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Clinical Case Seminar **CCS4 (1-6)**

A case of neonatal persistent hyperinsulinemichypoglycemia

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Abstract

Neonatal hypoglycemia (NH) is a common and important cause of morbidity in newborns. The most common cause of NH is congenital hyperinsulinism (CHI), a phenotypical and genotypical heterogeneous condition characterized by inappropriate insulin secretion. In our case a male, AGA, newborn from vaginal delivery at 37-week gestation, with no risk factors in maternal history, presented with asymptomatic hypoglycemia (30 mg/dL) at 30 minutes after birth. He was subsequently admitted to the NICU because of persistent hypoglycemia associated with symptoms development (peripheral tremors). Newborns can present with a wide variety of symptoms, including irritability, tremor, feeding impairment, coma, or be completely asymptomatic.
He was treated with continuous glucose infusions progressively increased to a rate of 12.7mg/kg/min. Because of persistent hypoglycemia (> 72h) and high i.v. glucose needs (>10 mg/kg/min) screening tests during fast-induced hypoglycemia were performed and isolated hyperinsulinism was detected. Oral medical therapy with diazoxide was started with benefit. Genetic testing was also performed to characterize CHI.
The diagnosis is usually based on clinical and biochemical findings. The mainstay of therapy is oral diazoxide administration. However, in cases refractory to medical therapy, 18F- DOPA-PET can be used to identify specific histological patterns which may need surgical intervention.
Neonatal CHI-induced hypoglycemia should always be considered in the differential diagnosis of NH. Prompt diagnosis and genotypic characterization of CHI through clinical, biochemical, radiological, and genetic testing is fundamental for a proper therapeutic management of the condition and for prevention of neurological sequelae.

Key-Words: hypoglycemia; congenital; hyperinsulinism; diazoxide

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Introduction

Neonatal hypoglycemia (NH) is a very common condition in the newborns and represents an important cause of morbidity in this group of patients. Congenital Hyperinsulinism (CHI) constitutes a clinically and genetically heterogeneous disorder characterized by a dysregulation in the process of β-cell insulin secretion. This condition is the most common and severe cause of persistent hypoglycemia in neonates-children and its frequency is approximately 1/30.000–1/50.000 [1, 2].

Insulin usually stimulates lipogenesis, inhibits free fatty acid release and ketone bodies formation through beta-oxidation process. Hyperinsulinism results in a strongly decreased availability of alternative fuels for cerebral metabolism [3]. The resulting severe hypoketotic state can permanently damage the brain of neonates and infants, which has commonly a higher rate of glucose consumption and it is more physiologically vulnerable to hypoglycemia compared to adult subjects.

Thus, prompt diagnosis and appropriate management of hypoglycemia disorder etiology are essential to prevent brain damage (e.g. cerebral palsy, epilepsy) and to improve neurological outcome, particularly in case of underlying CHI. This condition is histologically classified into two types, diffuse and focal disease. The former is inherited in an autosomal recessive (or dominant) manner, the latter is typically sporadic in inheritance and is localized inlimited areas of the pancreas. Lesions can be localized by using a positron emission tomography with Fluroine-18L-3, 4-dihydroxyphenyalanine isotope (18F- DOPA-PET) [4]. Eleven types of CHI-related genes have been found and are responsible for heterogeneity of this disease phenotype. Mutations in the genes ABCC8 and KCNJII usually cause alteration in the process of biosynthesis or intrinsic functioning of adenosine triphosphate (ATP)-sensitive potassium channel and they constitute the most common and clinically severe form of CHI, accounting for 40–50% of cases [5].

Diazoxide unresponsiveness and a high glucose infusion rate requirement associated with diffuse form disease, as well as focal one on 18F-DOPA-PET-CT scan, are considered indications for surgery.

For all this reasons, the management of CHI is still complex and the integration of clinical, biochemical, molecular, and imaging items is required to choose a prompt and appropriate treatment according to the different possible subtype.

Case Report

We report a case of a male infant with normal perinatal history. He was born to a primigravida mother at 37 week-gestation by vaginal delivery. Child's Apgar scores after birth were 7 and 9 at 1 and 5 minutes respectively. His weight was 2380 g (6^{th} percentile according to IneS Charts, therefore born "appropriate for gestational age"), with normal values for length and head circumference. There was no family history of diabetes, hypoglycemia, misdiagnosed infantile seizures or unexplained deaths, no intra-partum drugs were administered during pregnancy (e.g. oral hypoglycemic agents, glucose infusion). Antenatal ultrasound showed an intrauterine growth retardation in the last trimester of gestation.

His peripheral blood glucose level at 30 minutes after birth was 30 mg/dl, thus at first intravenous bolus of 10% glucose was administered, followed by a continuous infusion of same solution at

rate of 6 mg/kg/min and regular oral feeding every 2-3 hours. He was admitted to the neonatal intensive care unit at day 3 of age because of unresponsive persistent hypoglycemia and generalized tremulousness associated to irritability. Complete blood count and urinary metabolism were normal, septic markers were unremarkable.

First physical examination revealed the following: temperature of 36.3 °C, pulse of 138 beats/minute, slightly elevated respiration rate (51 breaths/min). No organomegaly, dysmorphic or syndromic features, cardiac, lung or abdominal abnormalities were identified. Acrocyanosis and slight tremors of extremities were present. The muscle tone was normal. Main primitive reflexes including Moro, grasping, sucking, and rooting reflex, were regularly observed. Because of more frequent episodes of hypoglycemia, central access was placed and intravenous glucose requirement was increased up to 12.5 mg/kg/min to maintain normoglycemia.

At 48 hours of life, neonatal screening for metabolic disorders on blood spot cards was performed and resulted negative. In the light of persistent hypoglycemia (lasting more than 72 hours) and high intravenous glucose infusion rate (≥ 8-10 mg/kg/min), screening tests during fast-induced hypoglycemia were performed. At the time of hypoglycemia (25 mg/dL) insulin levels were increased (24.8μU/mL), whileserum ketones were absent and acyl carnitine levels were low; similarly, fasting serum ammonia, lactate, cortisol, GH and IGF1 levels were normal. In addition, no inborn errors of metabolism or alterations of thyroid function were detected.

Thus, according to laboratory findings congruent with CHI, oral diazoxide treatment was started with a dosage of 6 mg/kg/day. This measure was effective after 7 days of therapy and glucose infusion was gradually reduced up to suspension, with no recurrence of hypoglycemia. After informed consent was obtained, samples of peripheral blood were collected from the child and his parents for genetic studies.The patient was discharged with oral diazoxide and regular feeding with infant formula.

Discussion

CHI is the principal cause of persistent hypoglycemia, constituting the majority of morbidity related to hypoglycemia in the neonatal age. The inappropriate and unregulated secretion of insulin in relation to the blood glucose concentration represents the mechanism underlying this condition and it is caused by mutations involving K-ATP channels coding genes of β cells. [6] The most common mutations responsible for diffuse CHI are located in the genes ABCC8 and KCNJ11, that encode respectively for two subunits of K-ATP channel, the SUR1 (sulphonylurea receptor 1 subunit) and Kir 6.2. These mutations stop the potassium channel opening, thus causing a continuous inward flux of calcium and persistent insulin secretion from β cells.

Patients affected by CHI have a higher risk of brain damage secondary to inhibition of fatty

acid release, ketone body synthesis and glucose production by glycolysis or gluconeogenesis [7], consequently depriving the brain of its primary and secondary energy fuel. Neonates with CHI and hypoglycemia can present a wide range of symptoms, ranging from non-specific adrenergic ones (palpitations, sweating, irritability, tremors, poor feeding) to severe neuroglycopenic ones, including seizures, unconsciousness, hypotonia, lethargy and coma. An asymptomatic condition, as our case report demonstrates in the early phase, does not exclude hypoglycemia. This condition most commonly develops during the neonatal period with most severe and life-threatening presentation, but it can also occur later during infancy, childhood and even adulthood.[8, 9]

In case of hypoglycemia, differential diagnosis is basedon both clinical and biochemical items, particularly considering the delay in the diagnosis confirmation of HH based on molecular analysis. Newborns with HH can be macrosomic. Nevertheless, even if hypertrophic cardiomyopathy and/or hepatomegaly (secondary to an increased storage of glucose as glycogen) can present as effects related to fetal hyperinsulinaemia, the absence of these items does not exclude the diagnosis of HH and their presence can be strictly related to fatty acid oxidation disorders and glycogen storage diseases, respectively. Other metabolic and endocrine causes of neonatal hypoglycemia should be excluded. Neonatal jaundice, micropenis, cryptorchidism and midline defects (such as a single central incisor, lip or palate defects, absence of the corpus callosum) can orient the diagnosis toward congenital hypopituitarism. Hyponatremia and weight loss are suspicious for an underlying adrenal insufficiency condition.

As regards biochemical findings in case of occurring hypoglycemia, the absence of acidemia excludes gluconeogenic disorders and glycogen storage diseases(lack of elevated lactate and ketone bodies levels, respectively), but it can orient the diagnosis to a fatty acid oxidation disorder, particularly if associated to elevated serum free fatty acids levels with low ketone bodies ones.

Main goals of medical treatment are to correct hypoglycemia and to inhibit inappropriate insulin secretion thus restoring production of ketone bodies as alternative energy source for the brain [10]. Increasing frequency or volume of feeds with formula can be considered as first line approach in neonates able to tolerate nasogastric or oral feeding and presenting mild or asymptomatic hypoglycemia. If symptoms occur, immediate treatment involves bolus of 2 ml/kg of 10% glucose followed by continuous infusion of same solution at starting rate of 6-8 mg/kg/min, which is slightly higher than physiological hepatic production rate (4 mg/kg/min). In some cases, an intravenous glucose infusion rate can be >25 mg/kg/min required to maintain normoglycemia and compensate the uncontrolled and persistent endogenous insulin secretion.

Repeated boluses should be avoided as potential additional trigger for insulin secretion.

If it is necessary to increase glucose concentration during infusion, central access placement should be considered.

Diazoxide is a K-ATP channel opener, ligand of SUR-1 subunit, used as first line medical therapy in many patients affected by CHI [6]. Its efficacy is verified in case of CHI with normal K-ATP channels function, therefore unresponsiveness to it is common in the presence of recessive (and some dominant) K-ATP channel mutations which affects the total amount of synthetized protein. The initial dose of treatment is 5 mg/kg/day, in three divided doses, which can be increased up to a maximum dose of 15-20 mg/kg/day [11]. Side effects such as electrolyte imbalance, fluid retention, pulmonary hypertension and cardiac failure should be carefully monitored during treatment. The use of a thiazide diuretic (such as chlorothiazide) is usually suggested in the neonatal period in order to prevent fluid retention.

Management in differential diagnosis, genetics analysis and therapeutic strategies of CHI is strictly influenced by initial diazoxide responsiveness. If first line treatment fails, blood glucose levels can be stabilized using high glucose infusion along with glucagon or octreotide.

Octreotide (somatostatin) works as an insulin secretion inhibitor by binding to K_{ATP}channel and somatostatin receptors 2-5. It has to be administered by subcutaneous injections with a recommended initial dose of 5 μg/kg/ day given at 6-8 h intervals with a maximum dose of 30-35 μg/kg/day. Side effects may include transient hyperglycemia expiring after 48 hours because of tachyphylaxis mechanism, therefore dose adjustment can be required during treatment.

Treatment of CHI sometimes includes combination of medical and surgical therapies. 18F-DOPA-PET scanning is nowadays the only diagnostic imaging tool able to localize lesions responsible for hyperinsulinemic hypoglycemia and to differentiate between focal and diffuse forms of CHI[12]. Focal disease and medically unresponsive diffuse disease on 18F-DOPA-PET-CT scan are indications for surgery in CHI. The treatment for patients with the focal form of CHI is partial pancreatectomy, while near-total pancreatectomy is considered in medically unresponsive diffuse form, leading to an important risk of pancreatic exocrine insufficiency and subsequent development of diabetes mellitus

Conclusions

The management of hypoglycemia induced by CHI is still challenging and requires a multi-disciplinary team approach (clinicians, geneticists, radiologists, surgeons) in order to properly manage the severe morbidity of this conditions in neonates [13]. Prompt diagnosis and specific treatment of the underlying cause of hypoglycemia is crucial to prevent neurodevelopmental retardation and improve neurological outcome. Integration of clinical, biochemical, radiological

imaging and even genetic items represent a milestone in establishing the correct treatment according to the phenotypically and genotypically specific subtype.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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