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Case Report

Congenital hyperinsulinism

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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.

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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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 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.

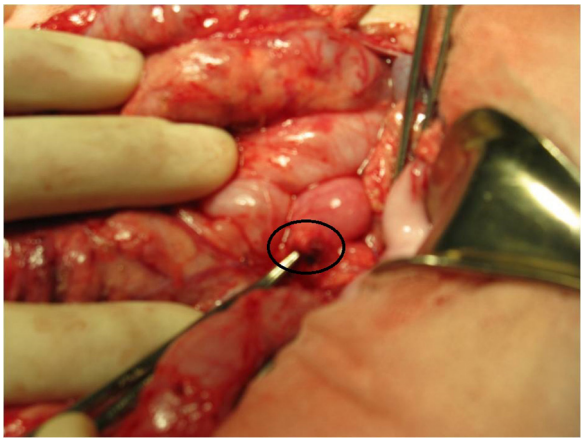

Fig. 1 – During surgery: nodular lesion in the head of pancreas.

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