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Rare presnetation of familial hyperinsulinemic hypoglycemia of infancy

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Abstract
Background: Familial hyperinsulinemia is the most common cause of persistent hypoglycemia in infancy and is due to defective negative feedback regulation of insulin secretion by low glucose level. It is also referred as Congenital Hyperinsulinism, Nesidioblastosis or Persistent hyperinsuinemic Hypoglycemia of Infancy.
Characteristics: A 2 day old baby with recurrent (persistent) and severe hypoglycemia along with g6pd variant Outcome Baby diagnosed to have hyperinsulenemic hypoglycemia on Next generation sequencing later on started on inj octrotide on which she improved and got discharged in stable condition.
Message: The condition should be considered in the differential diagnosis of severe and persistent hypoglycemia in neonates.

Keywords: hyperinsulinism, persistent hypoglycemia, infancy

Introduction: Case Report

A Single live term female baby was delivered via LSCS for bad obstetric history of previous neonatal death within few months of delivery and a previous IUD at 3 month of age of gestation. On 2nd PND, baby was found to have an episode of hypoglycemia and was managed outside and then baby was referred to us for further evaluation and management.

Baby presented to us with lethargy and hypoglycemia on admission. Sepsis was suspected and managed with IV fluids and IV antibiotics. But hypoglycemia was persistent, so glucose infusion was started @ 6mg/kg/min and increased to 12mg/kg/min since hypoglycemia was refractory. Later sepsis screening was found to be negative. Feeding was started but hypoglycemia persisted. Initially baby tolerated feed well and it was increased to 15ml 3hourly. But baby continued to have hypoglycemia and vomiting episodes in view of this Galactosemia was suspected, investigations were sent to screen for inborn errors of metabolism (Urine for reducing substance and ketones, ammonia, lactate and ABGA) and lactose free diet was given hourly following which the frequent episodes of hypoglycemia were reduced, but occasional hypoglycemic episodes persisted.

On investigations we found that sepsis screen was negative, urine for reducing substance and ketones were negative, blood lactate normal, ABGA showed normal blood gas parameters and Serum ammonia was also normal based on these findings we thought of 2 strong possibilities FHHI and FAOD and planned for serum insulin levels which came very high therefore the diagnosis of familial hyperinsulenimic hypoglycemia was made and investigation were planned to identify the cause of FHHI. To rule out the possibility of Pancreatic tumors etc USG abdomen and pelvis were done which showed mild hepatomegaly.

Baby showed improvement on hourly feeds however baby was not taking Katori spoon or breast feed well therefore we continues NG feeds alternate with spoon feeding which she had tolerated well.

DNA test revealed “A Homozygous missense variation in exon 2 of ABCC8 GENE that result in the amino acid substitutions of tryptophan for Arginine at Codon 74 Was Detected” Familial Hyperinsulinemic Hypoglycemia -1 Is Caused By Mutation In The Abcc8 Gene.

Also “A heterozygous missense variation in the exon9 of the G6PD GENE that results in the amino acid substitution of threonine for alanine at codon 365 was detected”. Nonspherocytic Hemolytic anemia is caused by mutations in G6PD gene. Due to partial phenotypic match, this G6PD variation is classified as a variant of uncertain significance and has to be carefully correlated with the clinical symptoms.

Once the baby was diagnosed with FHH-1 (PPHI), Zerolac was stopped. Baby was given normal formula feeds and complex carbohydrates with low glycemic index powder. Tab Hydrocorticosone was started @10 -15mg/m2/day)orally but the bay continued to have hypoglycemia in view of this, Diazoxide was started which also didn’t work well therefore injection Octreotide was started following which the Baby had improved, mainatained sugar well above 60mg/dl and discharged from the hospital after about 1 and ½ months of hospitalization. In last follow up the baby was 6 months old and achieved neck holding bidextrous grasp, and was recognize her mother and family members.

Discussion

Hyperinsulinemic hypoglycemia has increasingly been recognized as a cause of intractable hypoglycemia in neonates and infants. Hyperinsulinemic hypoglycemia occurs due to unregulated insulin secretion from β-cells of pancreas in relation to blood glucose levels [1]. Small for gestational age (SGA) infants and macrosomic infants born to diabetic mothers (IDM) are the two most common groups of infants at risk of hypoglycemia in the neonatal period [2]. Glucose is the principal energy source for the neonatal brain and hypoglycemia is known to cause irreversible neuronal injury when it is recurrent and severe; so prompt recognition and treatment of these infants with hyperinsulinemic hypoglycemia is paramount [3]. Hyperinsulinemic hypoglycemia can be transient, prolonged or persistent (congenital). Knowledge of blood glucose homeostasis and appropriate investigations for intermediary metabolites during an episode of hypoglycemia is the cornerstone for diagnosis and management of hyperinsulinemic hypoglycemia. The management of medically unresponsive hyperinsulinemic hypoglycemia still remains a challenge. Knowledge of the genetic mutations, newer imaging modalities like Fluorine 18L-3, 4-dihydroxyphenylalanine positron emission tomography (18F-DOPA-PET) scan and availability of histological differentiation of focal and diffuse forms of persistent hyperinsulinemic hypoglycemia has streamlined the management of congenital hyperinsulinemic hypoglycemia (CHI) [4].

Transient symptomatic hypoglycemia is the most common metabolic abnormality in the neonates and is seen in A per 1000 term infants and 6 per 1000 premature infants. However 1% of these infants have sustained or repeated episodes of hypoglycemia and call for prompt reorganization and management.

CHI is a heterogeneous condition presenting with hyperinsulinism, hypoketonemia, and hypo-fattyacidemia with severe and persistent hypoglycemia. The etiopathogenesis of CHI can be due to two major defects known as channelopathies and metabolopathies. Channelopathies refer to defects in the pancreatic â-cell ATP-sensitive KATP channel that lead to unregulated insulin secretion, the commonest genetic cause being autosomal recessively inherited inactivating mutation in ABCC8 and KCNJ11(chromosome11p15.1) genes [5]. Metabolopathies cause congenital hyperinsulinemic hypoglycemia either by altering the concentration of intracellular signaling molecules (such as ATP/ADP) or by accumulation of intermediary metabolites, triggering insulin release. The commonest cause for metabolopathies is Hyperinsulinism-Hyperammonemia (HI/HA) syndrome. The incidence of CHI is estimated to be 1:40,000-50,000 in the general population, but in familial forms it may be as high as 1:2500 in populations with substantial consanguinity [6].

These children are highly susceptible to develop neonatal damage, psychomotor retardation and neonatal death. Therefore it should be recognize and treated early. Management includes continuous supply of glucose through high rates of glucose infusion. Feeding was continued with glucose polymer orally or through nasogastric tube to maintain blood glucose level. Feeding should be continued even during sleep. Glucagone for emergency situations and somatostatin to inhibit glucose mediated release of insulin. Diazoxide as first line drug to stimulate secretion of catecholamine and to metabolize glycogen. Octrotide is used in patients with Diazoxide unresponsiveness. Surgery is indicated if there is failure of medical management or presence of focal lesion which is amenable to surgical resection or poor compliance to medical management.

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