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Research Paper

Hyperinsulinemic hypoglycemia in infant – A case report

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ABSTRACT: *Hyperinsulinemic hypoglycemia is an important condition usually identified during the neonatal period being a rare cause of neonatal hypoglycemia. In this case report, we discuss a case of the condition in an infant in the state of Minas Gerais – Brazil, and the management of its case.*
KEYWORDS: *Hyperinsulinemia, hypoglycemia, infant, diazoxide, octreotide, insulin*

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I. INTRODUCTION

Hyperinsulinemia is one of the most common causes of persistent hypoglycemia in neonates and infants, a life-threatening condition that affects their well-being and development. It is characterized by an imbalance between insulin production and insulin release at times when serum glucose levels are low and may clinically present in diverse ways.

Given the harm of hypoglycemia in the development of children affected by hyperinsulinemia, rapid identification of the condition and early management is crucial to avoid permanent neurological damage resulting from it.

Currently, management is by clinical measures using drugs such as insulin release regulators, insulin antagonists, or destruction of pancreatic islet cells. (5) In recent literature, the most common management of hypoglycemic hyperinsulinemia is the use of diazoxide, an insulin release regulator, or octreotide, a somatostatin analog (1, 5).

In patients that show resistance to clinical treatment, currently, surgical treatment can be planned to cure or alleviate the hyperinsulinemic condition in which the patient is, depending on the diagnosis received by the patient.

This study aims to report a case of hypoglycemic hyperinsulinemia in an infant and discuss the therapeutic possibilities.

II. CASE REPORT

An 8-month-old infant, born at term during normal gestation and delivery, weight appropriate for gestational age without intercurrence or hypoglycemia at the time of delivery. On examination, no physical atypia was noted, and neonatal screening was within the normal range. Immediate family members of the patient had no comorbidities or genetic conditions and were healthy.

The patient presented hypoglycemia since birth without a definitive diagnosis, under investigation for hyperinsulinism and/or probable innate error of metabolism. The patient was under pediatric endocrinological follow-up at home and was admitted to Santa Casa de Montes Claros for recurrent and refractory hypoglycemia that worsened after ingesting infant formula.

He was started on serotherapy with glucose infusion therapy of 4 mg/kg/min and oral dietary change with raw starch, with no response, requiring a progressive increase of glucose infusion therapy (GIT) up to the value of 6 mg/kg/min.

Propaedeutics were performed for hyperinsulinism with laboratory confirmation in a critical sample where an increased insulin level was observed in a sample with a result of 6.4 mmUI/mL and glycemia at

34mg/dL. Treatment with diazoxide associated with hydrochlorothiazide was initiated, and remained stable for 4 days, even with progressive reduction of glucose infusion therapy. After this period, hypoglycemia returned and the dose of diazoxide was adjusted, with no response.

On admission to the Hospital Infantil João Paulo II, a therapeutic plan was made for the patient in which glucose infusion therapy was maintained at 6 mg/kg/min, the use of diazoxide was maintained, and new interventions with pre-diet glycemic control every 3 hours with correction in case of hypoglycemia (if glucose measured <60 mg/dL), and octreotide 0.1 mg/mL in a subcutaneous dose of 0.24 mL every 6 hours was initiated.

Among the interventions for glycemic control, it was agreed in a multidisciplinary meeting to correct hypoglycemia <60 mg/dL with a bolus of hypertonic glucose (GH50%) 30mL with a new blood glucose measurement after 15 minutes. If hypoglycemia is maintained, perform a new bolus in a maximum of 3 attempts with measurement of capillary blood glucose every 15 minutes after infusion. If the patient is refractory to glucose bolus, administer glucagon 0.03mg/kg intramuscularly with a new blood glucose measurement after 20 minutes.

In case of hypoglycemia resistant to the administration of the above measures, was planned to perform a peripheral access site and start glucose infusion therapy at an initial dose of 3mg/kg/min, titrating the dose as needed until blood glucose levels of > 60mg/dL were reached.

III. DISCUSSION

Hyperinsulinemic hypoglycemia is a rare condition that manifests with increased insulin levels in the setting of hypoglycemia (1), such as the patient described. It is estimated to affect about 1 in every 40000 live births in the entire population.

The disordered release of insulin leads to rapid consumption of glucose by tissues that use it as a carrier, however, in the scenario of hyperinsulinism, no correlation between insulin levels and hypoglycemia severity is evidenced, and a normal insulin level for reference levels may be considered pathological in a scenario of hypoglycemia (7), as in the case of the aforementioned patient where insulin levels of 6.4 mmIU/mL were observed in the presence of blood glucose at 34mg/dL.

Besides reducing serum glucose levels by promoting its consumption by adipose muscle and liver tissues, which are sensitive to insulin (1), there is also the promotion of metabolic effects resulting from it, such as inhibition of hepatic gluconeogenesis and lipolysis, creating a state of hypoketotic hypoglycemia.

The mechanism of organic response to hypoglycemia varies according to the elapsed time, being the first mechanism the promotion of gluconeogenesis with the release of glucagon and use of hepatic glycogen and lipolysis, and in the latter, there is the production of ketone bodies. (2) It is observed in hyperinsulinism the antagonism to glucagon, not generating new glucose molecules by hepatic pathway and inhibition of lipolysis, thus not forming the expected ketone bodies in the presence of hypoglycemia.

The diagnosis must be made as early as possible to avoid brain damage due to hypoglycemia. Usually, this condition presents itself in the neonatal period and may also present itself in other phases of the individual's life, but more severely in the first. Neonates with hyperinsulinemic hypoglycemia may present macrosomia, cardiomyopathy, and hepatomegaly, but the absence of these does not mean the absence of the disease. (7).

Symptoms usually present during the neonatal period with symptomatic hypoglycemia. The symptoms are non-specific such as lethargy, irritability, feeding difficulty, and even convulsions and coma. Less aggressive forms are usually present later during childhood. (7)

Diagnosis is made with a blood sample at a time of hypoglycemia, showing an inappropriate level of insulin and ketone bodies for the condition, the former being increased, and the latter decreased. The rampant increase in insulin levels leads to glucose consumption by insulin-dependent tissues while suppressing hepatic glucose production, lipolysis, and ketogenesis.

The diagnostic criteria used for such a condition are (8):

-Glycemic level in blood sample <3mmol/L with detectable insulin and C-peptide level

-Glucose infusion rate >8mg/kg/min to maintain euglycemia

-Low ketone levels

-Low fatty acid levels

Lactate and ammonia levels are usually abnormal as a consequence of hypoglycemia (7) as well as other hormonal mechanisms that are under the regulation of insulin and glucose levels. Examples include glucagon and cortisol, which are regulated in part by glucose levels and may require replacement in some cases of the disease. (7).

The management of the condition is usually particular to each case because measures to control other conditions resulting from hyperinsulinemic hypoglycemia may be necessary. Treatment of these patients must be done in a multidisciplinary manner with medical and sometimes surgical therapy. The initial focus of treatment is on maintaining adequate blood glucose levels. (8).

Carbohydrate is usually provided by intravenous dextrose concentrate as well as oral or nasogastric nutrition with or without glucose polymers to increase carbohydrate intake. Administration of dextrose concentrate should be done by central venous or umbilical catheter. (8)

Among the drug treatments, diazoxide is considered the first-line treatment and is administered orally. Glucagon and octreotide are used subcutaneously or intravenously in cases refractory to regular treatment. (5)

Diazoxide exerts its action by controlling APT-dependent potassium channels in pancreatic β-cells, keeping them open and inhibiting insulin secretion. It generally has good tolerance among patients, and its initial dose is between 5-15mg/kg/day divided into two or three doses. (5)

Octreotide is used primarily in cases refractory to Diazoxide. It has a short half-life and should be administered subcutaneously every 6 to 8 hours or by continuous infusion pump, or intravenously. It has a maximum dose between 15-50 μg/kg and can evolve with tachyphylaxis to the drug, requiring reassessments throughout the treatment. (5)

The use of exogenous glucagon is indicated in cases where emergency treatment is needed in a scenario of severe hypoglycemia, but it is not indicated for long-term treatment (5).

Surgical treatment is indicated when the patient is resistant to conventional treatment and dietary recommendations to maintain euglycemia. This recommendation must be made individually evaluating the needs and clinical picture of the patient.

IV. CONCLUSION

Considering the discussion above, it can be inferred that the management and treatment of the patient in question were appropriate for his case of hyperinsulinemic hypoglycemia. In this case, adjuvant treatment with both glucagon and octreotide was required since poor response to treatment with diazoxide and dextrose infusion initially.

The patient responded well to the octreotide treatment, and it was maintained until further notice by the multidisciplinary team for later reevaluation. Initially, glucagon was prescribed as a rescue treatment in case of refractory to octreotide, dextrose infusion, and regular feeding.

The patient was kept hospitalized until access to the treatment with octreotide was assured. The medication was requested from the government health department due to its limited availability and high cost for the general population. Without its granting, it’s not possible to maintain the patient's treatment at home at the moment.

The child's family was also oriented about the administration of octreotide and required dietary measures when discharged from the hospital. It is necessary to emphasize the importance of family participation in cases like these as one of the pillars for successful treatment.

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