Case Report

Congenital hyperinsulinism

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ARTICLE INFO

ABSTRACT

Hyperinsulinism is the most common cause of hypoglycemia in infants. In many cases conservative treatment is not effective and surgical intervention is required. Differentiation between diffuse and focal forms and localization of focal lesions are the most important issues in preoperative management.

We present a case of persistent infancy hyperinsulinism. Clinical presentation, conservative treatment modalities, diagnostic possibilities of focal and diffuse forms, and surgical treatment, which led to total recovery, are discussed.

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1. Introduction

Hyperinsulinism in infancy is a condition characterized by severe hypoglycemia related to inappropriate insulin secretion in neonatal period or infancy [1,2]. This condition is particularly dangerous because glucose is the main energetic source of the brain. The infants' brain is especially sensitive to hypoglycemia and neuroglucopenia can cause seizures [1]. If episodes of hypoglycemia are frequent and/or long lasting, they can disturb brain development and cause severe irreversible neurological sequelae [1,2]. Prompt recognition and management of hypoglycemia are very important avoiding these consequences [1–3].

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Peer review under responsibility of Lithuanian University of Health Sciences.

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2. Case report

We are reporting a case of a boy with normal perinatal history (delivery at 38 weeks of gestation with birth weight (3760 g) and birth length (53 cm) appropriate for gestational age and gender), who was admitted to the intensive care unit at 3 months of age because of severe hypoglycemia with generalized seizures. At the time of hypoglycemia (0.9 mmol/L) insulin and C-peptide levels were increased (insulin, 15.88 µU/mL; C-peptide, 2.2 ng/mL), leading to the diagnosis of hyperinsulinism. Regular feeding every 2 h with increased amount of food was sufficient to maintain normoglycemia. The patient was discharged and an out-patient follow-up was instituted without any treatment.

The boy was admitted again at 5 months of age because of fever, diarrhea, viral upper respiratory tract infection, irritability, accompanied by recurrent episodes of hypoglycemia. The treatment was started with glucose infusions and Diazoxide 10 mg/kg/day with increasing dosage up to 25 mg/kg/day. This treatment was not effective and repeated episodes of hypoglycemia were observed 2–3 times a day. Hypoglycemia was accompanied by relatively high insulin secretion (glycemia, 1.09 mmol/L and insulin, 7.5 µU/mL; glycemia, 1.9 mmol/L and insulin, 4 µU/mL). Hydrochlorothiazide was added without substantial improvement. Only combined treatment with intramuscular injections of Octreotide (40 µg/kg/day) maintained glycemia within normal range for several days, yet it had to be discontinued because of side effects (persistent vomiting, functional invagination). Other medications (Hydrocortisone and Nifedipine) had no substantial effect on glycemic profile. Episodes of hypoglycemia became more frequent and intravenous glucose requirement increased up to 12 mg/kg/min to maintain normoglycemia. Therefore, surgical treatment possibilities and the extent of operation (total or partial pancreatectomy) were discussed. The main issue was differentiation between diffuse and focal lesion as abdominal MRI showed a normal pancreas and the PET scan was not available in Lithuania at that time. The 95% pancreatectomy was scheduled as there were no pancreatic nodular lesions on MRI, and diffuse nesidioblastosis was suspected. At laparotomy no nodular lesions in liver or other abdominal organs were identified. The body and the tail of the pancreas were exposed and examined. No nodular lesions were identified. Kocher maneuver was used to mobilize the duodenum and the head of the pancreas. At this point a 10 mm nodular lesion was identified at the level of junction of the right gastroepiploic and the middle colic vein (Fig. 1). The tumor was enucleated and sent for frozen section. No association with the main pancreatic duct was identified. As soon as the tumor was removed glycemia increased up to 11 mmol/L (prior to that the patient was on glucose infusion), and remained at the level of 6–7 mmol/L after glucose infusion was stopped. Four days later, glycemia was within normal range without any treatment. The patient was discharged after 3 months of hospitalization. The patient was reconsulted at the age of 6 and 12 months: his psychomotor development was evaluated as appropriate for age so far. Analysis of all coding and exon/intron boundaries of the KCNJ11 and ABCC8 genes (NM_000525.3, U63421 and L78208) was performed by Sanger
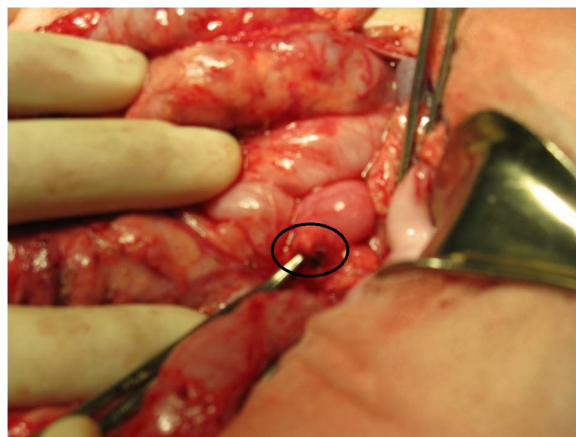

Fig. 1 – During surgery: nodular lesion in the head of pancreas.

sequencing. The boy was found to be heterozygous for an ABCC8 nonsense mutation, p.W232*. A second ABCC8 mutation has not been found and sequencing analysis of the KCNJ11 gene did not identify a change from the normal sequence. This result is consistent with a diagnosis of focal hyperinsulinism due to a (presumed) paternally inherited ABCC8 mutation. Testing of the boy's father was recommended to confirm his carrier status.

3. Literature review

3.1. Epidemiology

Incidence of congenital hyperinsulinism (CH) is reported in 1 out of 40 000–50 000 live births in general population [4]. Frequency is estimated to be much higher in consanguineous unions (1 in 2500 live births) [4].

3.2. Pathophysiology

Hyperinsulinemic hypoglycemia can be transient, persistent or as an accompanying symptom in several syndromes. Usually, transient hyperinsulinemic hypoglycemia is secondary (e.g., caused by increased pancreatic β-cells function because of maternal diabetes mellitus) [2]. In these conditions hypoglycemia usually settles within a few days after delivery and rarely requires treatment with Diazoxide and prolongs several months [5]. Hyperinsulinemic hypoglycemia may also be present in several overgrowth syndromes (Beckwith–Wiedemann, Perlman, Sotos, Kabuki, Usher, Timothy, Costello, Trisomy 13, mosaic Turner) [2,6].

CH is the most common cause of hypoglycemia in infants [2,7,8]. Mutations of several genes responsible for CH are identified (Table) [1,2,9–11].

However, in approximately 50% of the cases genes mutations are not established (or are not currently known) [1,2]. The most common causes of CH are "channelopathies", which refer to the pancreatic β-cell ATP-sensitive potassium

Table – Most frequent genes mutations responsible for CH.

ABCC8 gene, encoding SUR1 subunit of pancreatic β-cell ATP-sensitive potassium channels (K_{ATP} channels)

KCNJ11 gene, encoding KIR6.2 subunit of K_{ATP} channels

GLUD1 gene, encoding glutamate dehydrogenase, also associated with hyperinsulinism/hyperammonemia syndrome

GCK gene, encoding glucokinase (activation of GCK lowers the threshold of glucose-stimulated insulin secretion)

HADHSC gene, encoding short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD)

SLC16A1 gene, encoding monocarboxylate transporter 1 (associated with exercise-induced hyperinsulinism)

HNF4A gene, encoding hepatocyte nuclear factor 4a

UCP2 gene, encoding mitochondrial uncoupling protein 2

Insulin receptor gene

channels (K_{ATP} channels) defects [1,2,12]. The K_{ATP} channels consist of two subunits: the sulfonylurea receptor (SUR1), encoded by the ABCC8 gene, and the inwardly rectifying potassium channel (KIR6.2), encoded by KCNJ11 gene, both located in the 11p15.1 region [1,2,7]. Mutations of SUR1 gene are most frequent and are responsible for 50%–60% of CH [1]. Mutations of KIR6.2 gene are found in 10%–15% of CH cases [1]. It was established that paternally inherited mutations of the SUR1 or KIR6.2 genes and a concomitant loss of maternal 11p allele (11p15.1 to 11p15.5) results in focal pancreatic lesions with one ore multiple focuses [1,13–17]. The SUR1 and KIR6.2 germ-line mutations and mutations of other genes result in diffuse pancreatic lesions [1]. Loss of 11p15.5 allele heterozygosity leads to disturbance of the several imprinted genes expression and cell growth control [14].

Another, a less frequent subgroup of CH is "metabolopathies," caused by different genes mutations (GK, GDH or SCHAD or insulin receptor gene) [1,2]. These mutations are responsible for intracellular accumulation of intermediary metabolites or altered concentration of signaling molecules, such as ATP and ADP [1,2]. It causes functional abnormalities of β-cells and inappropriately high insulin secretion in the presence of hypoglycemia [1,2,7].

3.3. Clinical features

CH is a heterogeneous disorder and clinical severity varies with age at onset of hypoglycemia [1,2]. CH usually presents in first few days after birth with symptomatic hypoglycemia [18]. Symptoms of hypoglycemia are non-specific and the diagnosis sometimes can be delayed [2]. Hypoglycemia presents in infants with irritability, poor feeding, lethargy, seizures or coma [2]. Other symptoms are hypotonia, tremulousness, abnormal movements, cyanosis and hypothermia [1]. Some infants with CH are macrosomic (because of perinatal hyperinsulinemia) or may have mild facial dysmorphism, hepatomegaly, but absence of these features does not exclude CH [1,2,19]. Retardation of psychomotor development may manifest later in child's life.

3.4. Diagnosis and treatment

The main criterion of CH is inadequate insulin secretion, which may be diagnostic if insulin levels are increased, normal or detectable in the presence of hypoglycemia (<2.5 mmol/L) [1,2,7]. There is no correlation between severity of hypoglycemia and serum insulin levels [2]. Insulin increases glucose consumption in insulin-sensitive tissues (muscle, adipose tissue and liver) and suppresses hepatic glucose production and lipolysis [2]. Consequently, synthesis of free fatty acids and ketone bodies is suppressed during hypoglycemia. Inappropriately low levels of ketone bodies, free fatty acids and branched chain amino acids are other important features of CH [1,7,20,21]. The third criterion is intravenous glucose requirement higher than 8–10 mg/kg/min to maintain normoglycemia [1,2,7]. A good glycemic response to glucagon injection is also indicative of CH [1,2,7]. If insulin concentration is not clearly abnormal in the presence of hypoglycemia, a 4–6 h fasting test can be helpful in diagnosing CH [1]. Elevated serum lactate levels may also be found in some forms of CH [22]. Increased serum ammonia concentration during hypoglycemia may be associated with hyperinsulinism/hyperammonemia syndrome [1,23]. The molecular genetic analysis for SUR1 and KIR6.2 genes mutations may confirm the diagnosis of CH [7] (Fig. 2).

The aim of the treatment is to prevent episodes of hypoglycemia and to avoid permanent brain damage [1]. Frequent oral feeding, oral feeding via nasogastric tube, and in rare cases, continuous gastrostomy feeding may be helpful [1,20,24–26]. Usually this treatment is insufficient for infants with CH; therefore, intravenous dextrose infusion is necessary to achieve normoglycemia [20,24,25]. Diazoxide, administered in doses of 10–15 mg/kg/day, is the drug of choice [2,7]. Diazoxide acts as an agonist of the K_{ATP} channels. It suppresses insulin release by opening K_{ATP} channels and inhibiting β-cells stimulation [2,27]. Diazoxide is effective in some cases, such as transient, syndromic forms and "metabolopathies" since K_{ATP} channels are functional in these patients, whereas those with severe CH usually fail to respond [1,2,27,28]. The majority (82%) of cases with unresponsiveness to Diazoxide are related to the mutations of the ABCC8 or KCNJ11 genes [28]. Nifedipine has been used for patients with CH (0.5–2 mg/day), but vast majority of patients fail to respond [1,2]. Subsequently Octreotide may be added at doses of 10–50 μg/day [1,2,26]. Glucagon at doses of 1–20 μg/kg/h may be used for the acute management of hypoglycemia or in the short term infusion in combination with Octreotide [1,2].

Frequently, CH is unresponsive or partly responsive to conservative treatment; therefore, surgery has to be considered to ensure normoglycemia [1,3,29,30]. Differentiation of focal from diffuse forms of CH is the most important issue choosing further treatment strategies and extent of surgery [2,7,14,29]. Both forms share a similar clinical presentation; however, surgical treatment and outcomes differ considerably [26]. Focal disease (30%–60% of cases) can be completely cured with limited (partial) pancreatectomy or enucleation of tumor without long-term sequelae, while diffuse CH requires near total pancreatectomy with high probability of postoperative diabetes mellitus and other complications [1,2,7,13,21,26,29–32].

In some centers several years ago, near-total (95%) pancreatectomy was a standard procedure [7]. Radiological diagnostic procedures, such as ultrasound, CT, and MRI, rarely detect the pancreatic nodules, as these lesions are usually very
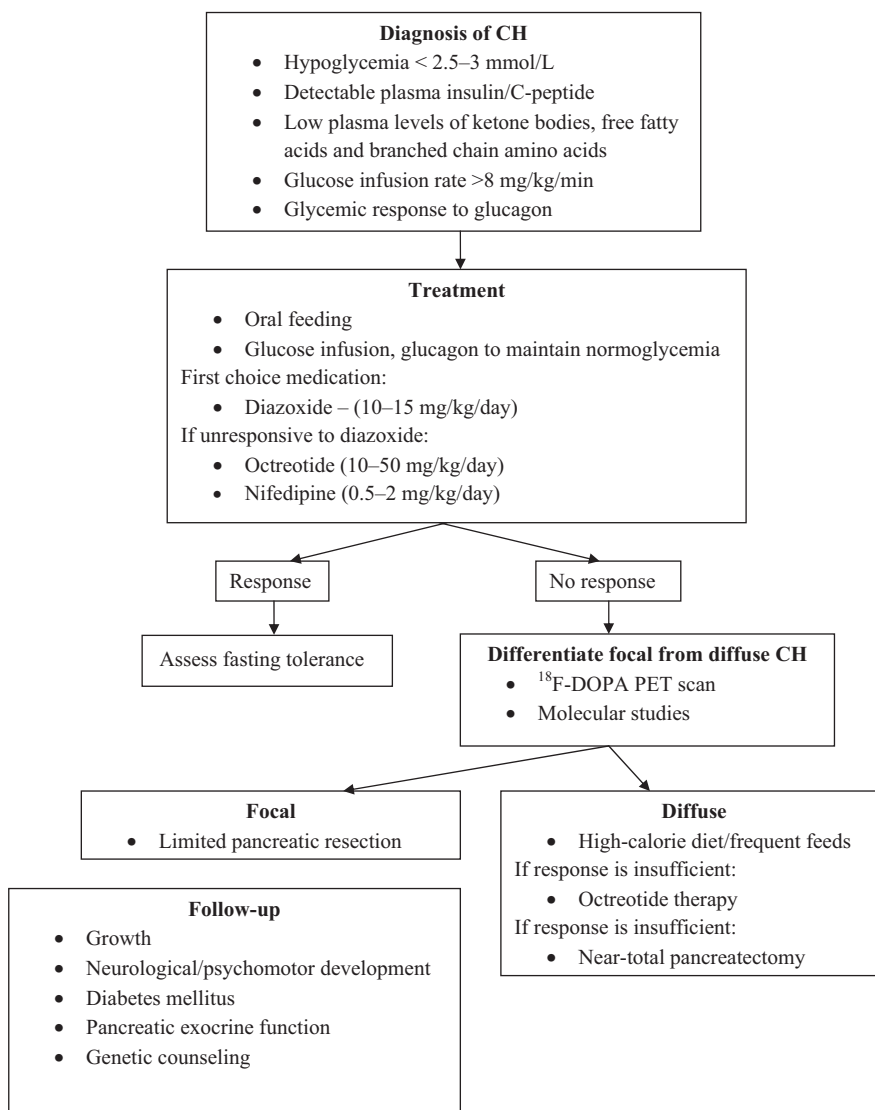
Diagnosis of CH
- Hypoglycemia < 2.5–3 mmol/L
- Detectable plasma insulin/C-peptide
- Low plasma levels of ketone bodies, free fatty acids and branched chain amino acids
- Glucose infusion rate >8 mg/kg/min
- Glycemic response to glucagon

Treatment
- Oral feeding
- Glucose infusion, glucagon to maintain normoglycemia

First choice medication:
- Diazoxide – (10–15 mg/kg/day)

If unresponsive to diazoxide:
- Octreotide (10–50 mg/kg/day)
- Nifedipine (0.5–2 mg/kg/day)

Response → Assess fasting tolerance

No response → **Differentiate focal from diffuse CH**
- ^{18}F-DOPA PET scan
- Molecular studies

Focal
- Limited pancreatic resection

Diffuse
- High-calorie diet/frequent feeds

If response is insufficient:
- Octreotide therapy

If response is insufficient:
- Near-total pancreatectomy

Follow-up
- Growth
- Neurological/psychomotor development
- Diabetes mellitus
- Pancreatic exocrine function
- Genetic counseling

Fig. 2 – Approach to investigation and treatment of CH.

small [1,7,26]. Sometimes measurement of insulin gradients in blood samples taken from catheterized pancreatic veins are used to differentiate between diffuse and focal forms of CH [1,2,7,26]. However, this method is invasive and complicated as well as multiple pancreatic biopsies during the laparoscopy [2,7].

Since 2003 the PET scan has been successfully used to distinguish the forms of CH [1,2,7,26,33]. Fluorine-18 labeled L-dihydroxyphenylalanine (^{18}F-DOPA) is used [2,7,26,33,34]. The uptake of ^{18}F-DOPA is increased in β-cells which produce higher rates of insulin [1,7,35]. Thus, PET scan imaging can detect primary or metastatic pancreatic tumors, hyperfunctional pancreatic islets and allows differentiate between diffuse and focal forms of CH and localize the lesion in focal forms [1,2,7,26,29,33,35]. This is very important for surgery planning, as enucleation of local lesions may result in complete cure [2,7]. It has been shown that ^{18}F-DOPA PET scan sensitivity was 89.0%–92.3% and specificity 98%–100% in diagnosing pancreatic tumors [33,36]. Another study showed

concordant results comparing PET scan with pancreatic venous catheterization [26].

The molecular analysis alone provides an informative genetic diagnosis for the clinical management of CH patients with recessively inherited pathogenic mutations [28]. Focal forms are observed mainly in patients who have one single fatherly inherited mutation in KCNJ11 or in ABCC8 gene [37]. In patients with a single K_{ATP} channel mutation, the molecular analysis should be systematically confronted with the parental segregation analysis and the PET imaging diagnosis. If the mutation is de novo or paternally inherited and the PET diagnosis is in favor of a focal form, the surgery will be offered for the resection of the focal lesion. However, when the PET imaging suspects a diffuse form, the molecular diagnosis has a limited added value for the clinical management of CH patients [28].

The PET studies should not be performed under the age of 1 month, to exclude patients with transient hyperinsulinism,

or in patients with a genetically proven suspected diffuse form (hyperinsulinism/hyperammonemia syndrome, syndromic hyperinsulinism and mutations in GCK, SLC16A1, HNF4A and HADH genes). Both PET and genetics give information about the form (focal or diffuse) of CH, and thus may be helpful in choosing the extent of surgical intervention [37]. Genetic counseling and prenatal diagnosis may be offered to families with such previous CH cases [28].

4. Conclusions

The diagnosis of CH in some cases may be delayed because of mild course of the disease; however, if hyperinsulinism is suspected, the diagnosing usually is not very difficult. In spite of good effect of conservative treatment in some cases, many cases will require surgery in order to avoid irreversible neurological sequelae. The extent of surgery depends on the form of CH: focal lesions may be completely cured with limited pancreatectomy or enucleation without long-term sequelae. While diffuse forms usually need near-total pancreatectomy with limited success and big chance of complications. Therefore preoperative diagnosis is of crucial importance. The form of CH (focal or diffuse) is usually not established by classical imagining. PET scan and molecular studies are strongly recommended.

Conflict of interest statement

The authors state no conflict of interest.

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