pancreatic B-cells (8) and DOPA decarboxylase is found in pancreatic islet cells (9). In focal hyperinsulinism in children the accumulation of 18 F-fluoro-L-DOPA is localized.

PET/CT co-registration makes the anatomic localization possible.

of the lesion.

Aims of the study.

- To study demographic and clinical features of patients with congenital hyperinsulinism
- To find out response to diazoxide, octreotide and the pancreatectomy.

Patients and methods

Case-series study was carried out on patients with congenital hyperinsulinism, who were diagnosed and treated at Children Welfare Teaching hospital, Baghdad Medical City from 1st of January 2013 to 30th of October 2019.

Information regarding (name, sex, birth weight, age at presentation, age at diagnosis, mode of delivery, family history, parents consanguinity, glucose level& insulin level of critical sample, response to diazoxide& octreotide, type of pancreatectomy) were obtained from the parents and the records of the patients. The presentation of patients with hypoglycemia includes poor feeding, lethargy, seizure, cyanosis& apnea. In this study out of 35 patients diagnosed as congenital hyperinsulinism, only 27 patients were studied (8 patients were excluded because of lost follow up). Patients with Beckwith-Wiedemann syndrome, hyperinsulinism relates to the infant of the diabetic mother were excluded. Critical samples were done for all patients and their results of growth hormone, adenocorticotropic hormone (ACTH) and cortisol levels were normal. MRI was done for all patients who were underwent pancreatectomy before operation and the results were normal.

The diagnosis was made according to critical sample. Statistical analysis was done using median. The definitions used to describe patients in this study

1. Critical Sample: Diagnostic criteria of hyperinsulinism by critical Samples (that are accomplished at fasting when the patient shows hypoglycemia: plasma glucose less than 50 mg/dl with the following findings:

A. Hyperinsulinemia (insulin level of more than 2 mU/mL), and an elevated or normal, C-peptide level.

B. High glucose need >6-8mg/kg/min to sustain blood glucose level of>50mg/dL. C. Low ketones level (- ve ketonuria).

C. (Inappropriate glycemic response to) glucagon, 1mg IV (delta glucose 30 mg/dl) (10).

2. Responsive to diazoxide (+ve): Diazoxide should be determined to have been effective at an endpoint of no less than 5 days after initiation. Good response would be manifested by the ability to maintain plasma glucose at above 3.3mmol/L (70 mg/dl) following fasting(11).

Unresponsive to diazoxide (-ve): No response to dosage of diazoxide.

15mg/kg/d following a minimum of 5 days of diazoxide (12-16).

3. Response to octreotide, the dose was started at 5 Mg/kg/day and in response to the glycemic control there was an increment of 5 Mg/kg/day at intervals of 3 to 5 days up to the maximum dose of 30 Mg/kg/day. Response to octreotid was positive in the maintenance of normoglycemia with no intravenous dextrose.

Unresponsive to octreotide: patients who were unable to be tapered off intravenous dextrose when taking maximum dose of octreotide (16-18).

4. Macrosomia: at birth, the weight is 4000 gm and above (19).

Results

All patients were full term except for one patient (no.2) was preterm.

All patients had mothers without diabetes mellitus except for one patient (no.11) who had mother with gestational diabetes. Seventeen (62%) patients were male & 10(38%) patients were female, with male: female ratio 1.7: 1

The birth weights were ranged from 3 to 5.2 kg (median 3.5 kg), with 11(40%) patients were macrosomic.

Table-1 birth weights of patients with CHI.

Sex	Birth weight <4 kg	Birth weight ≥ 4 kg
Male	10 (37%)	7 (25%)
Female	6 (23%)	4 (15%)
Total	16(60%)	11 (40%)

The age at presentation was ranged from 1 day to 45 months (median 1 day).

Table-2 the age at presentation of patients with CHI.

Sex	Neonatal period	Beyond neonatal period
Male	8 (30%)	9 (33%)
Female	10 (37%)	0
Total	18 (67%)	9 (33%)

The age at diagnosis was ranged from 2 day to 48 months (median 2 months), with different time intervals from 1st presentation till age of diagnosis, with delay in diagnosis in about one third of patients.

Table-3 the time intervals from 1st presentation till age of diagnosis in patients with CHI.

Sex	≤ 1 month	>1month-<1year	≥ 1year
Male	10 (37%)	5 (18%)	2 (8%)
Female	9 (33%)	1 (4%)	0
Total	19 (70%)	6 (22%)	2 (8%)

Thirteen (48%) patients were products of normal vaginal delivery, 14(52%) patients were products of caesarian section.

Five (18%) patients had family history of affected siblings.

The parent's consanguinity was found in 22(81%) patients.

The blood glucose level during critical sample was ranged from 8 to 49 mg/dl (median 30 mg/dl).

The insulin level during critical sample was ranged from 2.6 to 182 Mu/ml (median 16.5 Mu/ml).

The insulin to glucose ratio was ranged from 0.06 to 9.57 (median 0.72).

Nine patients were never treated with diazoxide because the drug was not available, the remaining patients (18) were treated with diazoxide, only 4(22%) patients were diazoxide – responsive.

Table-4 the response to diazoxide in patients with CHI.

Sex	Diazoxide-responsive(+ve)	Diazoxide-unresponsive(-ve)
Male	4 (22%)	8 (45%)
Female	0	6 (33%)
Total	4 (22%)	14 (78%)

All 27 patients were treated with octreotide, only 13(48%) patients were responded to octreotide.

Table-5 the response to octreotide in patients with CHI.

Sex	Octreotide-responsive(+ve)	Octreotide-unresponsive(-ve)
Male	10 (37%)	7 (26%)
Female	3 (11%)	7 (26%)
Total	13 (48%)	14 (52%)

The patient (no.5) was not responded to both diazoxide & octreotide but his family did not consent for surgery.

Thirteen (48%) patients were underwent subtotal pancreatectomy, with 1(8%) patient (no.25) was underwent 2nd pancreatectomy all those patients were underwent MRI of pancreas preoperatively &the results were normal (18f- L-dopa PET scan was not done for all patients because it was not available).

Table-6 patients with CHI underwent subtotal pancreatectomy.

Sex	***Subtotal pancreatectomy***	%
Male	6	46%
Female	7	54%
Total	13	100%

Postoperatively 1(8%) patient developed diabetes mellitus &required insulin therapy, 12(92%) patients were still hypoglycemic & required octreotide &frequent feedings to control their blood glucose level

Table-7 the Clinical characteristics of patients with CHI.

Patient	Sex	Birth Weight (gram)	Age at presentation	Age at diagnosis	Type of labor	Family history	Parents Consanguinity	Glucose level Mg/dl	Insulin level MU/ml	I/G Ratio	Response to diazoxide	Response to octreotide	Operation	Outcome
1	F	3500	1 d	3 d	Nvd	-ve	+ve	46	7.8	0.17	Not used	+ve	No	
2	F	3500	1 d	1 m	c/s	-ve	+ve	23	18.1	0.78	-ve	-ve	SP	Hypo
3	M	3400	1 d	7 d	Nvd	+ve	+ve	36	9.8	0.27	-ve	+ve	no	
4	F	4000	1 d	22 d	c/s	-ve	+ve	32	23.2	0.72	Not used	-ve	SP	Hypo
5	M	5000	1 d	5 m	Nvd	-ve	+ve	12	41	3.41	Not used	-ve	no	
6	F	3700	1 d	10 d	c/s	-ve	+ve	8	25.5	3.18	-ve	-ve	SP	Hypo
7	F	4250	1 d	2 d	Nvd	-ve	+ve	30	2.6	0.08	Not used	-ve	SP	Hypo
8	F	3000	1 d	4 d	c/s	-ve	+ve	13	19.9	1.53	-ve	-ve	SP	DM
9	M	5000	1 d	2 m	Nvd	-ve	+ve	27	15.5	0.57	-ve	-ve	SP	Hypo
10	F	5000	1 d	9 d	Nvd	+ve	+ve	17	161	9.47	-ve	-ve	SP	Hypo
11	F	5000	1 d	2 m	c/s	-ve	+ve	14	16.5	1.17	-ve	-ve	SP	Hypo
12	F	3500	1 d	1 m	c/s	-ve	+ve	42	100	2.38	Not used	+ve	no	
13	F	3000	1 d	5 d	Nvd	+ve	+ve	30	6.5	0.22	-ve	+ve	no	
14	M	5200	1 d	2 d	c/s	+ve	-ve	37	29	0.78	-ve	+ve	no	
15	M	4000	1 d	3 m	c/s	-ve	+ve	28	16	0.57	Not used	+ve	no	
16	M	4300	2 d	7 d	c/s	-ve	+ve	41	8.3	0.20	Not used	+ve	no	
17	M	3500	4 m	4.5 m	Nvd	-ve	+ve	46	162	3.52	+ve	+ve	no	
18	M	3250	45 d	55 d	c/s	-ve	-ve	49	5	0.10	Not used	+ve	no	
19	M	3400	3 m	24 m	c/s	-ve	+ve	39	2.8	0.07	Not used	+ve	No	

Patient	Sex	Birth weight (grams)	Age at presentation	Age at diagnosis	Type of labor	Family history	Parents consanguinity	glucose level MU/ml	Insulin level MU/ml	I/G ratio	Response to diazoxide	Response to octreotide	Operation	Outcome
20	M	3000	7 m	8 m	nvd	-ve	-ve	25	15.2	0.60	-ve	-ve	SP	Hypo
21	M	3000	12 m	42 m	nvd	-ve	-ve	33	4.4	0.13	+ve	+ve	No	
22	M	3000	18 m	20 m	nvd	-ve	+ve	30	6.6	0.22	-ve	-ve	SP	Hypo
23	M	3000	19 m	20 m	nvd	-ve	+ve	19	182	9.57	+ve	+ve	No	
24	M	4000	34 m	35 m	c/s	+ve	+ve	47	2.9	0.06	+ve	+ve	No	
25	M	3250	45 m	48 m	c/s	-ve	-ve	22	28	1.27	-ve	-ve	SP	Hypo
26	M	3250	2 d	1 m	nvd	-ve	+ve	18	37	2.05	-ve	-ve	SP	Hypo
27	M	4000	1 d	15 d	c/s	-ve	+ve	23	47	2.04	-ve	-ve	SP	Hypo

d, day. m, month. NVD, normal vaginal delivery. C/S, caesarian section.

–ve, unresponsive. +ve, responsive. SP, subtotal pancreatectomy.

Hypo, hypoglycemia. DM, diabetes mellitus.

Discussion

All patients were full term except for one patient was preterm, which was similar to studies done by C. T. Lee et al [20] &Mohammad Reza Alaei et al[21].

All patients had mothers without diabetes mellitus except for one patient who had mother with gestational diabetes, which was similar to study done by Mohammad Reza Alaei et al [21].

Seventeen (62%) patients were male & 10(38%) patients were female, which was similar to study done by Ayla Guven et al [22].

The birth weights were between 3 to 5.2kg (3.5kg median) which was comparable with Mohammad Reza Alaei et al (21) and Al-Nassar et al (23).

The median age of presentation ranged between 1 day and 45 months similar to Al-Nassar et al (23).

Diagnosis was between 2 day and 48 months (median of 2 months). with delay in diagnosis in about one third of patients because of delayed referral of patients to our hospital which was similar to Al-Nassar et al [23].

Thirteen patients (48%) were products of normal vaginal delivery, 14(52%) patients were products of caesarian section, which were comparable to that of Mohammad Reza Alaei et al [21].

Five (18%) patients had family history of affected siblings which was lower than that in Al-Nassar et al [23] because a smaller number of patients in this study compared with that in Al-Nassar et al [23].

The parents' consanguinity was high (81%), which was similar to Mohammad Reza Alaei et al [21] & Al-Nassar et al [23].

The blood glucose level during critical sample was ranged from 8 to 49 mg/dl (median 30 mg/dl), which was comparable with that in C. T. Lee et al [20] & Mohammad Reza Alaei et al [21].

The insulin level during critical sample was ranged from 2.6 to 182 Mu/ml (median 16.5 Mu/ml), with insulin to glucose ratio ranged from 0.06 to 9.57 (median 0.72), these results were lower than that in C. T. Lee et al [20] & Mohammad Reza Alaei et al [21] this might be attributed to different disease severity of affected patients.

From 18 patients were treated with diazoxide, only 4(22%) patients were diazoxide – responsive this result was similar to Al-Nassar et al [23].

All 27 patients were treated with octreotide, only 13(48%) patients were responded to octreotide, which was similar to that in study done by Demirbilek etal [24].

Thirteen (48%) patients were undergoing subtotal pancreatectomy, which was similar to that in Mohammad Reza Alaei et al [21], with one (8%) patient was underwent 2nd pancreatectomy which similar to that in Al-Nassar et al [23].

Postoperatively 1(8%) patient developed diabetes mellitus &required insulin therapy which was similar to Al-Nassar et al [23].

Twelve (92%) patients were still hypoglycemic Postoperatively & required octreotide &frequent feedings to control their blood glucose level and this result was higher than that in studies done by C. T. Lee et al [20], Mohammad Reza Alaei et al [21], Ayla Guven et al [22] & Al-Nassar et al [23] and this result was attributed to less resection of pancreas in our patients who were underwent subtotal pancreatectomy.

Conclusion

1. Delay in diagnosis was observed in approximately one third of the patients due to delayed patient referral to endocrine center.
2. We demonstrated that the I/G ratio employed as one of the diagnostic criteria of CHI has not been as reliable as it was claimed to be earlier. Thus, a wise step to take is to follow up patients who have measurable serum insulin levels during the episode of hypoglycemia as a measure of preventing late diagnosis of CHI.
3. Approximately half of the patients failed to respond to medical treatment and they had received subtotal pancreatectomy.
4. The majority of our patients undergoing subtotal pancreatectomy still had hypoglycemia and require life-long nutrition support to regulate the level of blood glucose.

Recommendations

1. Increase the awareness about CHI among general practitioner& pediatricians to prevent delay in diagnosis & appropriate treatment & to prevent mental retardation of patients with CHI.
2. There is need for diazoxide to be available for patients with CHI.
3. There is need for 18F-DOPA PET-CT scan to be available for improvement of surgical outcomes.
4. There is need for genetic studies to be available for patients with CHI to facilitate the diagnosis and proper treatment.

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