PERSISTENT HYPOGLYCEMIA - CONGENITAL HYPERINSULINISM OF INFANCY
A CASE REPORT.

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Abstract:
Congenital hyperinsulinism of infancy (CHI) is a condition in which there is inappropriate insulin secretion by the pancreatic beta islet cells secondary to various genetic disorders. Recurrent episodes of hyperinsulinemic hypoglycemia may expose the infant to the risk of brain damage. CHI is characterized by high glucose requirement to correct hypoglycemia, hypoglycemia which responds to exogenous glucagon and absence of ketone bodies during the hypoglycemic period. CHI presents with two main clinically indistinguishable histopathological lesions diffuse and focal. Partial pancreatectomy effects complete cure in focal lesions whereas in diffuse variety even after Near total pancreatectomy the long term outcomes may not be satisfactory. Here we report about an infant who presented with altered sensorium, recurrent seizures, persistent hypoglycaemia, respiratory failure and shock due to congenital hyperinsulinism. She required glucose infusion rates upto 20mgkgmin and Octreotide 20mcgkgday to maintain euglycemia until thirty days of life. She did not respond to medical management with Diazoxide and Nifedipine. Subsequently 68 Ga-DOTANOC PET scan of the pancreas revealed diffuse pancreatic hyperplasia. She required Near-total pancreatectomy and subsequently the infant maintained euglycemia.

Keyword: Congenital hyperinsulinism, Persistent hypoglycemia, DOTANOC scan, Pancreatectomy.

INTRODUCTION:
Congenital hyperinsulinism of infancy (CHI) is a clinically and genetically heterogeneous disorder with both familial and sporadic forms, characterized by dysregulation of insulin secretion. The main characteristic findings of CHI are high glucose requirement to correct hypoglycemia, responsiveness of hypoglycemia to exogenous glucagon and absence of ketone bodies during hypoglycemia. In children with CHI, the normal relationship between plasma glucose concentration and insulin secretion is disturbed and insulin is...
released even during periods of hypoglycemia. In the absence of glucose, brain tends to utilize the ketone bodies as an alternative substrate. (1) However, in Congenital Hyperinsulinism brain is deprived of both glucose and ketones as insulin inhibits both lipolysis and ketogenesis. (2) Congenital Hyperinsulinism (CHI) is usually isolated but may be rarely a part of a genetic syndrome (e.g. Beckwith–Wiedemann syndrome, Sotos syndrome, etc.). The severity of CHI is indicated by the glucose infusion rate required to maintain normoglycemia and the responsiveness to medical treatment. Neonatal onset Hyperinsulinism is usually severe and the response to medical and surgical therapy also varies.

CASE REPORT:
A term (38 weeks) female neonate weighing 3100 grams was referred to our Institution on day two of life with recurrent seizures. There were no maternal medical illness including gestational diabetes and her fetal period was unremarkable. She had normal transition at birth. She was on direct breast feeds and had no problems with breastfeeding. She presented with recurrent seizures at 38 hours of life. On admission, she had altered sensorium, hypoglycemia (17mg/dl), fluid responsive shock and respiratory failure, which required four days of ventilation.

She was treated initially with a bolus of 2 ml/kg of 10% dextrose and commenced on Glucose infusion of rate (GIR) of 6mg/kg/min. When her glucose requirements increased above 12mg/kg/min she was investigated for refractory hypoglycemia. Her recurrent episodes of hypoglycemia spanned a period of more than 7 days and she required a maximum GIR of 20mg/kg/min to maintain euglycemia. She had raised serum insulin levels (36.5µU/ml – normal <2µU/ml) sampled during the hypoglycemic episode suggesting hyperinsulinism. Her serum cortisol level and thyroid function tests were normal. Urine analysis was negative for ketone bodies. Hence a diagnosis of Congenital Hyperinsulinism was made.

Intravenous hydrocortisone 10mg/kg/day and oral medications with diazoxide 15 mg/kg/day and Nifedipine 2mg/kg/day did not produce any clinical response in the baby. She responded only to octreotide infusion of 20mcg/kg/min. She could not be weaned off the octreotide infusion even at 30 days of life. Her persistent requirement for a high GIR and octreotide mandated special investigations like 18F DOPA PET scan and genetic analysis for planning further management.

fig 1:Ga 68 DOTANOC PET scan- Increased uptake and persistence of DOTANOC in the pancreas while the DOTANOC has reached the kidneys for excretion

To delineate whether the pathology was focal or diffuse and for making decision regarding decision on further management, 18F DOPA PET scan was necessary. But due to non availability of 18F DOPA PET scan we searched for an alternative imaging modality available. 68Ga DOTA-NOC PET scan is an alternative imaging modality available in India in very few centres. Our state neonatal transport facilities helped us to transport the baby to another centre 300 kilometers away from our centre with high glucose infusion rates through a central line. 68Ga-DOTA-NOC PET scan showed
diffuse uptake in the head and body of pancreas suggestive of Diffuse Pancreatic Hyperplasia.

Fig 2 : NEAR TOTAL PANCREATECTOMY - Image showing the pancreas being dissected after resection of the lesser omentum.

In consultation with endocrinologist and the pediatric surgeons near-total pancreatectomy was planned. At sixty days of life, the baby underwent near-total pancreatectomy. On the 8th post operative day she was able to maintain euglycemia with breast feeds alone. Octreotide was tapered and stopped. Baby had no further episodes of hypoglycemia. MRI brain at discharge showed subtle loss of grey-white matter differentiation in the parieto-occipital regions. At present, she is eight months old with mild developmental delay and on neurodevelopmental follow up and regular assessment of glucose tolerance. She has no evidence of exocrine pancreatic insufficiency.

DISCUSSION:

Congenital hyperinsulinism is most commonly caused by mutations causing abnormal function or regulation of the ATP-dependent potassium (K\textsubscript{ATP}) channel of the pancreatic beta cells (7,8). The molecular basis of CHI involves genetic defects in eight different genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2) that are involved in regulating insulin secretion by cells (9). Identification of the genetic subtype of PHHI is helpful because this information can guide clinical management. Neonates with the most common genetic mutations (ABCC8 and KCNJ11 genes) are unlikely to respond to diazoxide treatment, as compared with those with GLUD1, HNF4A, and HADH mutations. Uniparental disomy (insertion of paternal DNA into the maternal allele in a patient with a specific ABCC8/KCNJ11 mutation) usually results in focal rather than diffuse disease. This forms the basis for genetic screening in areas where 18F DOPA scan is not available. But unfortunately, these genetic studies are also not available commonly. An estimated 40 to 65% of CHI is characterized as focal form and the remainder as diffuse form (10).

The laboratory features of CHI are related to excessive exposure to insulin and include (11, 12, 13)

- Inappropriately elevated plasma insulin concentrations ( 5 mcU/mL) during hypoglycemia
- Inappropriately low plasma concentrations of free fatty acids (FFA) and ketone bodies during hypoglycemia

Congenital hyperinsulinism of infancy is characterized by inappropriate insulin secretion in the presence of low plasma glucose. It is the most common cause of persistent hypoglycemia in the neonate. It is often referred to by various names such as nesidioblastosis(4), islet dysregulation syndrome, and persistent hyperinsulinemic hypoglycemia of infancy. Currently the preferred term is congenital hyperinsulinism of infancy. The incidence of CHI can vary from 1 in 35,000 to 40,000 in the general population (5) to 1 in 2500 in some communities with high rates of consanguinity (6).
Increased glucose requirements (>8 to 10 mg/kg per minute) to maintain blood glucose concentration in a safe range (>60 to 100 mg/dL)

An increase in blood glucose greater than 30 mg/dL within 30 - 40 minutes after IM or IV administration of 1 mg glucagon

An improvement in the blood glucose in response to octreotide can be used as both a therapeutic and diagnostic step. A glucose infusion rate higher than 10 mg/kg/min in a neonate proves an insulin related hypoglycemia. The neonate in this case report required a maximum GIR of 20 mg/kg/min. Prompt diagnosis and initiation of appropriate management of hypoglycemia in congenital hyperinsulinism will reduce the risk of brain injury in these neonates. It is important to maintain the blood glucose concentrations within the normal range (63 to 108 mg/dL) which may necessitate the use of high concentrations of glucose infusion through a central venous catheter. In neonates, Diazoxide is started for a 5 days trial and response assessed. If hypoglycemia persists on diazoxide, octreotide is started at an initial dose of 5-10 g/kg/day and titrated up to 15 – 50 g/kg/day. Diazoxide responsiveness can be useful guide to resort to medical management alone.

Somatostatin receptor PET tracer 68Ga-DOTANOC have shown promising results in patients with neuroendocrine tumors with a higher lesion detection rate similar to 18F-fluorodihydroxyphenyl-alanine PET scan. 68Ga-DOTANOC has high affinity for somatostatin receptor subtypes 2, 3, and 5. 68Ga-DOTANOC can be used to differentiate focal versus diffuse forms and thus helps in tailoring the management of the infant. It is also possible to delineate important anatomic landmarks such as the blood vessels and the relationship of the main pancreatic duct and the intrapancreatic common bile duct to the pancreatic foci.

Some infants with focal pancreatic hyperplasia may respond to medical and dietary therapies. Those who show no response need Partial pancreatectomy to maintain normoglycemia. Recent literature supports near-total pancreatectomy as the definitive management option for diffuse pancreatic hyperplasia. Kramer et al have shown the efficacy of “Near-total” pancreatectomy and recommended it to be the procedure of choice. Near-total pancreatectomy incorporates removal of the tail, body, uncinate process, and part of the pancreatic head. Only small islands of pancreatic tissue are left along the pancreaticoduodenal arcade bordering the duodenum.

The focal form is curable with partial pancreatectomy and has an excellent prognosis, whereas diffuse disease requires Near total pancreatectomy with subsequent development of diabetes mellitus in approximately half and persistence of hypoglycemia in a third of affected infants.

Conclusion:
Congenital hyperinsulinism is the most common cause of persistent neonatal hypoglycemia. It is important to identify and promptly manage congenital hyperinsulinism to prevent brain damage caused by hypoglycemia. 68Ga-DOTANOC PET scan can be a useful adjunct in resource limited settings where 18F-DOPA PET scan is not available. The anatomical details may also guide surgeons to plan the type of surgery needed depending on the extent of the lesion. High index of suspicion and early institution of appropriate treatment improves the outcome in such neonates.
Key messages: Aggressive correction of hypoglycemia may prevent hypoglycemic brain injury. · Workup for hyperinsulinism should be instituted as early as possible as it can spare a significant amount of pancreatic tissue in case of focal lesion. · 68Ga-DOTANOC scan plays a promising role in localizing the focus in CHI.

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