



CASE REPORT

Persistent hyperinsulinemic hypoglycemia of infancy: case report

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Abstract

Objective: to report a case of persistent hyperinsulinemic hypoglycemia in twins, which constitutes a situation not yet reported in the literature.

Methods: report of seizures in monozygous twins born from consanguineous parents and with persistent hypoglycemia as cause of seizures. Etiologic investigation of hypoglycemia included thyroid hormones (T4 and TSH), insulin, cortisol, growth hormone, glucagon for assessment of insulin/glucose ratio, and histopathological study of the pancreas.

Results: laboratory investigations indicated persistent hypoglycemia with hyperinsulinism; diagnosis was confirmed by glucagon test. Histopathological exam showed persistent first generation pancreatic islet with hyperplasia and hypertrophy of Langerhans islets, thus confirming diagnosis of persistent hyperinsulinemic hypoglycemia of infancy (current designation for nesidioblastosis).

Conclusion: although rare, persistent hyperinsulinemic hypoglycemia of infancy should be considered in early evaluation of hypoglycemia of young infants, or even older children, especially if parents are consanguineous. Appropriate therapy should be initiated promptly in order to prevent neurological sequelae.

J Pediatr (Rio J) 2000; 76(2): 162-8: hypoglycemia, hyperinsulinism, seizures, twins.

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) consists of an important etiology that should be considered in cases of intractable persistent hypoglycemia.

PHHI requires precise etiologic diagnosis and represents a serious therapeutic problem. The designation PHHI was proposed by Glaser in 1989, and it has been used in recent literature replacing the terms nesidioblastosis and islet cell dysregulation syndrome in the designation of pancreatic anomalies associated with hypoglycemia and hyperinsulinism.¹⁻⁷

Hypoglycemia associated with PHHI results from inadequate secretion of insulin, or hyperinsulinism. In carriers of PHHI, fasting hypoglycemia always occurs with inappropriately increased plasma insulin concentration in relation to low concomitant glucose concentration in

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blood.^{8,9} Some authors have suggested that PHHI is more related to a global increase in activity of endocrine pancreas function than to an increase in the number of pancreatic beta-cells.^{10,11} Insulin secretion depends on the activity of potassium channels in pancreatic beta-cells, which respond to variation in blood levels of glucose. According to recent studies, the referred activity is altered in carriers of PHHI.^{2,12}

PHHI occurs sporadically (1:40,000 live births). In communities with higher levels of consanguinity, however, PHHI has presented increased prevalence.² An autosomal recessive inheritance has been suggested to explain these cases.¹³⁻¹⁶ Even though serious cases of hypoglycemia are rare, the increased frequency of brain damage and mental deficiency as a consequence of hypoglycemia indicates the need for early etiologic diagnosis and for immediate treatment in children with intractable hypoglycemia.¹⁷⁻²⁰

The following is a case report of PHHI in monozygous twins. We have not found a similar case in the literature published in English in the last 30 years.

Case report

Case 1 - Caucasian female patient, first twin born from healthy and consanguineous parents (first-degree cousins). A C-section had to be performed at birth due to gestational hypertension after 35.7-week term. Patient's weight and height at birth were 1,590 g and 39.5 cm, respectively. During the 1st week of life, patient presented adaptive respiratory distress, physiologic jaundice, and hypoglycemia. The latter was controlled with intravenous infusion of

glucose at 4 to 6 mg/kg/minute. The patient remained in the hospital for weight-gaining purposes, and was dismissed weighing 1,860 g. At home, her condition remained stable for 2 months.

At 3.5 months of age, the patient was admitted to the Pediatric Emergency Department, at the University Hospital, Universidade de São Paulo. The patient presented with 2-day history of apathy, and occurrences characterized by repetitive movement of limbs and by apparent loss of conscience. Physical examination upon hospital admission indicated that the patient was hydrated and hypoactive. Weight and height were, respectively, 3,880 g and 49 cm, both below the 2.5 percentile according to the National Center of Health Statistics.²¹ The patient presented tonic-clonic seizure while under observation, at which point we observed glycemia of 16 mg/dl. Intravenous glucose was administered, starting at 5.4 mg/kg/min, and the patient was admitted for etiologic investigation of hypoglycemia.

While at the hospital, the patient was given progressively higher quantities of glucose (up to 12 mg/kg/minute). Hypoglycemia and seizures, however, were still observed. Table 1 presents the results of exams carried out during investigation of the patient. Glucagon infusion test (Table 2), which was carried out after discontinuing intravenous infusion of glucose, indicated baseline glycemia of 5 mg/dl with concomitant insulinemia of 39.5 mU/ml. The insulin (mU/ml) to glucose (mg/dl) ratio was 7.9:1 for an expected maximum of 1:4, thus characterizing hyperinsulinism.

On the 40th day of hospital admission, the patient was transferred to the Endocrinology Unit of the Instituto da Criança, Hospital das Clínicas, School of Medicine,

Table 1 - Laboratory, ultrasonography, and electroencephalography exam results

Exams	1st twin	2nd twin
TSH	5.43 µ UI/ml (nl)	2.85 µ UI/ml (nl)
T ₄	13.6 m g/dl (nl)	15.5 m g/dl (nl)
Growth hormone (GH)	13 ng/ml (nl)	13.4 ng/ml (nl)
Cortisol	278.3 ng/ml (nl)	208.5 ng/ml (nl)
Uric acid	3.1 mg/dl (nl)	3.2 mg/dl (nl)
Cholesterol	142 mg/dl (nl)	119 mg/dl (nl)
Triglycerides	116 mg/dl (nl)	155 mg/dl (nl)
Lactate	normal	normal
Inborn errors of metabolism	negative	negative
Chromatography of sugars (urine)	negative	negative
Abdominal ultrasonography	negative	negative
Electroencephalography	normal	paroxysmal abnormality (potentially epileptiform)

Table 2 - Glucagon infusion test results (case 1)

Time (minutes)	Glycemia (mg/dl)	Insulinemia (mU/ml)	Insulin/Glucose*
0	5	39.5	7.9/1
3	10	87.7	8.77/1
5	20	195	9.75/1
15	40	158	3.95/1
30	64	32.8	0.5/1
60	18	11.7	0.65/1

* Normal = up to 1/4

Universidade de São Paulo. In addition to glucose, the patient was administered growth hormone subcutaneously at 2 U per day. The patient presented less frequent seizures; hypoglycemia, however, still persisted. Due to strongly suspected PHHI, the patient was submitted, at first, to subtotal pancreatectomy. The procedure was not satisfactory. Another pancreatectomy was carried out. Due to persistent hypoglycemia, the patient was administered diazoxide at 10 mg/kg/day; the response to diazoxide was not satisfactory either. We decided to administer prednisone at 1 mg/kg/day and hypercaloric diet; this resulted in control of glycemia and of seizures. Patient was dismissed from the hospital after 44 days with fractionated hypercaloric diet, prednisone, and phenobarbital at 5 mg/kg/day.

At 2 years and 10 months of age, the patient presented satisfactory neuropsychomotor development. The use of phenobarbital was discontinued without any intercurrent. At 3 years of age, after a progressive reduction of prednisone dosage, its use was also discontinued. The patient remained asymptomatic until 3 years and 7 months of age, when she presented hypoglycemia, which was reversed with oral ingestion of sugar.

At present, the patient is 4 years and 9 months old, and presents unsatisfactory weight and height development. The patient's weight is of 11,500 g, and her height is of 89.3 cm, both below the 2.5 percentile.²¹

Case 2 - Caucasian female patient, second twin. A C-section had to be performed at birth due to gestational hypertension after 35.7-week term. Patient's weight and height at birth were 1,760 g and 39 cm, respectively. During the neonatal period, the patient presented adaptive respiratory distress and physiologic jaundice, and was submitted to phototherapy until the 8th day of life. At 33 hours of life, hypoglycemia was observed (22 mg/dl); glucose was administered at 15 mg/kg/min intravenously in order to maintain normal glycemia. Infusion of glucose was progressively reduced and discontinued on the 6th day of life. The patient remained in the hospital for 20 days for weight-gaining purposes. At hospital dismissal, the patient weighed 1,850 g.

Tabela 3 - Glucagon infusion test results (case 2)

Time (minutes)	Glycemia (mg/dl)	Insulinemia (mU/ml)	Insulin/Glucose*
0	14.5	112	7.7/1
15	54.0	285	5.2/1
30	42.0	101	2.4/1
60	13.0	46	3.5/1
90	54.7	20	0.36/1

* Normal = up to 1/4

At 1 month and 9 days of age, the patient was admitted elsewhere with indication of progressive irritability and refusal to eat. Hypoglycemia was observed (30 mg/dl) and initially remedied with intravenous glucose (6 mg/kg/min), which was progressively reduced and discontinued on the 6th day. The patient was dismissed on the 6th day without having been submitted to etiologic investigation of clinical status.

The patient remained asymptomatic until 3.5 months of age, at which point she was admitted to the Pediatric Emergency Department, at the University Hospital, Universidade de São Paulo. The patient presented with history of three tonic-clonic seizures in the previous 8 days. Upon her admission to our hospital, the patient presented masticatory movements, hypertonia, perioral cyanosis, all of which ceased spontaneously. We observed that glycemia was, at that moment, 18 mg/dl; consequently, the patient was administered intravenous glucose and admitted to the hospital for investigation. The patient's weight and height were 4,600 g and 51 cm, respectively. Both measurements were below the 2.5 percentile.²¹ Despite intravenous infusion of glucose at 10 mg/kg/min, the patient persisted with hypoglycemia and seizures. Doses of hydrocortisone at 10 mg/kg/min were administered without satisfactory clinical and laboratory response.

Table 1 presents results of exams carried out. Glucagon infusion test (Table 3) indicated basal glycemia of 14.5 mg/dl, with concomitant insulinemia of 112 mU/ml. The insulin/glucose ratio was 7.7:1 for an expected maximum of 1:4, thus characterizing hyperinsulinism.

On the 43rd day of hospital admission, the patient was transferred to the Endocrinology Unit of the Instituto da Criança, Hospital das Clínicas, Universidade de São Paulo, and persisted with hypoglycemia and seizures. Subtotal pancreatectomy was carried out without satisfactory results. Subsequently, another pancreatectomy was carried out. Due to persistent hypoglycemia, the patient was administered prednisone at 1 mg/kg/day, and presented evolution to a stable condition. The patient was dismissed from the hospital after 34 days with fractionated diet, prednisone, and phenobarbital. During the following 2 months, the patient had three occurrences of hypoglycemia, and required intravenous infusion of glucose in addition to prednisone.

At 2 years and 11 months of age, administration of phenobarbital was discontinued; at 3 years and 5 months, prednisone dosage was progressively reduced until discontinuation. No interurrences were observed. At 4 years and 7 months of age, the patient presented seizures related to the decrease in food intake.

At present, patient is 4 years and 9 months old, and is being followed up on an outpatient basis. The patient has satisfactory neuropsychomotor development. Her weight is of 11,600 g, and her height is of 89.3 cm, both below the 2.5 percentile.²¹

Anatomicopathological exam: pancreatic tissue examination of the two children indicated persistence of first generation pancreatic islets, characterized by hyperplasia and hypertrophy of islets of Langerhans with cell structure dysregulation, cell size variation, and islet proliferation from the ductule epithelium. Cells presented unusual enlargement of up to six times that of other cells, and unusual contour.

Discussion

Persistent hyperinsulinemic hypoglycemia of infancy has been used to replace the term nesidioblastosis in order to include diffuse or focal pancreatic anomalies associated with hyperinsulinism and hypoglycemia.¹⁻⁷

In 1983, Laidlaw described abnormalities of pancreatic islet cell in patients with suspected pancreatic adenoma.²² These cell abnormalities, called nesidioblastosis, were also observed by other authors in hypoglycemic patients.^{23,24} In 1976, Polak & Wiggesworth suggested that hypoglycemia secondary to nesidioblastosis could be an important cause of sudden infant death.²⁵ Polak & Wiggesworth's finding was confirmed during that same year by Cox et al., who identified excess beta-cells in the pancreas of 36% of autopsied children after sudden infant death syndrome.²⁶ Dahms, however, observed that these same abnormalities were present in the pancreas of normoglycemic children submitted to autopsy.²⁷

Later, Gould²⁸ and Rahier²⁹ described cell abnormalities that are characteristic of the pancreas of children with persistent hypoglycemia and hyperinsulinism; in other words, carriers of PHHI. The histology of pancreatic islets in patients of these two studies was highly variable, including structural dysregulation, cell-size variation, and islet proliferation. In our study, pancreatic histopathological findings, which were similar to those described by Gould and Rahier, associated with laboratory and clinical data (Tables 1, 2, and 3), confirmed diagnosis of PHHI.

Currently, the most widely accepted hypothesis for occurrence of PHHI is the presence of dysfunction of potassium channels - K(ATP) - in pancreatic beta-cells, which perform an important role in the regulation of insulin secretion.² In normal cells, K(ATP) responds to variation in blood levels of glucose by opening or closing. This yields changes in the membrane's potential action and cellular inflow of calcium. The described phenomenon is essential for insulin secretion.¹² In carriers of PHHI, dysfunction of potassium channels in beta-cells yields blockade of these channels independently of the glucose levels, which results in depolarization of cell membrane, secondary inflow of calcium, and inappropriate secretion of insulin.^{2,12}

The potassium channel is a functional complex of the sulfonylurea receptor 1 (SUR1), and an inward rectifier

potassium channel subunit, Kir6.2. Separately, these two proteins cannot operate adequately as a potassium channel. Mutation of regulator genes of the two proteins may determine three different PHHI phenotypes. The first phenotype is related to familial PHHI, with SUR1 blockade and absence of K(ATP); this is the most serious type of PHHI, and its patients usually do not respond well, or do not respond at all, to clinical treatment.^{2,3,6} The second phenotype, related to sporadic cases of PHHI, presents loss of K(ATP) function; this type, however, presents partial response to clinical treatment due to neofunction of ion and potassium channels. Finally, the third phenotype is related to late manifestation and less seriousness, since patients present K(ATP) and respond to clinical treatment.^{2,6}

Most cases of PHHI are sporadic, and there is no evidence of prevalence related to sex. Usually, patients affected by PHHI have healthy parents.³ Familial PHHI is common in communities with high rates of consanguinity (1/2,500 live births). We have not found in the literature a report of PHHI in twins.²⁻⁵ Occurrence of familial PHHI as persistent severe neonatal hypoglycemia was first described by Woo *et al.*, in 1976, in a family of Greek Cypriots.³⁰ Subsequently, familial PHHI was described by other authors.^{13,16,31-34}

Regulator genes of sulfonylurea receptors and potassium channels were recently mapped to chromosome 11p14-15.1 (lod score = 9.5, theta = 0 at D11S921).^{2,4,5,32,35} Even though we were not able to carry out chromosome investigation in our patients, our findings suggest familial PHHI. It may also be a case of autosomal recessive inheritance, since both parents are healthy and consanguineous. Moreover, our patients are monozygous twins. Persistence of first generation pancreatic islets, observed at anatomicopathological examination, confirms the possibility of inborn errors that may have affected the development and function of pancreatic beta-cells.

Most PHHI patients are larger-sized newborns for their gestational age. This is a consequence of hyperinsulinism, though without significant hepatomegaly. PHHI patients present persistent hypoglycemia symptoms, including intractable seizures as early as the neonatal period.³⁶ The fact that our patients were small according to their gestational age may explain the presence of short-term hypoglycemia during the neonatal period, which possibly made PHHI difficult to diagnose during the same period. Patient 2, in turn, presented acute hypoglycemia (30 mg/dl) at 1 month of age, whose etiology could probably be attributed to PHHI.

Altered insulin/glucose ratio and maintenance of high levels of insulin during hypoglycemia are important parameters in the diagnosis of hyperinsulinemia. In this sense, if the patient's glycemia is below 40 mg/dl, plasmatic concentration of insulin should be lower than 5, and never higher than 10 mU/ml.^{9,37} In infants with hyperinsulinism, however, insulin concentrations are usually higher than 10 mU/ml, and the insulin-to-glucose ratio presents values

over 1:4.^{9,37} Our patients presented elevated insulin values and insulin-to-glucose ratio of 7.9:1 for patient 1 and of 7.7:1 for patient 2, thus characterizing hyperinsulinism (Tables 2 and 3).

Treatment of hyperinsulinism includes agents that inhibit insulin secretion (diazoxide, somatostatin, epinephrine, diphenylhydantoin, and calcium channel inhibitors), that antagonize insulin effect on tissues (glucocorticoids, epinephrine, glucagon, and growth hormone), and that destroy islet cells (alloxan, surgery). No treatment method has indicated uniformly successful results when employed separately.^{1,6,7,38-45} Drugs used in the initial clinical treatment of our patients were not effective.

After unsuccessful clinical treatment, surgical treatment is immediately indicated in order to avoid neurological sequelae due to sustained hypoglycemia. Initially, an 80% pancreatic resection should be carried out to the pancreaticoduodenal artery.^{18,38,46-49} In case surgery is not successful, a second clinical treatment is indicated, using diazoxide or corticoid.³⁸ In some patients, this procedure may present effective, whereas in others, it may be as ineffective as the treatment carried out before surgery, which is the case of our patients. If the second treatment is ineffective, total pancreatectomy, retaining the spleen and duodenum, is indicated as the only way to control hypoglycemia.⁴⁶⁻⁴⁹ Long-term complications due to total pancreatectomy have been reported, and they include insulin-dependent diabetes mellitus, and need to restore pancreatic enzymes; the latter, in some cases, may be a lifelong necessity.^{38,46} Until this date, the above complications were not observed in our patients. Our patients do, however, still present significant weight and height deficit despite their good quality of life.

Prognosis of PHHI depends essentially on early diagnosis, on correct diagnosis, and on immediate therapy for treatment of hypoglycemia. Prompt surgical treatment may also be necessary.

In conclusion, pediatricians should be alert to the possibility of PHHI as a cause of neonatal persistent hypoglycemia or, still, of hypoglycemia at later stages. Our report underscores the latter possibility, especially in cases of consanguineous parents. In cases of consanguinity, genetic medical counseling is important for neonatal diagnosis of PHHI and for avoiding permanent sequelae.

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