Persistent Hyperinsulinemic Hypoglycemia of Infancy: A Clinical Case Report

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ABSTRACT

Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI) poses a significant challenge due to congenital hyperinsulinemia leading to low blood sugar levels, requiring immediate intervention to prevent potential long-term neurological complications. This case study outlines the presentation, diagnosis, and management of a 5-day-old infant exhibiting severe hypoglycemia symptoms, despite conventional glucose infusion rates. Notably, genetic mutations in ABCC8 and KCNJ11 genes underlie the pathogenesis, with diagnostic confirmation aided by specialized imaging techniques like 18F-DOPA-PET. Treatment modalities encompass pharmacotherapy targeting insulin secretion, including diazoxide, octreotide, and glucagon, alongside surgical options for refractory cases. This comprehensive analysis underscores the importance of advancing diagnostic strategies and therapeutic interventions to optimize outcomes for patients with PHHI.

Keywords: Persistent Hyperinsulinemic Hypoglycemia of Infancy, Neurological Injury, Surgery, Glucose

INTRODUCTION

PHHI, or Persistent Hyperinsulinemic Hypoglycemia of Infancy, arises from congenital hyperinsulinemia, leading to an excessive release of insulin within the body, ultimately resulting in low sugar levels. Insulin, a peptide hormone, is produced by the Langerhan cells in the pancreas and plays a crucial role in regulating glucose, carbohydrates, and lipid metabolism in the body [1]. It reduces blood glucose levels by boosting its peripheral utilization, stimulates glycogen formation, and inhibits glycogen breakdown and gluconeogenesis. Given that neonates and infants have a higher rate of glucose utilization in the brain compared to adults, they are more prone to neurological injury caused by hypoglycemia as a result of these processes [2].

Transient episodes of hyperinsulinism can arise briefly due to certain predisposing factors, including perinatal asphyxia, intrauterine growth restriction, maternal diabetes mellitus, or in association with various congenital disorders of glycosylation. However, Congenital hyperinsulinism (CHI) is caused by genetic mutations that disrupt insulin secretion regulation and primarily involves genes like ABCC8, KCNJ11, GLUD1 etc [2]. The disease also shows histological variability, encompassing a diffuse form affecting the entire pancreas, a focal type called focal adenomatous hyperplasia, and isolated cases known as insulinomas [3].

Diagnosing hyperinsulinism (HI) hinges on obtaining a critical blood sample during spontaneous or provoked hypoglycemia, typically when plasma glucose is < 50 mg/dL (2.775 mmol/L). Key indicators also include a glucagon stimulated rise in glucose.

Detectable insulin during hypoglycemia suggests inappropriate insulin secretion, though absence of elevated insulin doesn't rule out HI as diagnosis relies on a comprehensive assessment of biochemical markers rather than solely on insulin levels [4]. Lastly, the main objective of treatment is to avoid severe hypoglycemia and achieve blood glucose levels near to normal. Treatment options encompass diet, pharmacotherapy, and surgery. Diet including frequent carbohydrate rich meals is generally favored over pharmacotherapy, which in turn is preferred over surgical approaches depending upon the severity of the disease [5].

CASE PRESENTATION

A 5-day-old female infant weighing 4.5 kilograms came with initial symptoms of poor feeding, lethargy, respiratory distress and irritability. She was born at full term via spontaneous vaginal delivery and weighed 4kgs. The mother had an uneventful pregnancy with no gestational diabetes or hypertension. Upon admission, the infant exhibited profound hypoglycemia, with a blood sugar level of 22mg/dl (1.22 mmol/L). A thorough general physical examination including the vitals along with the genital examination was done to look for any dysmorphic features, signs of hypopituitarism and cutaneous stigmata. No significant findings like cleft lip or palate, any skin pigmentations, or ambiguous genitalia were found. The infants heart rate was noted to be 110 beats per min (bpm), Respiratory rate was 44 breaths per minute and temperature was afebrile. Oxygen saturation was 90% at room air. Moreover, bilateral crepitations were appreciated on chest examination and there were no other signs of respiratory distress found.

To stabilize her condition, we initiated O2 delivery via nasal prongs and administered 10% dextrose saline. We conducted initial tests, including complete blood count (CBC), urea and electrolytes (UCE), C-reactive protein (CRP), and blood cultures. Additionally, we started treatment with claforan and amikacin injections and presumed that she had sepsis. The glucose infusion rate (GIR) was initiated at 8mg/kg/min but despite that, her blood sugar levels remained persistently low. We started treatment with injection Hydrocortisone and later on added Diazoxide 5 to 10mg/kg/day divided in 3 doses. The IV fluids level started at 10%, were increased up to 12.5% but there was no improvement in her blood sugar levels. The glucose infusion rate was then increased to 10mg/kg/min on the 6th day of life(DOL). The infant continued to experience multiple hypoglycemic episodes with RBS being as low as 35 mg/dl (1.94 mmol/L). Critical sampling was sent the following day and ultrasound abdomen was done. There were no significant findings on the ultrasound abdomen and the results of critical sampling are provided in the table below. Glucose levels were observed to be as low as 20 mg/L and insulin was slightly raised. Additionally, C peptide levels were also raised indicating the increased endogenous insulin release. There was a significant increase in cortisol, lactate and ammonia providing further evidence of the hypoglycemic state.

Furthermore, we started injections of Octreotide 0.5-5 mcg/kg/dose SC Q12H and glucagon to address the ongoing hypoglycemia. The patients condition seemed to improve the following day and there were no hypoglycemic episodes noted. The fluid levels were shifted to 10% on the 11th DOL, the infant was alert, active and off O2, GIR was gradually decreased from 10mg/kg/min to 6mg/kg/min on the following days, antibiotics were stopped and Hydrocortisone was slowly tapered off.

On the 13th DOL there was another hypoglycaemic episode noted which further led to increased dosage of Diazoxide and Octreotide. Positron emission tomography scan with Fluroine-18L-3,4-dihydroxyphenyalanine isotope scan (18F- DOPA-PET) was done which showed focal area of overexpression of somatostatin receptors at the body and tail of pancreas.The IV fluids were stopped after 2 days when the RBS returned to its normal range. The patient was then

referred to the surgical department for partial pancreatic resection. The parents received guidance on the long term management plan and the ongoing care required for their child, which involved regular monitoring of blood sugar levels and identifying the symptoms of hypoglycemia. They were informed about potential complications such as neurological development delays, necessitating frequent visits for follow-up appointments. Additionally, they were provided with the option of genetic counseling to understand the genetic implications and the risks of the condition recurring in future pregnancies. They were also encouraged to breastfeed regularly and informed about the crucial significance of timely vaccinations.

Our Case	Normal Range	
Glucose	40-150 mg/dL(2.22-8.33 mmol/L)	20 mg/dL(1.11mmol/L)
Insulin	5-20 µIU/mL	23.60 µIU/mL
Cortisol	3-21 ug/dL	66.4ug/dl
C peptide	0.5-2.0ng/dL	5.24ng/ml
Lactate	4.5-19.8 mg/dL	44.81mg/dl
Ammonia	15-35 umol/L	88.4umol/L
Testosterone	<10-20 ng/dL	7.97ng/dl
Growth Hormone	1-20 ng/mL	2.51ng/ml
Free Androgen Index	No established range	1.09%
Sex hormone binding globulin	No established range	25.21nmol/L

CASE DISCUSSION

hyperinsulinism hypoglycemia represents the predominant cause of hypoglycemia in infants and children. It may manifest as transient or permanent, typically attributed to genetic mutations and poses a potential risk of life-threatening consequences, including neurological harm. This condition, though uncommon, affects approximately 1 in 40,000 births within the general population [6].

ABCC8 and KCNJ11 gene mutations are the main genetic causes of neonatal diabetes and hyperinsulinism and can be identified by rapid molecular genetic testing. These genes control the ATP-sensitive potassium channels in β-cells, crucial for glucose-triggered insulin secretion. Dysfunctional channels disrupt potassium efflux, causing membrane depolarization and unregulated calcium entry, resulting in insulin release regardless of glucose levels [7,8].

Congenital Hyperinsulinism (CHI) presents in two histological forms which are diffuse and focal. In diffuse CHI, which can be inherited in an autosomal recessive or dominant pattern, the entire pancreas is impacted. Focal CHI occurs sporadically and affects only a portion. A specialized 18F-DOPA-PET scan is used to differentiate between the lesions [9].

Recognizing hypoglycemia symptoms is vital, given their spectrum from mild indicators like inadequate feeding and lethargy to more severe outcomes such as apnea, seizures, or coma. Therefore, it is important to avoid any delays in making a diagnosis to prevent serious brain injuries [10]. The diagnosis mainly depends on its clinical presentation and The criteria to diagnose includes recurring or prolonged hypoglycemia despite a glucose infusion rate (GIR) exceeding 8mg/kg/min, with normal being 4-6 mg/kg/min. Any patient experiencing multiple hypoglycaemia episodes despite glucose administration indicates a CHI. Such newborns could also be macrosomic at the time of birth along with having cardiomegaly or hepatomegaly but the absence of that doesn't necessarily rule out the condition [9]. Plasma insulin levels might not show a significant increase, rather there's insufficient suppression of insulin when blood glucose levels are low [11]. Moreover, there might be observable C-peptide levels during hypoglycemic episodes, alongside low levels of ketones and fatty acids. When uncertainty arises regarding diagnosis, a favorable glycemic response (>1.5mmol/L) to glucagon or octreotide therapy provides additional evidence supporting hyperinsulinemic hypoglycemia [11]. In our case, there was a notable demand for high glucose infusion rates, starting at 8 mg/kg/min. Along with that there was a slight increase in insulin levels supporting the diagnostic criteria mentioned above.

Maintaining plasma glucose levels above 3.5 mmol/L is crucial for brain function, with treatment options including medical, surgical, or combined therapies. Glucagon is vital for managing CHI, especially in emergencies, inducing a rapid increase in glucose levels. Moreover, Diazoxide, a KATP channel opener, inhibits insulin release and is effective for most CHI cases but not for those with certain mutations, in which further molecular testing and scans like 18F-DOPA-PET/CT are indicated to identify those patients who could have the focal form of CHI. Diazoxide is given orally in the dose of 5-20 mg/kg/ day in 3 divided doses along with thiazide diuretics to counteract its side effects [12,13]. A known calcium channel blocker, Nifedipine, can be used in the cases where diazoxide fails to work. Second line treatment includes Octreoride, which is a somatostatin analogue, activating the somatostatin receptor 5, stabilizing the Katp channel and inhibiting the insulin release.It is given as 6-8 hourly subcutaneous injections in a dose of 5-25 mcg/kg/day [14]. Additional treatment options encompass the use of long-acting somatostatin analogs, administered subcutaneously every four weeks, enhancing family adherence. Sirolimus, an mTOR inhibitor, diminishes β-cell proliferation and suppresses insulin production. Lastly, Exendin, a GLP-1 receptor antagonist, represents another viable therapeutic avenue [15].

For patients with Diffuse CHI unresponsive to medical intervention, near-total pancreatectomy is recommended. Conversely, in cases of Focal CHI, 18F-DOPA-PET aids in pinpointing the precise lesion location, guiding the choice between Laparoscopic lesionectomy and open laparotomy. Laparoscopic lesionectomy is preferred when the lesion is readily reachable in the body or tail, whereas open laparotomy is necessary for lesions in hard-to-access areas like the head of the pancreas [6]. After the surgical treatment, irrespective of the underlying diagnosis, it's crucial to assess all children to ascertain whether they exhibit euglycemia, experience persistent hypoglycemia, or develop hyperglycemia necessitating insulin therapy [16].

CONCLUSION

Through our detailed examination of the patient's clinical course and therapeutic response, we have elucidated the urgency of early detection and intervention in managing this condition effectively. The profound implications of sustained hypoglycemia on neurological function underscore the necessity for swift and comprehensive treatment protocols. It also highlights the importance of having a multidisciplinary approach involving neonatologists, neurologists and endocrinologists for effective long-term management strategies. Moving forward, continued research and careful clinical monitoring are essential to refine our approach to PHHI diagnosis and management, ultimately improving outcomes for affected individuals.

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