

ORIGINAL ARTICLE

CONGENITAL HYPERINSULINISM - TWO DECADES OF SPECIALIZED CARE IN A TERTIARY PEDIATRIC HOSPITAL

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ABSTRACT

Introduction: Congenital hyperinsulinism (CHI) is a rare disease, with a variable spectrum of severity. It is the main cause of persistent hypoglycemia in pediatric age patients.

Objective: The aim of this study is to characterize children with CHI followed in a tertiary care hospital.

Methods: Retrospective and descriptive study by consulting clinical files from 2003 to 2023.

Results: Eleven children (5 female). Background: prematurity (n = 2), large for gestational age (LGA) (n= 4). Maternal history: diabetes mellitus (DM) type 1 (n=1), DM type 2 (n=1) and gestational DM (n=1). Initial manifestation: in the neonatal period (n=6); between 4 and 14 months of life (n=5). Among the patients with a later presentation, most (n=4) presented with seizures. In five cases, an associated mutation was identified, two in the KCNJ11 gene, two in the ABCC8 gene, and one in the hexokinase 1 pathway. All patients were started on diazoxide, and in eight it was necessary to replace it with another drug. Two patients underwent subtotal pancreatectomy and were histologically classified as diffuse and atypical, and diffuse, respectively. At follow-up, two patients discontinued drug therapy due to clinical improvement, including one of the patients who underwent surgery. One child continues to have frequent hypoglycemic episodes. The remaining six, with tight therapeutic control, are stable and show good psychomotor development.

Discussion/Conclusion: The diagnosis and follow-up of patients with CHI remain challenging due to the heterogeneity and complexity of this condition.

Introduction**Epidemiology**

Congenital hyperinsulinism (CHI) is the most frequent cause of persistent hypoglycemia in pediatric patients.^{1,2,3} It is a rare and potentially fatal disease characterized by inappropriate secretion of insulin by pancreatic beta cells.⁴ Its global incidence is 1:50 000 live births, and it is more prevalent in regions with higher parental consanguinity (1:35 400 in Japan, 1:25 400 in Finland, and 1:2 675 in Saudi Arabia).⁵

Genetics

Several mutations have been implicated in CHI, and so far, mutations in 16 key genes involved in the regulation of insulin secretion have been described (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, KCNQ1, PGM1, PMM2, CACNA1D, FOXA2 and EIF2S3).^{3,6} The most frequent mutations correspond to genetic defects of the pancreatic beta cell ATP-sensitive potassium channels (KATP), with mutations in the ABCC8 and KCNJ11 genes, which respectively encode the SUR-1 and Kir6.2 subunits of the channel. In up to 50% of CHI cases, no pathogenic mutation is identified.^{3,4,7}

Histology

Histologically, CHI can be diffuse, focal or atypical, with the histological subtype being associated with the mode

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of heritability of the implicated mutation. Recessive mutations in homozygosity or compound heterozygosity give rise to the diffuse subtype, with involvement of all pancreatic beta cells, present in up to 60-70% of the cases. In contrast, in the focal subtype, the abnormal pancreatic beta cells are located in a delimited region of the pancreas and have their origin in two events: the inheritance of a paternal somatic mutation in the ABCC8 or KCNJ11 gene on chromosome 11p15 and, secondarily, the loss of the corresponding maternal allele. These events contribute to an imbalance in the imprinting expression of these genes, leading to focal cellular hyperplasia. The atypical subtype corresponds to a mosaicism of these two patterns.³ Although the histological subtypes are clinically and biochemically indistinguishable, their differentiation is crucial for the therapeutic approach.⁸ In this context, the role of imaging techniques, using positron emission tomography (PET) with 18-fluoro-L-dihydroxyphenylalanine (18F-DOPA), enabled making a precise differentiation between the diffuse and focal forms.^{8,9,10,11}

Clinical

The clinical manifestations of CHI are those arising from hypoglycemia and vary according to the age of onset. Usually, they are nonspecific (feeding difficulty, failure to thrive, seizure, hypotonia, irritability, apnea, tremor, cyanosis, and hypothermia, among others). Newborns may be macrosomic and/or present with hepatomegaly and hypertrophic cardiomyopathy, due to fetal hyperinsulinemia.¹¹

Diagnosis

The diagnosis of CHI is established by the presence of detectable insulin and/or C-peptide in a sample collected in hypoglycemia (plasma glucose <50 mg/dL). Suppression of free-chain fatty acids (<1.7 mmol/L) and ketone bodies (predominantly 3- β -hydroxybutyrate <1.8 mmol/L and the absence of ketonuria) is highly suggestive of the diagnosis. In some situations, a glucagon stimulation test may be required, in which the rise in blood glucose to a value greater than 30 mg/dL confirms the diagnosis of CHI.^{11,12}

In CHI, hypoglycemia persists despite continuous glucose administration. The need for a glucose infusion rate above physiological needs (4-6 mg/kg/min), especially if it exceeds 8 mg/kg/min, allow for the consideration of this entity.^{9,13} Along with the response to medical therapy, the need for a high glucose infusion rate to achieve normoglycemia is one of the parameters for assessing the severity of CHI. Severity tends to be greater when the manifestations of the disease present earlier. In fact, neonatal hypoglycemia is usually the most severe, regardless of the histological form of CHI.¹³

The absence of alternative substrates to maintain neuronal function (conditioned by the suppression of lipolysis and ketogenesis, resulting from the action of insulin) makes the hypoglycemia that occurs in CHI particularly deleterious to the brain, with increased risk of permanent neurological damage. It is estimated that about 50% of patients have neurodevelopmental disorders resulting from hypoglycemia-induced neurological sequelae. Early recognition and timely

treatment of CHI is, therefore, crucial.^{5,9}

Treatment

The main goal of therapy is the maintenance of normoglycemia (plasma glucose >70 mg/dL) and the prevention of brain damage. Treatment of acute hypoglycemia involves the use of glucose or glucagon as rescue therapy in persistent hypoglycemia and/or if associated with seizures. Long-term treatment involves a multidisciplinary approach, encompassing personalized nutritional support with oral caloric supplementation or, frequently, through percutaneous endoscopic gastrostomy (PEG), associated with pharmacological and/or surgical therapy.^{3,9}

Diazoxide, which acts on KATP channels, constitutes the first-line pharmacological treatment. However, in the presence of mutations, inactivating KATP channels becomes ineffective, determining the need for other drugs. Somatostatin analogues, such as octreotide and lanreotide, are the second line of treatment and may be used in association (in situations of partial response to diazoxide) or as substitutes for diazoxide. Other approaches include the synergistic combination of a thiazide diuretic with diazoxide in the initial phase, a calcium channel blocker with diazoxide or octreotide (in situations of partial response and/or after surgical intervention) and also mTOR pathway inhibitors, since this pathway may be hyperactivated in patients with diffuse CHI.³ Surgical treatment is reserved for focal CHI, in which excision of the lesion with aberrant pancreatic beta cells is potentially curative, and for diffuse CHI refractory to pharmacological therapy.^{3,14}

The aim of this study was to characterize clinically, histologically and molecularly all pediatric patients with the diagnosis of CHI followed at the Pediatric Endocrinology Unit of Hospital Dona Estefânia in Lisbon, as well as their therapeutic approach.

Methods

A retrospective and descriptive study was carried out by consulting the clinical files of pediatric patients diagnosed with CHI between 2003 and 2023. The diagnosis was established by the presence of persistent hypoglycemia requiring high glucose intake (>10 mg/kg/min), accompanied in all cases by an abnormally high insulin value in a sample collected during hypoglycemia (<50 mg/dL). Family history, gestational age, birth weight, perinatal risk factors, age and clinical manifestations at presentation, complementary diagnostic exams (including the genetic study), and therapy, including clinical response and adverse effects, were analyzed. In the evaluation of birth weight, the weight between the 10th and 90th percentiles according to the Fenton curves, or between the two standard deviations of the reference population in the growth curves, was considered as appropriate for gestational age (AGA). Large for gestational age (LGA) was defined as having a weight above the 90th percentile or greater than two standard deviations.¹⁵

We identified eleven cases of CHI and all of them were included in the case series.

The present study was approved by the hospital's Ethics Committee.

Table 1. Description of the patients: gender, birth year, gestational age and birth weight; age of beginning symptoms and maximum glucose infusion rate; genetic analysis.

Patient	Gender	Birth year	GA (weeks)	Birth weight (g)	Fenton curves	Beginning of symptoms	Maximum glucose infusion rate (mg/kg/day)	Implicated gene	Pathogenic variants
1	F	2003	40	4100	AGA	1 day	14	-	-
2	F	2010	40	3880	AGA	4 months	10	-	-
3	F	2016	39	3055	AGA	14 months	4	-	-
4	M	2016	39	4060	LGA	1 day	11	ABCC8	c.3644G>A and c.4256G>A
5	M	2016	38,9	4305	LGA	8 months	8	-	-
6	F	2016	39	3385	AGA	1 day	12	Via HK1	-
7	M	2018	34,3	2890	LGA	1 day	10	KCNJ11	c.403G>T, p.(Gly135Trp) and c.776A>G, p.(His259Arg)
8	M	2020	31	2080	LGA	1 day	14	KCNJ11	c.403G>T, p.(Gly135Trp) and c.776A>G, p.(His259Arg)
9	M	2020	39,4	3540	AGA	4 months	8	-	-
10	F	2022	38,9	4374	LGA	1 day	12	ABCC8	c.2797C>T (p.(Arg933*)) and c.1631-2A>Tp
11	M	2023	41	3720	AGA	4 months	3	ABCC8	c.1332G>T (p.Gln444His)

F- female; M - male; GA - gestational age; AGA - adequate for gestational age; LGA - large for gestational age

STATISTICAL ANALYSIS

Data analysis was performed using IBM SPSS Statistics (version 26, Armonk, New York).

Results

For the period studied, a total of eleven patients diagnosed with CHI were followed (Table 1). In regard to maternal family history, there were three mothers with DM: type 1 DM (case 4), type 2 DM treated with insulin therapy during pregnancy (case 8), and gestational DM treated with oral antidiabetic therapy (case 9). Additionally, one of the mothers had celiac disease (case 3). None of the patients had known consanguineous parents.

Two patients were premature, one was born at 31 weeks and suffered from perinatal asphyxia and the other was born at 34 weeks. Most patients were born through cesarean section (n=9). Regarding the birth weight, 54.5% were AGA and 45.5% LGA.

Clinical manifestations occurred within the first 24 hours of life in six cases: one with hypoglycemia detected in the context of hypotonia and five detected during the standard screening of high-risk newborns for neonatal hypoglycemia (4 were LGA and 1 was macrosomic). The remaining five cases had their first manifestation of disease during their first two years of life and most (n=4) presented with seizures.

Hypoglycemia was associated with insulinemia and detectable C-peptide in all cases (insulin between 4.4 and 147 uUI/mL). Blood glucose ranged from 9 to 38 mg/dL with a median of 27 mg/dL (Table 1).

None of the patients had a syndromic form of hyperinsulinism. However, two have dysmorphic facial features (cases 6 and 8) and one, with a family history of developmental delay, has severe developmental delay and epilepsy (case 2).

As for the genetic study, mutations in key genes were identified in five patients: cases 4 and 10 with pathologic variants in the ABCC8 gene, cases 7 and 8 in the KCNJ11 gene, and case 6 with loss of suppression of hexokinase 1 gene expression (Table 1).

All patients were started on diazoxide in increasing doses (maximum dose 20mg/kg/day) and, in seven patients, octreotide was added. In five of these cases octreotide was then replaced by lanreotide. In case 4, due to refractory hypoglycemia, mTOR pathway inhibitor sirolimus was initiated in a clinical trial at Great Ormond Street Hospital (GOSH). Subsequently, this drug was replaced by lanreotide (Table 2). It should be noted that in case 4, diazoxide was initiated in association with hydrochlorothiazide; in case 5, lanreotide was initiated in association with nifedipine; and in case 10, hydrochlorothiazide and spironolactone had to be associated with diazoxide. In case 11,

Table 2. Pharmacological and surgical therapy, and classification.

Patient	Diazoxide (duration of therapy)	Another therapy (duration of therapy)	Pancreatectomy	Classification	Current therapy
1	21M	Octreotide (10M)	Surgical removal of 95% of the pancreas by 2 months of age (2 surgical procedures)	Diffuse (histology)	None
2	Up to the present	Octreotide (12M) → Lanreotide	-	-	Diazoxide 3 mg/kg/day + Lanreotide 90 mg every 10 days
3	Up to the present	-	-	-	Diazoxide 2 mg/kg/day
4	2M	Octreotide → Sirolimus (7M) → Lanreotide	-	Diffuse (PET)	Lanreotide 60 mg every 28 days
5	8M	Octreotide (3W) → Lanreotide (4Y) → Octreotide infusion	-	-	Octreotide infusion 9 mcg/kg/day
6	Up to the present	Octreotide (3M) → Lanreotide (12M until surgery)	Surgical removal of 30% of the pancreas at 2 years old	Atypical and diffuse (histology and PET)	Diazoxide 11 mg/kg/day
7	2M	Octreotide (6W) → Lanreotide (12M) → Octreotide infusion	-	Diffuse (PET)	Octreotide infusion 3 mcg/kg/day
8	6W	-	-	-	None
9	Up to the present	-	-	-	Diazoxide 13 mg/kg/day
10	At least 2M	Octreotide → Lanreotide	-	Diffuse (PET)	Lanreotide 60 mg every 28 days
11	2W	Hydrochlorothiazide (2W) → Lanreotide	-	-	Lanreotide 30 mg every 28 days

M - months; W - weeks; Y - years; → - therapeutic switch

hydrochlorothiazide was associated with diazoxide for two weeks and was then replaced by lanreotide.

At the time of this publication, nine patients were under medical therapy. Most patients (n=10) were stable and had good psychomotor development, except case 2, who had asymptomatic hypoglycemic episodes and a severe developmental delay associated with epilepsy. Remarkably, in cases 3 and 9 there was a good response to diazoxide and in case 8 it was even possible to discontinue pharmacologic therapy.

Six patients who were treated with diazoxide presented adverse effects: hypertrichosis (cases 1, 2, 3, 6 and 9) and drug-induced autoimmune thrombocytopenia (case 5), which led to discontinuation of diazoxide, despite good clinical response. Two patients medicated with octreotide also had adverse effects: hypothyroidism (case 2), tachyphylaxis and biliary lithiasis (case 4).

Two patients underwent subtotal pancreatectomy and

were histologically classified as diffuse (case 1) and as atypical and diffuse (case 6). So far, none of them has developed DM. In addition to the patients who underwent surgery, three other patients were classified as diffuse through PET with 18F-DOPA.

All patients had individualized nutritional support and most required supplementation with slow-release carbohydrates to control blood glucose in the first months after diagnosis. Three patients needed a gastrostomy to ensure continuous glucose supply during the night (cases 4, 5 and 10). In nine patients, continuous glucose monitoring (CGM) was performed and six currently maintain these devices. The remaining patients use fasting, preprandial and exercise capillary blood glucose.

Discussion

Although rare, CHI is the main cause of severe

and persistent hypoglycemia in pediatric patients. Therefore, in order to minimize hypoglycemia-induced neurological complications, it should be detected very early.

In our cohort, we found a slight male predominance, compared to other case series in Europe, where male predominance was observed in 60% to 75% of the sample.^{16,17}

More than half of our patients were LGA. According to the literature, there is a higher probability of LGA newborn due to fetal hyperinsulinemia, and subsequently, in 20% of the cases the delivery is by cesarean section.¹³ In one of the previous series, LGA newborns were reported in 87% of the cases. However, in another case series, the weight was AGA in 62.5% of cases.^{16,17}

Severe non-ketotic hypoglycemia is the main feature of CHI. Symptoms can appear in the neonatal period and between the first and twentieth months of life. Half of the reported cases describe the first manifestation as possibly being a seizure.¹³ All of our patients presented with a non-ketotic hypoglycemia, and in most (n=6), the diagnosis was made in the neonatal period. The remaining patients were diagnosed during early childhood and the hypoglycemia was almost always detected in the context of a seizure. Diagnosis beyond the neonatal period is usually associated with a critical clinical manifestation. At this time, glucose requirements are lower and there is greater tolerance to hypoglycemia, leading to later, but potentially more severe, manifestations.¹³ It should be noted that glucose intake was higher in the subgroup diagnosed in the neonatal period, in line with what has been previously described.¹

To date, mutations in 16 key genes have been associated with CHI, even though pathogenic mutations occur in the ABCC8 and KCJN11 genes in 40 to 50% of the cases.^{3,6} In our study, in agreement with the literature, pathologic variants associated with the condition were identified in four patients (36.3%), two in the KCJN11 gene and two in the ABCC8 gene. In a similar series conducted in Gran Canaria on ten patients diagnosed with CHI since 2001, a pathologic variant associated with CHI was identified in 80% (n=8), 87% of which (n=7) presented a mutation in the ABCC8 gene.¹⁶

Reports indicate that mutations in the aforementioned genes may downregulate insulin secretion and result in an opposite function. Inactivating mutations may lead to increased insulin secretion early in life and activating mutations may lead to decreased insulin secretion later in life. This leads to a biphasic profile in the same individual, with CHI in the neonatal period and DM in the young adult.¹⁷ In case 8, the pathologic variant identified in the ABCC8 gene inherited from the mother may explain the child's CHI in the neonatal period, responsive to diazoxide therapy, and the DM diagnosed in the mother.^{6,17} Skilar Z and Berberoglu M described the case of two Turkish brothers with a heterozygous mutation in the ABCC8 gene inherited from their mother. These brothers presented with a CHI during childhood and DM in the prepubertal period. The mother was diagnosed with DM at age 28 and had no changes in blood glucose in the neonatal period.¹⁸

More than half of the patients in our cohort were unresponsive to the first-line therapy (diazoxide), including two with mutations in the genes encoding the KATP subunits where this drug acts. It is known that a large proportion of patients do not respond to diazoxide and require therapeutic association with another drug and/or even surgery.⁶ However, in rare cases of compound heterozygous mutation in the ABCC8 gene, clinical response to diazoxide has been described.¹⁹

In up to 60-70% of cases, CHI may be classified histologically as diffuse. Clinical presentation is similar to the other subtypes, but the molecular mechanism is different.¹⁸ In this study, four patients were classified as diffuse and one patient was classified as diffuse and atypical. The diffuse subtype is caused by recessive mutations in homozygosity or compound heterozygosity in the ABCC8 or KCJN11 genes, and patients are usually non-responders to medical therapy.¹⁷ Three of our patients classified as diffuse CHI had a mutation in these genes: case 4, in the ABCC8 gene, treated with lanreotide; case 7, in the KCJN11 gene, treated with octreotide infusion; and case 10, in the ABCC8 gene, also treated with octreotide in infusion. In the other two, pancreatotomy was performed, due to unresponsiveness to medical therapy: cases 1 and 6 (partial pancreatotomy), with case 6 still being treated with diazoxide. In the comparative study by Lord K et al., only 23% of children with the diffuse subtype achieved normoglycemia after surgery.¹

Other variants may be involved with diffuse and atypical subtypes, including variants associated with the heterogeneous expression of hexokinase 1, an enzyme involved in glucose phosphorylation, which is normally suppressed in pancreatic cells. Variants in the non-coding regions of hexokinase 1 result in its inappropriate expression and are the cause of dominant forms of CHI responsive to diazoxide, as observed in case 6.¹⁴

All patients, except for case 2, had an age-appropriate psychomotor development. According to Mannisto JM, in a series of 106 cases in recent years, therapy and normoglycemia were achieved earlier, and psychomotor and cognitive impairment were less frequent.²⁰ Maintenance of normoglycemia is the main goal in the approach to CHI. Recent CGM devices, especially those with an alarm if a hypoglycemic event occurs, provide an alternative approach to subcutaneous blood glucose monitoring, increasing the frequency of monitoring and improving the families' day-to-day life.^{12,21} Most of our patients started their blood glucose monitoring with one of these devices, which we believe has contributed to the optimization of care, including the prevention of hypoglycemia.

One of the limitations of our study is the sample size, since it presents data from a single center. However, it was possible to describe the experience and multidisciplinary approach of a complex disease that, despite being rare, should be suspected when dealing with patients with persistent hypoglycemia.

In 54.5% of our sample, we were not able to identify underlying genetic defects, highlighting the importance of future investigations to discover new deregulated mutations/pathways associated with CHI.

Conclusion

Despite advances in genetic diagnosis, therapeutic agents, monitoring, and delivery technology, the management of CHF remains a challenge. Personalized medicine is crucial, due to the heterogeneity of this condition. Furthermore, updated international guidelines for the management of CHI are needed. Early recognition and approach in specialized centers are critical in preventing and minimizing neurological complications resulting from hypoglycemia.

Compliance with Ethical Standards

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Conflict of Interest None

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