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Case Report

Prolonged Neonatal Transient Hyperinsulinism without Predisposing Perinatal Factors

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Abstract

Prolonged neonatal transient hyperinsulinism can occur in newborns without predisposing perinatal factors. It can present as congenital hyperinsulinism responsible for severe hypoglycemia requiring early treatment to reduce the risk of long-term neurological sequelae. We report a case of prolonged neonatal transient hyperinsulinism in a full-term infant born by spontaneous vaginal delivery, without intrauterine growth retardation, maternal diabetes, or perinatal asphyxia. On the 2nd day of life, the newborn developed symptomatic hypoglycemia varying between 1.2 and 2 mmol/L, non-ketotic, associated with high plasma insulin levels varying between 42 and 59 mUI/L, persistent despite high glucose infusion rate up to 18 mg/kg/min and resisted to glucagon, hydrocortisone and somatostatin. However, the newborn was sensitive to diazoxide at dose of 13 mg/kg/day started on the 18th day of life and stopped at 32 days of age due to normalization of glycemia and insulinemia at 7.6 mUI/L. After 24 months follow-up, no further hypoglycemic episodes were recorded, growth and psychomotor development were normal.

Keywords: Hypoglycemia; Transient hyperinsulinism; Newborn; Diazoxide

Introduction

Transient neonatal hyperinsulinism is a common cause of hypoglycemia in newborns, most often favorable before the 3rd day of life. It is generally associated with perinatal stress such as intrauterine growth retardation, unbalanced maternal diabetes and perinatal asphyxia [1]. However, in some of these newborns, hyperinsulinism can persist beyond a few days and lead to severe hypoglycemia requiring early treatment to reduce the risk of long-term neurological sequelae. Most of these cases respond well to diazoxide, and the hyperinsulinism eventually resolves within few weeks to few months [2,3]. However, in the absence of such predisposing factors, prolonged transient neonatal hyperinsulinism is rarely reported in the literature [1,4,5]. We report the clinical presentation and the course of prolonged transient neonatal hyperinsulinism in a newborn without predisposing perinatal factors and we discuss the clinical and therapeutic aspects of this condition.

Case Presentation

This male infant was born by spontaneous vaginal delivery at 40 weeks gestation, to non-consanguineous parents, to primigravida mother, with a birth weight of 2900 g and Apgar score was 9 at 5 min. The pregnancy was uneventful and maternal oral glucose tolerance test was normal. His clinical examination at birth was normal. There was no sign of perinatal asphyxia or neonatal infection. On the 2nd day of life, the newborn developed hypotonia, poor feeding and left upper limb seizures with a blood glucose capillary at 1.1 mmol/L, which was stabilized transiently with infusion of glucose solution. Persistent hypoglycemia and seizures required increased glucose infusions with phenobarbital and antibiotics parenterally for maternofetal infection. The initial biological assessment showed severe hypoglycemia at 1.4 mmol/L, negative ketones, normal full blood count and blood gas analysis, lactate at 3.7 mmol/L, ammonia at 76 µmol/L, normal blood calcium and magnesemia, normal renal and hepatic function, normal lumbar puncture and negative C-reactive protein. Despite continuous gavage feeding with preterm formula and glucose infusions up to 16 mg/kg/min, persistent hypoglycaemia required intramuscular injection of 1 mg of glucagon, given on the 6th day of life at the time of severe hypoglycemia to 1.2 mmol/L, which increased blood glucose to 2.2 mmol/L. Blood samples for investigation demonstrated an elevated plasma insulin levels ranging from 42 to 59 mIU/L in the presence of hypoglycaemia and appropriately elevated levels of growth hormone at 20 µg/L and cortisol at 634 µg/L with normal ACTH. Thyroid function tests were normal for age. Ammonia levels were normal. Amino acid and organic acid screening excluded underlying metabolic disorders. Abdominal ultrasound, brain and pancreatic MRI was without anomalies. The karyotype was normal, 46, XY. Faced with the non-availability of diazoxide, hypoglycaemia persists despite high glucose infusion rate up to 18 mg/kg/min and resists to 3-day course infusions of glucagon at l mg per day, hydrocortisone at 8 mg/kg per day and somatostatin at 20 µg/kg per day. The infant was started on diazoxide at a dose of 13 mg/kg/day on the 18th day of life, which led to normalization of blood glucose levels, gradual reduction of intravenous requirements for glucose and stopping the infusion. Diazoxide was gradually reduced and stopped at 32 days of age without recurrence of hypoglycaemia and normalization of insulinemia to 7.6 mIU/L. The patient was discharged at 35 days of age on enteral feedings of first age infant milk and treatment with phenobarbital which was stopped at 3 months of age because of the absence of seizures and EEG without anomalies. During 24 months

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of follow-up, no further hypoglycemic episodes were recorded, his growth and psychomotor development were normal.

Discussion

Hyperinsulinism is the most common cause of refractory hypoglycaemia in newborns. It represents a group of clinically and genetically heterogeneous disorders, characterized by inappropriate insulin secretion by pancreatic β-cells [6,7]. Persistent neonatal hyperinsulinism is a form of congenital hyperinsulinism that is usually severe, commonly due to genetic mutations, often refractory to treatment with diazoxide and requires pancreatectomy in the majority of cases. Previously published studies show that 38 to 79% of cases of persistent neonatal hyperinsulinism are associated with pathogenic genetic variants, and currently 14 genes are identified to be associate with this disorder: ABCC8, KCNJ11, GCK, GLUD1, HNF4A, HNF1A, HADH, SLC16A1, UCP2, HK1, PGM1, PMM2, FOXA2 and CACNAD1 [4,5]. Conversely, there is a severe form of prolonged transient neonatal hyperinsulinism, which is usually associated with certain perinatal complications and is most often resolved within weeks after birth, but it can also be very severe and last up to a few months and resembles the clinical course of persistent neonatal hyperinsulinism [2,6]. However, as in our patient, prolonged transient neonatal hyperinsulinism without predisposing perinatal factors is rarely reported in the literature and is generally excluded from discussion in large series [1,3,5]. Genetic testing for these mutations was not performed in our patient due to the excellent response to diazoxide and resolution of hyperinsulinism within a few weeks, which led to the diagnosis of idiopathic prolonged transient neonatal hyperinsulinism due to hyperactivity of glutamate dehydrogenase [1,8]. Our case suggests that there is a broader spectrum of perinatal factors causing prolonged transient neonatal hyperinsulinism whose etiology is often unknown and may represent a mild form of persistent neonatal hyperinsulinism. To our knowledge, transient neonatal hyperinsulinism has been reported in neonates of mothers with poorly controlled type 1 or gestational diabetes, in premature, in neonates with intrauterine growth retardation, in severe perinatal stress secondary to asphyxia, rhesus or platelet isoimmunization, in infants prenatally exposed to maternal drugs such as sulfonylureas or β-blockers, in erythroblastosis fetalis, and in certain syndromes such as Beckwith-Weidemann syndrome and hyperinsulinism-hyperammonemia syndrome [2,6,9,10]. The pathogenetic mechanism of hyperinsulinism in neonates of diabetic mothers is better understood. In this case, persistent maternal hyperglycemia leads to fetal hyperglycemia and insulin hypersecretion, which persists after birth leading to neonatal hypoglycemia that resolves after several days [1,7]. However, in neonates with intrauterine growth restriction or severe perinatal asphyxia, hyperinsulinism is usually more prolonged and may persist for several months. It has been suggested that the association of asphyxia and intrauterine growth retardation predisposes to more severe prolonged hyperinsulinism and hypoglycaemia [11]. Recently, Louvigne et al. [12] reported that mothers of newborns with prolonged transient hyperinsulinism had significantly higher gestational weight gain suggesting higher caloric intake compared to those consuming fresh vegetables and low-fat products. Although the etiology of hyperinsulinism in this group of neonates remains an enigma, it is clear that their hypoglycemia is part of a multifactorial phenomenon, which includes glycogen depletion, impaired gluconeogenesis and increased glucose demand and utilization [1,10]. Our case illustrates well that prolonged transient hyperinsulinism can occur in neonates without predisposing perinatal factors. The clinical manifestations of transient neonatal hyperinsulinism are variable and non-specific. Clinical symptoms of hypoglycemia appear usually within the first 48 hours of life and depend on the severity of hypoglycemia and the patient's age, ranging from asymptomatic hypoglycemia revealed by routine glucose monitoring, to symptomatic hypoglycemia revealed by hypothermia, hypotonia, poor feeding, or neuroglycopenic symptoms such as irritability, lethargy, apnea, seizures, especially in the most severe cases [4]. These clinical manifestations do not make it possible to differentiate between the transient form and the persistent form of hyperinsulinism during the neonatal period. Therefore, genetic testing has been suggested by some authors for patients who do not respond or who require a high dose or have a prolonged need for diazoxide [13]. Our patient developed severe symptomatic hypoglycemia on the 2nd day of life, revealed by poor feeding, generalized hypotonia and seizures requiring very high intakes of glucose and glucagon, reflecting the markedly elevated plasma insulin level, and suggesting the possibility of severe persistent neonatal hyperinsulinism. However, the response to diazoxide treatment in our patient allowed us to retain the diagnosis of prolonged transient neonatal hyperinsulinism. The diagnostic criteria for neonatal hyperinsulinism include persistent fasting and post-prandial hypoketotic hypoglycemia lower than 3 mmol/L after the 3rd day of life, high plasma insulin concentrations >10 mUI/L, elevated C-peptide levels concomitant to hypoglycemia, high rates of glucose infusion greater than 10 mg/kg/min required to maintain the blood glucose above 3 mmol/L and positive response within 30 minutes after subcutaneous or intramuscular administration 0,5 mg of glucagon with increase blood glucose concentration by 2 to 3 mmol/L [5,14]. Insulin levels are not a significant predictor of transient hyperinsulinism. Indeed, insulin has a short half-life and therefore low or undetectable serum insulin levels during hypoglycemia do not exclude the diagnosis of hyperinsulinism. Because C-peptide has a longer half-life than insulin, C-peptide testing is more reliable than insulin in diagnosing hyperinsulinism. Higher C-peptide levels and higher glucose infusion rates requirements may serve as clinical tools to identify neonates with transient hyperinsulinism who may benefit from diazoxide treatment [15]. Although hypoglycemia can be managed by using high calorie milk formula with frequent feeding in some patients, pharmacological intervention is necessary for most infants with prolonged transient neonatal hyperinsulinism [1,3,5]. In our patient, the effective glycemic control could only be achieved after the start of diazoxide therapy with resolution of the hyperinsulinism within a few weeks without fluid retention and without rebound hypoglycemia upon discontinuation of treatment. Indeed, more than 90% of patients with transient hyperinsulinism respond to diazoxide at the initial dose of 5 to 15 mg/kg/day [3]. Diazoxide suppresses insulin secretion by activating the KATP channel in pancreatic cells [3,4]. The existence of severe forms of transient neonatal hyperinsulinism reinforces the importance of maintaining diazoxide therapy for a sufficient duration, even in the most severely affected patients, particularly in diazoxide-sensitive neonates. Therefore, it is important to wait at least 4 weeks before considering pancreatic surgery to exclude transient neonatal hyperinsulinism [1,13]. Admittedly, diazoxide is generally well tolerated and effective for the treatment of prolonged transient neonatal hyperinsulinism as in our patient. However, diazoxide has a number of side effects which need careful monitoring such as fluid retention, excess body hair, cardiopulmonary instability and severe thrombocytopenia [4,13]. In case of non-responsiveness to diazoxide, second-line treatment

involves somatostatin receptor analogues, typically octreotide, which act to inhibit insulin release. The drug is administered as subcutaneous or intravenous injections 4 to 6 times/day and can also be administered as continuous infusion by either rout. Initial doses of 5 µg/kg/day need adjustment upwards to doses at the limit of the normal doses range 30 to 35 µg/kg/day. In most children, treatment beyond these doses is of no therapeutic value. However, in exceptional cases, octreotide dose may be as high as 50 to 60 µg/kg/d. Tachyphylaxis may limit the effectiveness of octreotide. It causes a rapid decrease in the response to octreotide, 24 to 48 hours after the initiation of this treatment. The mechanisms responsible for tachyphylaxis have not been determined, but are likely to involve desensitization of receptor-mediated responses. Consequently, response to octreotide can only be assessed 2 days after initiation of a new daily dose. However, side effects may occur just at the start of treatment such as vomiting, diarrhea, abdominal distension, necrotizing enterocolitis in preterm babies, which resolve spontaneously within 7 to 10 days. However, fatal necrotizing enterocolitis has also been reported in some neonates [13,14].

Conclusion

The prolonged transient hyperinsulinism can occur in neonates without predisposing perinatal factors. The unusual sensitivity to diazoxide highlights the importance of prompt detection and early treatment of severe forms of transient neonatal hyperinsulinism while maintaining euglycemia, prevent refractory hypoglycemia and adverse neurodevelopmental sequelae. Studies investigating genetic mutations in these patients may elucidate new mechanisms in the pathophysiology of prolonged neonatal hyperinsulinism.

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