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CASE REPORTS

HYPERINSULINEMIC HYPOGLYCEMIAS IN INFANCY AND CHILDHOOD -
DIAGNOSTIC THERAPEUTIC ALGORITHM WITH CONTRIBUTION OF TWO CASES

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ABSTRACT

Hypoglycemia is not an independent diagnosis. It is a pathophysiologic syndrome whose cause needs to be identified. Identifying it is just the first step to making the diagnosis as precisely as possible and to preventing brain damage. Timely diagnosis and treatment are factors of paramount importance for the prognosis of affected patients.

The aim of this study was to present two of our patients with hyperinsulinemic hypoglycemia because of the rarity of the condition and to propose a diagnostic-therapeutic algorithm of hypoglycemic syndrome in childhood.

Identifying the genetic mutations using DNA analysis for both children enabled us to determine the prognosis and to provide genetic counseling about the next pregnancies in the affected families.

We make a detailed classification of different types of hypoglycemia and the various therapeutic modalities: dietary, medicinal and surgical depending on the etiology.

It is concluded that the highly specialized examinations which ensure the etiological diagnosis, treatment, prognosis and genetic consultation demand the participation of a well trained medical team - both in the clinical division and in the laboratory.

Key words: hyperinsulinism, hypoglycemia, infancy, genetic analysis, diagnostic algorithm

INTRODUCTION

Glucose homeostasis is critical for the realization of brain metabolism; insufficient supply of glucose may cause seizures, irreversible brain damage and even death. In infants the percentage of the brain in relation to the other parts of the body is relatively greater than that in adult individuals. That is why glucose requirements of infant’s brain are relatively greater than those of adult’s brain (6-8 mg/kg/min for infants and 2 mg/kg/min for adults). The brain of the newborn and the infant enlarges and develops rapidly which makes it extremely sensitive to hypoglycemia. Lack of good adaptation to starvation is the most common reason for hypoglycemia in children. The adaptation mechanisms of homeostasis during starvation are: 1. glycogenolysis, 2. gluconeogenesis, 3. lipolysis and 4. fatty acid oxidation and ketogenesis (Fig. 1).1

Each of these mechanisms is strictly regulated by hormones. Insulin suppresses adaptation to hypoglycemic conditions, while counterinsulin hormones such as glucagon, growth hormone, cortisol and epinephrine improve it.

Hyperinsulinism is the most frequent cause of persistent hypoglycemia in infancy. An estimated incidence of hyperinsulinemic hypoglycemia (HH) is 1 in 30 000-50 000 live births. It first appears most often in the neonatal period and in infancy. Its clinical presentation is: high weight at birth, plethoric facies, enlarged internal organs, muscular hypotonia, hypothermia, seizures or loss of consciousness. Later in life the symptoms of hyperinsulinemic hypoglycemia vary - hunger, sleepiness, excessive sweating, confusion, behavioural changes, seizures. No matter what the cause is, hypoglycemia should be identified and treated immediately because of the risk of irreparable brain damage if it persists.

Further examinations aim to determine the etiology of hyperinsulinemic hypoglycemia which is a guarantee for an adequate approach - concerning treatment (surgical or medicinal), nutrition (the necessity of a specific diet), prognosis (transient or permanent) and heredity with possible risks of involving other children of the family too.1-3 To date there have been only 5 case reported in Bulgaria of patients with hyperinsulinemic hypoglycemia and 4 of them

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proved to have mutations of ABCC8 gene, which codes for SUR 1 subunit of the ATP-dependent K\textsuperscript+ channels. According to Robert S. Gillespie et al., the incidence of hyperinsulinemic hypoglycemia worldwide is 1 in 25,000 newborns.\textsuperscript{1}

The aim of our study was to present two cases with the extremely rare disorder of hyperinsulinemic hypoglycemia in infancy and the difficulties we had in their diagnosing, genetic specification and treatment, as well as to propose a diagnostic and therapeutic algorithm for the treatment of this rare pathological condition.\textsuperscript{4-8}

**CASE HISTORY**

**CASE 1**

M.F.Ch. - a female infant admitted to the Clinic of Pediatric and Genetic Diseases for the first time 8 days after birth (disease summary № 3607/09). The baby was born at the Department of Obstetrics and Gynecology of the Smolyan Hospital for Active Treatment after 6th pathological pregnancy at 35 weeks gestation by C-section because of breech presentation and fetal distress. The parents are Bulgarian Mohammedans and they are third cousins. Previously the mother had given birth to a healthy boy who is now 9 years old and she had had 4 spontaneous abortions all of them in the 3rd lunar month. The baby’s weight at birth was 4500 g, her height was 51 cm, she had macrosomia with Cushingoid habitus and was in a condition of perinatal asphyxia. Ductus arteriosus persistent was also found with a small left-to-right shunt. Laboratory test at the Smolyan hospital showed early neonatal recalcitrant hypoglycemia (on from day 2) with glucose levels down to 0.89 mmol/L. For this reason the infant was transferred to the Department of Neonatology at St. George University Hospital in Plovdiv on day 4 after birth. Because of the persistent hypoglycemia concomitant with apneic pauses and cyanosis independent of the intravenous treatment with carbohydrate solutions and for more accurate determination of diagnosis the baby was transferred to the Clinic of Pediatric and Genetic Diseases in Plovdiv 8 days after birth. The neurological status at admission showed muscular hypotonia, hyporeflexia and suppressed sucking and swallowing reflexes. Transfontanell ultrasound examination showed evidence of grade II hypoxic-ischemic encephalopathy. The general physical status of the baby was unsatisfactory, her height was 52 cm, the weight was 4260 g, she had 2-3/6 grade systolic murmur at the left sternal border, her liver was palpable 2 cm below the costal arch with soft-elastic consistency, the spleen was not palpable. Laboratory findings showed hypoproteinemia with total protein levels of 54-49-53 g/L, hypoalbuminemia with albumin levels of 32-29-30 g/L, without other pathological deviations of the biochemical indicators. The baby had anemic syndrome, which
was corrected by blood transfusion. The lactate levels were normal - 1.4 mmol/L (referent values <1.9 mmol/L) and ammonia levels were 51 \text{\mu mol/L} (referent values <47 \text{\mu mol/L}). Blood glucose levels were low - down to 1.3 mmol/L, indicating data of a 72-hours monitoring, during which in 59% of the time the blood glucose levels did not exceed 2.2 mmol/L. The metabolic screening for organic acids and defects of fatty acids \textbeta-oxidation was negative. The results of the hormonal tests were as follows: basal immunoreactive insulin - 34.4 uU/mL (referent values for the corresponding age are below 5.0 uU/mL) as the examination was repeated at 4 weeks and showed 9.0 uU/mL; cortisol and thyroid hormone levels were within the referent range; the levels of basal growth hormone (GH) were elevated - 5.92 ng/mL, which was probably associated with the hypoglycemia and the contrainsulin effect of GH. Imaging studies: abdominal ultrasound revealed enlarged hyperechoic liver and mild splenomegaly 4 weeks after hospitalization; magnetic resonance imaging revealed normal dimensions, topic and signal characteristics of the abdominal organs and no macro-morphologic pancreatic hyperplasia was found; transfontanellar ultrasound - the width of the interhemispheric fissure was at upper limits - a risky factor for atrophy of the cerebral cortex. Electroencephalographic studies showed sharp waves in the right frontal region. Echocardiography revealed open foramen ovale with a left-to-right shunt, enlarged heart volumes and more granulated structure of the tissues (gluconeogenesis -?).

Case 2.

M. S. K. - a male infant who was hospitalized for the first time at the age of five months (disease history No. 4074/09). The baby was born normally after a second normal pregnancy at 38 weeks gestation. His weight at birth was 2940 g, the height was 48 cm, and the head circumference was 35 cm. There was no data of perinatal asphyxia. Twenty hours after birth because of seizures the baby was transferred to the Intensive Care Unit of the Neonatal Department at the Plovdiv Hospital for Active Treatment. The boy was found to have hypercalcemia (2.1 mmol/L) and hypoglycemia (2.3 mmol/L) and after treatment with glucose solution, calcium preparations and anticonvulsives the child was discharged from hospital on day 8 after birth. No developmental problems were reported till the age of 3 months when after including fruit mashes in his diet the following symptoms appeared: restlessness, screaming out during sleep and when awake, staring and seizures (with hands flexion, staring and lack of response in the course of 30-40 seconds). In the days before hospitalization the baby ceased to follow with his eyes. He was admitted to the clinic to further specify the neurological symptoms. From the status at admission: the general status of the baby was not satisfactory, the child had generalized muscle hypotonia, increased amount of subcutaneous adipose tissue; his weight was 7900 g (an increase of 5 kg for 3 months). No hepatosplenomegaly was found. The boy was found to have neuropsychological developmental delay of about 2 months. The laboratory studies showed low levels of blood sugar (1.2 mmol/L), normal complete blood count, normal biochemical indicators - transaminases at the upper limits, normal ionogram and residual nitrogen. The blood-gas parameters were also normal. Urine analysis did not show any pathological findings, including lack of ketonuria. Imaging studies revealed: slightly enlarged liver with normoechogenic parenchyma; transfontanellar ultrasound - the width of the interhemispheric fissure was at upper limits, unconvincing cavitation around the anterior horns of the lateral ventricles; magnetic resonance tomography - without pathological findings in the images of the internal organs (including the pancreas) which were of normal dimensions and structure for the age. Electroencephalographic findings: basic activity of theta and delta waves, synchronous sleep spindles and vertex potential sharp and slow waves in the left posterior temporal leads. Hormone examinations showed normal levels of ACTH, growth hormone.

Genetic analysis: the examination of KCNJ11 and ABCC8 genes revealed two ABCC8 mutations in exons 19 and 26, which confirmed the diagnosis of congenital hyperinsulinism with autosomal-recessive heredity. The father of the baby was found to be a heterozygote in exon 26, and the mother - in exon 19 of ABCC8, which makes a 1/4 risk of congenital hyperinsulinism for every following pregnancy (PENINSULA Medical School -UK).

The baby received diazoxide (3 x 15 mg) and somatostatin - 6 x 20 \text{\mu g} (20 \text{\mu g/kg}). Her diet consisted of Frisolac 7 x 95 ml which was later replaced by Frisolac introduced through a permanent nasogastric tube in increasing quantities corresponding to the age of the infant as well as fractionated feeding (at intervals of 6 hours) with 40 ml of rice pap. The intravenous glucose drips of the first weeks after hospitalization were substituted with 10% glucose solution - 7 x 20 ml.
and cortisol rhythm; the levels of the basal immunoreactive insulin were high (6.0 U/mL) at low blood sugar levels (1.4 mmol/L) and it increased at 60 minutes of the oral glucose tolerance test up to 41.7 U/mL at blood sugar levels of 5.6 mmol/L. Extended blood sugar profiles showed low levels of blood sugar - between 1.7 and 3.4 mmol/L. The increase of blood sugar levels during the glucagon test from 1.8 mmol/L at baseline to 6.3 mmol/L at 60 minutes ruled out any of the forms of glycogenosis with concomitant hypoglycemia. Based on the conducted tests we were able to rule out also some other forms of hypoglycemia: ketogenic hypoglycemia - because of the lack of ketonuria and the normal results of the blood gas analysis; fructosemia - because of the lack of acidosis; glycogenosis - because of the negative glucagon test and the lack of hepatomegaly (at palpation and ultrasound examination). The normal MRI image of the pancreas ruled out adenoma in that region. Finally, the diagnosis that was accepted at the clinic was hyperinsulinemic hypoglycemia and along these lines some genetic studies were also carried out but the routine examinations of KCNJ11 and ABCC8 genes did not show any mutations. Further studies of HNF4A gene and search for mutations of GLUD1 is forthcoming (PENINSULA Medical School - UK).

The child was given carbohydrate solutions - first intravenously and later on orally through a nasogastric tube; he was fed with mother’s milk, adapted milk and fractionated intake of rice pap; he was also treated with diazoxid in a dose of 3-4 x 15 mg/kg/24 hours/ and anticonvulsants (depakrin). At discharge the baby had normal blood sugar levels - 5.1 - 6.4 mmol/L. But only 4 days after discharge the baby developed oliguric syndrome (one of the complications of diazoxid treatment) and petechial rash which made it imperative to hospitalize him again. There were no other pathological findings in his status except the quick-transient petechial rash on the back of the feet. During his stay at the department the baby developed dyspeptic syndrome with feverility. The laboratory studies at the time of hospitalization showed: normal complete blood count, elevated urea levels - 8.9 mmol/L with normal creatinine levels, high urine specific gravity - 1027 and no other pathological findings; fibrinogen levels were slightly decreased - 1.6 g/L. The hemoculture was positive for coagulase-negative staphylococcus. Medical treatment with antibiotics, diuretics, rehydration, depakins and diazoxid (in lower doses 3 x 10 mg) resulted in improvement of the baby’s general status, the infectious syndrome was successfully managed, the diuresis was restored, urea levels became normal and at oral nutrition with adapted milk and rice pap the values of blood glucose levels were at the upper limits, while basal insulin levels considerably decreased (0.1 u/mL). There was no further worsening of the electroencephalographic findings. But our attempts to reduce the dose of diazoxid were not successful - blood sugar levels decreased again and that necessitated going back to the high-dose treatment of 10 mg/kg/24 hours.

The rarity of hyperinsulinemic hypoglycemia is the reason we report these two cases treated at the Clinic of Pediatric and Genetic Diseases in Plovdiv. In connection with the diagnostic and therapeutic difficulties in each of the cases with hypoglycemia in childhood we offer a contemporary classification of these conditions and a practical diagnostic-therapeutic algorithm for rapid diagnosing and adequate etiological treatment.

**Diagnostic Algorithm Of Hypoglycemia**

**History:** family, time of onset and relation to nutrition:
- early postprandial hypoglycemia - a defect of glycogenolysis or hyperinsulinism
- late hypoglycemia - after continuous fasting - disturbances of fat metabolism, glyconeogenesis and of the hormones which control it - cortisol and epinephrine.

**Status:** overweight, growth retardation, hepatomegaly, hypogentalism. The symptoms associated with hypoglycemia may develop in two phases: first phase - associated with the sympathoadrenal system and increased secretion of catecholamines and neurotransmitters, and second phase - neurohypoglycemia which causes brain hypoxia and edema.

Laboratory studies: blood glucose, blood gas analysis, insulin, C-peptide, cortisol, ACTH, growth hormone, TTH, thyroxin, free fatty acids, β-hydroxybutirate, lactate, ammonium, carnitine. Tests - oral glucose tolerance test (GGT), glucagon test. Urine - ketones, organic acids, non-glucose reducing substances.

Figure 2 presents a diagnostic-therapeutic algorithm applicable for everyday practice. When genetically dependent hyperinsulinemic hypoglycemia is suspected it is possible to carry out additional genetic examination of the child and its family. Several gene mutations have been described in congenital hyperinsulinemic hypoglycemia - ABCC8,
Figure 2. Diagnostic and therapeutic algorithm for hypoglycemic conditions in childhood (modified from Sperling et al.)
GH - growth hormone; IRI - immunoreactive insulin; SGA - small for gestational age.
Hyperinsulinemic Hypoglycemias in Infancy and Childhood – Diagnostic Therapeutic Algorithm with Contribution of Two Cases

KCNJ11, GLUD-1, GCK, HADH, MPI, HNF4A with autosomal recessive or autosomal dominant heredity; sporadic cases were also reported.11-13

Classiﬁcation of hypoglycemias

I. Transient neonatal hypoglycemia - it is caused by endogenous or exogenous substrate insufﬁciency and/or immature enzyme and endocrine function as well as by increased consumption. It appears in 10% of the mature newborns and more frequently in cases of prematurity, in infants who are too small for their gestational age, in children of diabetic mothers, in discordant twins and in cases of perinatal asphyxia. In such cases transient hyperinsulinemia is supposed secondary to the perinatal stress.

II. Persistent neonatal hypoglycemia, hypoglycemia in infancy and hypoglycemia of later age - it is most often determined by genetic defects of the insulin secretion, but all congenital metabolic and endocrine disorders are also included in this group.

1. Hyperinsulinism - it is the most common cause of hypoglycemia in the neonatal period and the second in frequency after ketogenic hypoglycemia in older children.14 It is characterized by early manifestation - in 60% of the cases it occurs early as in the first week of life. The clinical presentation is dominated by the neurological symptoms of hypoglycemia - seizures, lethargy, neuropsychological developmental delay. Laboratory constellation in all of these forms is associated with the high insulin levels > 2 μIU/ml, free fatty acids levels < 1.5 mmol/L, hypoketonemia - plasma-β-hydroxybutyrate < 2.0 mmol/L and positive glycemic response to the glucagon stimulation test - over 2.5-fold increase of the initial blood glucose levels, which indicates good hepatic glycogen reserves and glycogenolysis enzymes. The introduction of the genetic tests has made it possible to identify several forms of hyperinsulinism with different course, treatment, inheritance and prognosis:

A. Congenital hyperinsulinism as a result of K ATP /SUR1 and KIR6.2 - channel mutations.15 Gene locus - 11p15.1, diffuse forms of recessive or dominant inheritance, ABCC8 gene which codes for SUR1 and KCNJ11 gene which codes for KIR6.2. These are the most frequent forms of congenital hyperinsulinism but there are more than 100 mutations of ABCC8 gene and 20 of KCNJ11 gene which are also well known. SUR1 subunit is sensitive to changes of β-cells energetic status; it regulates the mechanisms of opening and closing of the potassium channel pores. The forms of recessive inheritance have a heavier course. The constant open state of the K ATP channels results in disturbances of β-cell function regarding the decrease of insulin secretion in hypoglycemia. Hyperinsulinism in this genetic variant is additionally enhanced by the intake of amino acids with food because they have a depolarization effect on the cell membrane. The frequency of this condition is about 1 in 40 000 newborns, but in a country with high rates of consangunuity such as Saudi Arabia the reported frequency is 1/3000. The focal form is associated with a mutation of the paternal K ATP channel and with a specific loss of maternal allele and imprinting of 11p15 chromosome locus. The loss of the normal tumor-suppressing gene of the maternal allele leads to focal expansion of abnormal β-cells and to the development of focal pancreatic lesions.

B. Congenital hyperinsulinism as a result of gene GLUD-1 mutation, which codes for the mitochondrial enzyme glutamate-dehydrogenase. In it hypoglycemia is combined with hyperammonemia.

C. Glucokinase hyperinsulinism - glucokinase catalyzes glucose phosphorylation which is the first step of glycolysis.

D. Congenital hyperinsulinism associated with SCHAD-deﬁciency. It is an autosomal-recessive hereditary disorder which is associated with a defect of the enzyme activity of SCHAD (short chain 3-hydroxyacyl-CoA-dehydrogenase) - a mitochondrial enzyme which catalyzes the conversion of 3-hydroxyacyl CoA into 3-ketoacyl CoA - the third step of the β-oxidation cycle of the fatty acids.

E. Congenital hyperinsulinism associated with carbohydrate-deﬁcient glycoprotein syndrome type 1B. Carbohydrate-deﬁcient glycoprotein syndromes present a heterogeneous group of disorders which are characterized by psychomotor and mental retardation, coagulation disturbances and glycoprotein hypoglycylazion. Type 1B is characterized by hyperinsulinemic hypoglycemia, sometimes by protein-losing enteropathy and congenital hepatic fibrosis, but it does not affect neuropsychological development. Genetically, it is connected with mutation of phosphomannose isomerase, but for the present moment there is no explanation of the hyperinsulinemic hypoglycemia. Clinically it presents with protein-losing enteropathy and hypoglycemic conditions.

F. Hyperinsulinemic hypoglycemia in children with diabetic mothers. Hyperglycemia in utero to which the fetus of poorly compensated diabetic mother is subjected results in compensatory hyperinsulinemia and macrosomia.
G. Hyperinsulinism associated with peripartal stress - it usually affects newborns with low weight for their gestational age, prematurely born infants and infants who were born with asphyxia.

H. Insulinoma - Insulinomas are the most frequent functioning neuroendocrine tumors of the pancreas in adults and their incidence is 4/1 000 000/yearly. In the children population insulinomas are very rare.

I. Beckwith-Wiedemann syndrome - genetically it refers to a paternal isodisomy of 11p15.5 chromosome.

J. Hypoglycemia in diabetes mellitus

2. Counter-regulatory hormonal deficiency
   A. Panhypopituitarism
   B. Isolated growth hormone deficiency
   C. ACTH deficiency
   D. Addison's disease
   E. Epinephrine deficiency

3. Disorders of glycogenolysis
   Glycogenosis - this is a hereditary autosomal-recessive disorder caused by enzyme defects of glycogen degradation, which is stored in the liver, kidneys, heart, muscles, central nervous system, etc. With hypoglycemia are associated glycogenolysis type I, type III, type VI, type IX and type O. Type I is the most frequent of them - Gierke's disease.

4. Disorders of gluconeogenesis
   A. Galactosemia - this is a genetic autosomal recessive disorder which is a result of defects of three main enzymes, as in the most frequent classic form it is connected with deficiency of galactose-1-phosphate-uridyltransferase.
   B. Hereditary fructose intolerance - it is an autosomal recessive disorder in which fructose-1-phosphate accumulates in the liver, kidneys and the intestine as a result of fructose-1-phosphate-aldolase deficiency.
   C. Disorders of fatty acid oxidation - various enzyme defects are known which affect the α-oxidative cycle, the synthesis of ketones, the carnitine cycle and the mitochondrial transfer. B-oxidation of fatty acids is closely associated with the generation of energy for gluconeogenesis and because of that hypoglycemia is the main symptom. The most common defects are deficiency of medium-chain acetyl-CoA dehydrogenase and carnitine deficiency. They cause hypoketogenic hypoglycemia at the age between 6 and 24 months at continuous fasting, vomiting and infections which often cause encephalopathy and death.
   D. Disorders of amino acid and organic acid metabolism
      - Maple syrup urine disease - Leucinosis - Tyrosinosis - Propionic acidemia - Methylmalonic acidemia - Hydroxy-3-methylglutaril acidemia.

The diagnosis in such cases is proved by metabolic screening. Prenatal diagnosing is also possible.

5. Hypoglycemias in substrate deficiency
   A. Ketogenic hypoglycemia - it is the most common cause of hypoglycemia in older children. Usually it occurs after continuous fasting or is associated with different infections.
   B. Hypoglycemias in:
      - malnutrition
      - malabsorption
      - diarrhea
      - burns
      - shock
      - Munchhausen syndrome

6. Hypoglycemias in hepatic and systemic disorders
   - Reye's syndrome
   - Hepatitis
   - Cirrhosis
   - Sepsis
   - Heart failure
   - Renal failure etc.

7. Drug-induced hypoglycemia - insulin, calculates, ethyl alcohol, oral anti-diabetic drugs etc.

8. Defects of glucose transporters - GLUT 1 and GLUT 2 deficiency - they induce hypoglycemia at normal plasma levels of glucose.

CONCLUSIONS

Hypoglycemias in neonatal period and infancy are comparatively frequent and need immediate diagnosis and treatment. Rarer even is the condition of hyperinsulinemic hypoglycemia, which needs exact biochemical, hormonal, imaging and genetic diagnosing. Over the last decades, thanks to the highly improved laboratory methods a number of disorders have been found other than insulinoma, which was described by Gerhard Katsch 70 years ago. Highly specialized examinations which ensure the etiological diagnosis, treatment, prognosis and genetic consultation require participation of a well trained medical team - both in the clinical divisions and in the laboratories. Modern pharmacology has made treatable a number of diseases with fatal outcomes in the near past. The two cases presented by us are of casuistic interest because of their rarity as disorders and because of our success to diagnose the extremely rare double hemizygosity of
the pathologic genes in the first case. The favourable effect of the medical treatment with diazoxid and somatostatin and with an adequate diet which resulted in improved blood glucose levels also illustrates the accuracy of the diagnosis and supports literature data which was cited in the review. The practical diagnostic therapeutic algorithm presented by us may be suitable to help precise diagnosing without unnecessary examinations. A part of the diagnostic procedures which refer to the specific gene defect for the present moment are inaccessible in our country.

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