Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Reports | Praca kazuistyczna
Pediatr Endocrinol Diabetes Metab 2015;23,1:46-50
DOI: 10.18544/PEDM-21.01.0024

redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Congenital hyperinsulinism: course and consequences – case report

Wrodzony hiperinsulinizm: przebieg i następstwa – opis przypadku

[1]Aleksandra Gonera, [2]Marta Buraczewska, [3]Maciej Borowiec, [4]Ewa Barg

[1]SKN Endokrynologii, Hematologii, Onkologii, Uniwersytet Medyczny we Wrocławiu,
[2]Katedra i Klinika Pediatrii, Diabetologii i Endokrynologii, Gdański Uniwersytet Medyczny w Gdańsku
[3]Katedra Genetyki Klinicznej i Laboratoryjnej Zakład Genetyki Klinicznej, Uniwersytet Medyczny w Łodzi
[4]Katedra i Zakład Podstaw Nauk Medycznych, Uniwersytet Medyczny we Wrocławiu

Abstract
Congenital hyperinsulinism (CHI) is one of the most common causes of persistent hypoglycemia during infancy. There are two morphological forms: diffuse and focal. Early recognition of CHI is vital in preventing neuroglycopaenic brain injury. An appropriate therapy can protect against long-term sequelae, such as diabetes mellitus. We present the case of a 13-year-old girl who was diagnosed with congenital hyperinsulinism during first weeks of life. Initially, medical management with somatostatin analogues (octreotide) was attempted. Because medical therapy failed, subtotal pancreatectomy was performed. During the 13-year observation following this treatment, no hypoglycemia recurrence or carbohydrate metabolism disorders were observed. Patient's current problems are overweight and hypercholesterolemia, as well as a recently diagnosed autoimmune thyroid disease. The paper presents characteristic aspects, diagnostic difficulties, and the consequences of congenital hyperinsulinism.
Key words
congenital hyperinsulinism, hypoglycemia, pancreatectomy

Streszczenie
Wrodzony hiperinsulinizm (CHI) to jedna z najczęstszych przyczyn nawracających epizodów hipoglikemii we wczesnym dzieciństwie. Wyróżnia się dwie formy morfologiczne: rozsianą i ogniskową. Wczesna diagnostyka umożliwia zapobieganie poważnym następstwom choroby, zwłaszcza uszkodzeniu struktur mózgowych, a odpowiednie postępowanie terapeutyczne może uchronić przed odległymi powikłaniami, m.in. cukrzycą. Opisano przypadek 13-letniej pacjentki, u której w pierwszych tygodniach życia zdiagnozowano wrodzony hiperinsulinizm. Początkowo zastosowano leczenie zachowawcze analogiem somatostatyny (oktreotydem), a następnie w związku z brakiem poprawy przeprowadzono zabieg subtotalnej resekcji trzustki. Podczas 13-letniej obserwacji po leczeniu u dziewczynki nie wystąpiły nawroty hipoglikemii. Nie wykazano też innych zaburzeń gospodarki węglowodanowej. Obecnymi problemami pacjentki są nadwaga oraz hipercholesterolemia, a także niedawno rozpoznana autoimmunologiczna choroba tarczycy. Praca przedstawia charakterystyczne aspekty wrodzonego hiperinsulinizmu, trudności diagnostyczne oraz następstwa choroby.
Słowa kluczowe
wrodzony hiperinsulinizm, hipoglikemia, pankreatektomia

Introduction

Congenital hyperinsulinism (CHI) comprises a group of different genetic disorders with the recurrent episodes of hyperinsulinic hypogycemias due to inappropriate secretion of insulin [1]. Nesidioblastosis is a diffuse, ducto-endocrine β cell proliferation [1–3]. Often, both of these definitions mean one disease, which usually manifests a few days after the birth (most cases appear within 72hrs after birth). Majority of the children are macrosomic at birth (mean birth weight of 3.7kg). Clinical presentation depends on severity of hypoglycemia and includes hunger, somnolence, seizures, apnea, cyanosis, hypotonia, and hypothermia, sometimes even coma or status epilepticus [1,2,4].The diagnostic criteria of CHI are: fasting and postprandial hypoketotic hypoglycemia (blood sugar level less than 36 mg/dl), hyperinsulinemia (plasma insulin level above 2 μU/ml), C-peptide concomitant to hypoglycemia, need for high rate of glucose infusion (6–8, sometimes even above

dr hab. Ewa Barg
Katedra i Zakład Podstaw Nauk Medycznych,
Uniwersytet Medyczny we Wrocławiu
ul. Borowska 211, 50-556 Wrocław, Polska
tel. +48717840478, e-mail: ewa.barg@umed.wroc.pl

Received: 2015-07-28.
Acccepted: 2015-10-25.
Conflict of interests: none declared.

10mg/kg/min) in order to maintain blood glucose level above 54 mg/dl, spectacular rise in blood glucose level in response to administration of glucagon (rise by 18-36 mg/dl after administration of 0.5 mg of glucagon by subcutaneous or intramuscular route), normalization of glycaemia following administration of somatostatin, and low fatty acids level [1,2,4,5]. There are two main histological forms of CHI: focal hyperplasia and diffuse hypertrophy of pancreatic beta cells [4]. Usually CHI is caused by genetic defects. The most often are recessive inactivating mutations in ABCC8 and KCNJ11 (which encode the two subunits of the adenosine triphosphate sensitive potassium channels) in beta-cells. The other forms of CHI are due to mutations in HADH1, GK, GLUD1, SLC16A1, UCP2, and HNF4A. The molecular basis of CHI is responsible for histological form and response to treatment [6–8].

Management of CHI involves drugs which: inhibit insulin secretion (diazoxyde, somatostatin, epinephrine, calcium channel blockers and diphenylhydantion), antagonize the insulin effect of body tissue (epinephrine, glucagon, growth hormone), or destroy islet cells (alloxan) [5,9]. About 80% cases of CHI are resistant to pharmacological treatment [1] and often surgical treatment is required. In patients with focal CHI, a localized resection of the focal lesion is curative. Diffuse CHI requires subtotal or near-total (80–95%) pancreatectomy [1,2,4,5]. Recurrent hypoglycemia, diabetes mellitus, and exocrine pancreatic insufficiency are the most common complications of extensive surgery, being next challenges for doctors [4].

Case report

The patient is a 13-year-old girl, who was diagnosed with congenital hyperinsulinism during first weeks of life.

She was born at term with weight 3850 g and length 56 cm. Health status in the first minute of life was evaluated at 8 points in Apgar Scale. Mother has not developed diabetes mellitus during pregnancy. In family, only girl`s mother has a Hashimoto disease. During the 2nd day of life the patient was diagnosed with pneumonia. Despite antibiotic treatment, her health status declined in the 5th day of life. Hypoxemia (pO2= 54.7 mmHg, SatO2= 88.6%) and hypoglycemia occurred. Oxygen therapy, infusion of glucose, hydrocortisone, and diazoxide were introduced into the treatment. Galactosemia and adrenal insufficiency were excluded. In 12th day of life no pathological respiratory sounds were heard and further oxygen therapy was not required. Despite treatment, proper feeding, and increased glucose infusing speed, decreases in blood sugar level down to 28.8 mg/dl were observed. Insulin levels and C-peptide controlled during hypoglycemia were high [table I]. Results of test with glucagon confirmed preliminary diagnosis of hyperinsulinemic hypoglycemia [table II]. Viral infections caused by HSV-1, Rubeolla virus, Toxoplasmosis, CMV, and bacterial L. monocytogenes infection were excluded as the cause of hypoglycemia. Radical treatment (subtotal pancreatectomy) was not conducted, but an alternative therapy with somatostatin analogues (octreotide – 4 x 10μg), but not with diazoxide, was introduced instead. Blood sugar level was normal until the 6th week of life.

Table I. Insulin and C-peptide levels during hypoglycemia
Tabela I. *Stężenie glukozy i insuliny w hypoglikemii*

Glycaemia / *glikemia* [mg/dl]	17	38
Insulin [μIU/ml]	28	6,7
C-peptide [ng/ml]	3,67	1,39

Table II. Blood glucose level after administration of glucagon
Tabela II. *Stężenie glukozy po podaniu glukagonu*

Test with glucagon / *test z glukagonem*			
Time [min] / *czas* [*min*]	0’	5’	15’
Glycaemia [mg/dl] / *glikemia*	17	23	41

In the next weeks,episodes of hypoglycemia occurred. In the 8th week of life the patient was qualified for subtotal pancreatectomy including tail and body up to the forks of the portal vein and superior mesenteric artery. The microscopic examination of resected pancreas fragment revealed the presence of diffuse architectural changes (islet cell dysplasia) and endocrine cells dispersion. The image corresponded to nesidioblastosis. After surgery, increases in blood glucose levels were observed; occasional drops were successfully controlled by somatostatin analogues and diet (regular feeding). The postoperative period was marked by functional gastrointestinal and motility disorders (vomiting, constipation, diarrhea). Patient required partial parenteral nutrition.

Check-up in 10th month of life revealed normal development of the girl (body mass – 0.82 SD, height +0.52 SD), the lowest value of blood glucose level was 44mg/dl, levels of liver and pancreas enzymes were normal. EEG scan showed generalized paroxysmal changes, which were probably secondary to repeated episodes of hypoglycemia; the group of paroxysmal slow waves with a frequency of 3–5 Hz and amplitude of 120–160 microV and sharp waves with an amplitude of 130–255 microV were observed several times above both hemispheres of the brain. Phenobarbital was administered.

At the end of the 1st year of life, blood glucose level was normal (usually not lower than 55mg/dl, isolated episodes of approximately 45 mg/dl). Somatostatin analogues were discontinued and diet containing maltodextrins was introduced. In the 14th month of life, due to problems with swallowing, chewing and speaking, speech therapist was consulted. Exercises for the articulatory apparatus were advised. Psychological consultation revealed normal development of the child.

Control laboratory tests results in 9th year of life showed a normal glucose level and liver functions, increased total cholesterol (257 mg/dl) and LDL (182 mg/dl). HDL and triglyceride levels were normal. OGGT and insulin levels were within

normal range. The patient has not been taking any medication during this period. Puberty at this stage of life was assessed as normal. Because of the patient was overweight (BMI 90-97 percentyle) weight reduction was recommended.

Additional genetic testing, performed in the 9th year of life, revealed heterozygous inactivating mutation in HADH (I290V) [fig. 1]. Because of autosomal recessive inheritance, this defect was determined as not being the reason for congenital hyperinsulinism in the patient.

Apart from congenital hyperinsulinism, the patient was also suffering from urinary tract disorders. The first episode of urinary tract infection appeared in the 2nd month of life (after subtotal pancreatectomy), the next one 3 months later. In the 14th month of life, after another episode of infection, urinary tract was evaluated. Cystography revealed vesicoureteral reflux (VUR) II grade. No pathological changes were found in the USG examination. Laboratory tests revealed hypogammaglobulinemia and increased phosphorus levels in urine. Antimicrobial therapy was administered and the patient was recommended to perform: urinalysis every 10 days, urine culture analysis once a month for 6 months, cystography after a year, as well as changing diet to one with particular emphasis on anticalculus prevention. In the 3rd year of life, due to the progression of changes to VUR III grade, the patient was initially qualified for surgical treatment. Despite the recommendations, the operation was not performed, and dietary treatment was continued.

In the 4th year of life regression of changes was noted. The active VUR II grade on the right side and active VUR I grade on the left side were observed. Urinary tract infections did not recur. Uroflowmetry confirmed the proper function of the lower urinary tract. Control renography in 9th year of life was normal.

During the 10th and 11th years of life dyslipidemia continued to be present, with blood glucose levels still being normal. Laboratory tests also revealed an increased titer of antibodies against thyroid peroxidase (47.2 IU/ml), with normal values of TSH, FT4 and aTG. Medical history revealed that patient's mother had been diagnosed with Hashimoto disease.

Currently, the patient requires the monitoring of glucose and lipid metabolism, as well as thyroid function.

Disscusion

This case illustrates many characteristics, but also unusual aspects, of congenital hyperinsulinism. High birth weight and distinctive laboratory test results (high levels of insulin and C-peptide, rise in blood glucose levels in response to glucagon) indicated a fairly typical picture of the disease. However, due to a history of perinatal infection, it was suspected that hypoglycemia may be temporary. During first seven weeks of life, the patient was managed with diazoxide and somatostatin analogues. Because medical therapy failed, subtotal pancreatectomy was performed.

Surgical procedure is the first line of treatment for focal lesion and second choice for diffuse CHI, especially when there is no response to diazoxide, somatostatin analogues, and other medical therapy [10,11]. The extent of the surgery depends on morphological form of CHI (diffuse or focal), which should be confirmed preoperatively, e.g. using pancreatic venous sampling (PVS) or F-fluoro-L-DOPA PET [12]. The diffuse form usually requires subtotal or near-total (80–96%) pancreatectomy. Majority of procedures are still conducted without prior verification of the form of beta cell proliferation, as the so-called

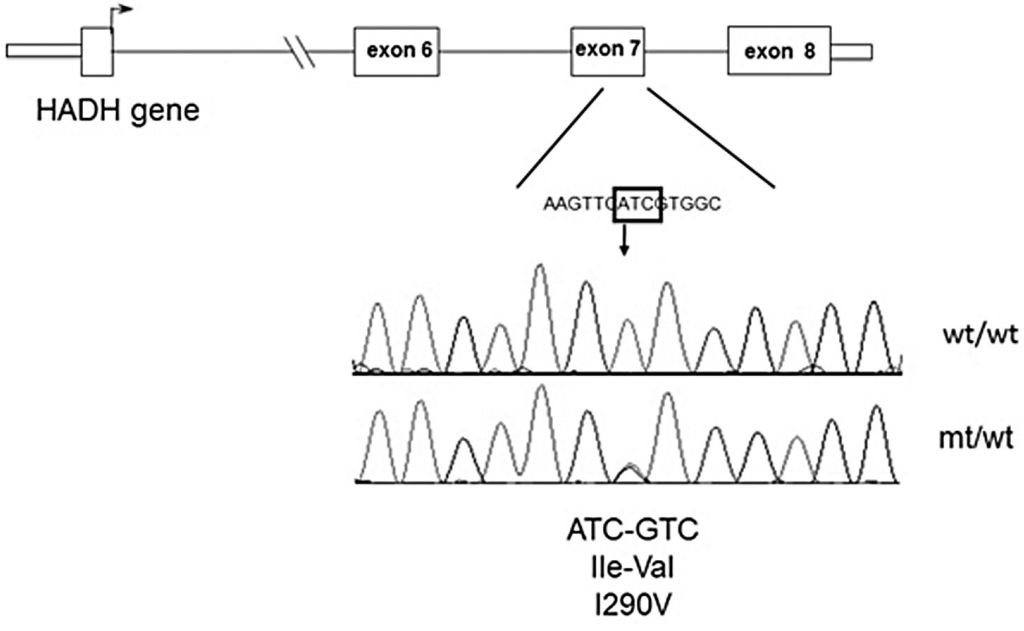

Fig. 1. Results of genetic test. Heterozygous inactivating mutation in HADH (I290V)
Ryc. 1. *Wynik badania genetycznego pacjentki. Heterozygotyczna nieaktywna mutacja w HADH (I209V)*

"blind" pancreatectomy [13]. This might result in numerous complications, such as diabetes mellitus (due to extensive nature of the surgery) or hypoglycemia relapses (indicating procedure inefficiency) [1,4,11,13].

Our patient was diagnosed with the diffuse form of CHI, therefore she was also exposed to complications listed above. Some authors suggest that long-term aggressive medical treatment with diazoxyde or somatostatin analogues, together with proper feeding, should replace subtotal or near-total pancreatectomy [11,14]. In our patient, subtotal pancreatectomy was the most appropriate treatment. Neither recurrences of hypoglycemic episodes, nor diabetes mellitus were diagnosed during 13 years of follow-ups. Selecting the appropriate therapy is therefore still disputable [11,13,17].

Neurological disorders are the most significant complications of congenital hyperinsulinism. Mental retardation, epilepsy and developmental delay are frequently observed [13,14]. Factors contributing to the neurodevelopmental outcome include: long-term glucose deficiency, low or absent alternative energy pools (because of insulin-suppressed lipolysis), and different genetic mechanisms. All of the above contribute to mental retardation in CHI [14]. In our patient, abnormal EEG results were observed at the 10th month of life, caused most probably by multiple episodes of hypoglycemia. In addition, in the 14th month of life there were swallowing and chewing disorders, which were corrected by the exercises recommended by a speech therapist. It seems that in the case of so many hypoglycemic episodes during childhood, regular neurological supervision is necessary.

Genetic tests and F-fluoro-L-DOPA PET diagnosis should be primary differential tools for diazoxide-unresponsive cases of CHI [6]. In our patient, heterozygous mutation in the HADH gene was diagnosed. The HADH gene encodes 3-hydroxyacyl-CoA dehydrogenase, the mitochondrial enzyme that catalyzes the penultimate step in β-oxydation of fatty acids. This form of CHI is usually responsive to medical treatment with diazoxide [15,16]. Autosomal recessive inheritance of HADH excluded the role of this mutation in this case. Poor response to diazoxide clinically confirmed this statement. Further molecular studies would be necessary to verify the patient`s diagnosis. In our patient, genetic testing was conducted several years after the surgical intervention [17]. They have had no influence on the decision about the treatment. Some authors point out the important role of genetic tests results on the therapeutic process, especially in the case of resistance to diazoxide. It makes it possible to distinguish morphological forms, choose the most appropriate treatment, and predict the response to the therapy [15,17]. Limited availability of these studies, high costs, and long waiting times for results still constitute difficulties in the diagnostic process.

Multiple, recurring urinary tract infections caused by presence of vesicoureteral reflux are worth noting. Literature does not specify any connection between the occurrence of this type of urinary tract defects and congenital hyperinsulinism. It seems that VUR is a separate, coexisting disease entity which can affect the course of congenital hyperinsulinism.

Currently, the main problem of the patient is overweight and significant hypercholesterolemia. Despite lipid disorders, OGTT was assessed as normal. According to the literature, overweight occurs quite frequently in patients with a history of congenital hyperinsulinism. Some authors explain this fact by the tendency of parents to overfeed these children for fear of hypoglycemia, which may lead to the habit of overeating [12]. In our patient, dyslipidemia may be associated with puberty, which can favor the accumulation of body fat. However, this requires further studies and implementation of an appropriate diet.

References

1. Arnoux J.B., Verkarre V., Saint-Martin C. et al.: *Congenital hyperinsulinism: current trends in diagnosis and therapy*. Orphanet J Rare Dis, 2011:6, 63-63.
2. Prabudh G., Subhasis R.C.: *Persistent hyperinsulinemic hypoglycemia of infancy: An overview of current concepts*. J Indian Assoc Pediatr Surg., 2012:17, 99-103.
3. Kaczirek K., Niederle B.: *Nesidioblastosis: an old term and a new understanding*. World J Surg., 2004:28, 1227-1230.
4. Ziora K., Oświęcimska J., Dyduch A.: *Some clinical and pathological aspects of persistent hyperinsulinic hypoglycemia in children*. Pediatric Endocrinology, 2006:5, 65-74.
5. Aynsley-Green A., Hussain K., Hall J. et al.: *Practical management of hyperinsulinism in infancy*. Arch Dis Child Fetal Neonatal Ed., 2000:82, F98-F107.
6. James C., Kapoor R.R., Ismail D. et al.: *The genetic basis of congenital hyperinsulinism*. Journal of Medical Genetics, 2009:46, 289-299.
7. Meissner T., Beinbrech B., Mayatepek E.: *Congenital hyperinsulinism: molecular basis of a heterogeneous disease*. Hum Mutat., 1999:13, 351-61.
8. Palladino A.A., Stanley C.A.: *Nesidioblastosis no longer! It's all about genetics*. J Clin Endocrinol Metab., 2011:96, 617-619.
9. Koklu E., Ozkan K.U., Sayar H. et al.: *Treatment of hyperinsulinemic hypoglycemia because of diffuse nesidioblastosis with nifedipine after surgical therapies in a newborn*. J Pediatr Endocrinol Metab., 2013:26, 1153-1156.
10. Rahmah R., Hayati A.R., Kuhnle U.: *Management and short-term outcome of persistent hyperinsulinaemichypoglycaemia of infancy (nesidioblastosis)*. Singapore Med J., 1999:40, 151-156.

11. Arya V.B., Senniappan S., Demirbilek H. et al.: *Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism*. PLoS One, 2014:19, 9, e98054.
12. Leibowitz G., Glaser B., Higazi A.A. et al.: *Hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission: high incidence of diabetes mellitus and persistent beta-cell dysfunction at long-term follow-up*. J Clin Endocrinol Metab., 1995:80, 386-392.
13. Meissner T., Wendel U., Burgard P. et al.: *Long-term follow-up of 114 patients with congenital hyperinsulinism*. Eur J Endocrinol., 2003:149, 43-51.
14. Ludwig A., Ziegenhorn K., Empting S. et al.: *Glucose metabolism and neurological outcome in congenital hyperinsulinism*. Semin Pediatr Surg., 2011:20, 45-49.
15. Mohamed Z., Arya V.B., Hussain K.: *Hyperinsulinaemichypoglycaemia: genetic mechanisms, diagnosis and management*. J Clin Res Pediatr Endocrinol., 2012:4, 169-181.
16. Molven A., Helgeland G., Sandal T. et al.: *The Molecular Genetics and Pathophysiology of Congenital Hyperinsulinism Caused by Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency Front Diabetes*. Basel, Karger, 2012:12, 137-145.
17. Buraczewska M., Szymanska E., Brandt A. et al.: *Congenital hyperinsulinism in Polish patients – how can we optimize clinical management?* Endokrynol Pol., 2015:66, 322-328.

