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Case Report

Diazoxide Unresponsive Congenital Hyperinsulinism in Neonates: A Case Report

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ABSTRACT

Glucose is the prime energy source for brain and other vital organs of the body. Congenital hyperinsulinisms occur due to dysregulated insulin secretion. Persistent hypoglycemia can cause irreversible damage to neurons. Patients with Hyperinsulinemic Hypoglycemia (HH) present in first 24-48 hours of life in newborn period with non-specific symptoms of hypoglycemia as lethargy, poor feeding, high pitched and irritable cry, apnea, jitteriness, exaggerated reflexes, seizure and coma. Cornerstone of clinical management involves early diagnosis and appropriate therapy for all forms of HH. Analysis of blood sample, collected during hypoglycemia for intermediary metabolites and hormones is critical for diagnosis and management of hypoglycemia in neonates. Managing patients with persistent and prolonged hypoglycemia will require frequent blood glucose monitoring and central venous access for administration of high concentrated dextrose infusions. Treatment options include medical and surgical or sometimes combination therapy based on underlying etiology for hypoglycemia. However, management of medically unresponsive hyperinsulinemic hypoglycemia remains a challenge. Octreotide (short acting somatostatin analogue) and sirolimus (Mammalian Target of Rapamycin (MTOR) inhibitor) appear more promising in neonates with diazoxide unresponsive hypoglycemia. Neurological development should be closely followed in evaluating long term outcome of patients with HH. Septic markers and metabolic screen were negative and genetic studies revealed *ABCC8* mutation. Baby was treated with oral diazoxide, subcutaneous octreotide and oral sirolimus to maintain glycemic status. This case highlights the importance of monitoring glucose in infants prone to hypoglycemia for appropriate management to prevent the developmental delay.

Keywords: *ABCC8*; Hyperinsulinemic hypoglycemia; Diazoxide; Octreotide; Sirolimus

INTRODUCTION

Glucose homeostasis is maintained by balance between secretion of insulin and counter regulatory hormones (glucagon, growth hormone, adrenaline and cortisol). Glycogen stores in a healthy full-term infant last for 10-12 hours from birth, glucose production is around 4-6 mg/kg/min and maintains it until exogenous nutrition supply is established [1]. Untill the neonate is fed with exogenous nutrition, endogenous production of glucose through gluconeogenesis and glycogenolysis maintain homeostasis. Substrate essential for gluconeogenesis such as alanine, pyruvate, glycerol and lactate are present in newborn infant. Lactate generation from proteolysis and beta oxidation of fatty acids helps in substrate synthesis, whereas hepatic glycogenolysis provides glucose [2]. These are considered to be neuroprotective by acting as alternative substrate during hypoglycemic insult to brain. Infants with defects in glycogenolysis present at 48-72 hours of fasting and defects in gluconeogenesis usually present at overnight fasting but infants with hyperinsulinism present any time after last feed [3].

Congenital Hyperinsulinism (CHI) a heterogenous group of disorder associated with altered insulin secretion. It is the most common cause of prolonged hypoketotic hypoglycemia causing permanent brain damage, as the ketones are utilized in higher rates by neonatal brain. Incidence of CHI can vary from 1 in

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35000-45000 in general population to 1 in 2500 in some communities with high rates of consanguinity [4]. Three sub-groups of CHI exist histologically namely diffuse, focal and atypical form based on the areas in the islets of pancreas that gets affected. HH can be transient in certain neonates with birth asphyxia, Intra Uterine Growth Restriction (IUGR), or in an Infant of Diabetic Mother (IDM) [5]. Metabolic action of insulin on glucose allows peripheral utilization of glucose, stimulates glycogen synthesis and inhibits glycogenolysis and gluconeogenesis. Insulin is an anabolic hormone as it stimulates lipogenesis, inhibits beta oxidation and free fatty acid release; inhibits ketone body formation, accounting for hypoketotic state [6]. Hence the brain is deprived of its primary and secondary metabolites (glucose and ketone bodies). Impaired gluconeogenesis, poor glycogen stores, increased insulin secretion are common in hypoglycemia [7]. Three forms of HIH exists, Transient HIH usually seen in IDM, IUGR and fetal distress presents soon after birth. This form is often self-limiting or responds to glucose infusion. Congenital HH also called persistent HH often occur due to genetic mutation of channels controlling insulin release from pancreatic beta cells. Mutations in 12 different genes are involved in dysregulated insulin secretion from pancreatic beta cells commonest being *ABCC8* and *KCNJ11* [8]. Prolonged HH mostly in SGA infants respond with high GIR. These SGA babies usually present within 48 hours of life and resolve within few weeks or months with diazoxide administration. Diazoxide–A KATP channel opener can be considered as a first line in long term therapy and somatostatin analogues for diazoxide unresponsive hypoglycemia [9]. Increased plasma levels of glucagon and catecholamine release and decreased insulin levels happen when endocrine changes start to appear. Medical management of hypoglycemia in newborns involves use of corticoseteroids, diazoxide, octreotide (short acting somatostatin analogue) or Lanreotide (long acting somatostatin analogue) to suppress insulin secretion and maintain normoglycemia.

CASE PRESENTATION

We present a case of female neonate with normal perinatal history born at 41 weeks gestation by caesarean section and a birth weight of 2.6 Kg. She was born from a non-consanguineous parent. There was no family history of diabetes or hypoglycemia. Antenatal ultrasound scans showed normal growth. APGAR were 8 and 10 at 1 and 5 minutes respectively. She was not dysmorphic and her anthropometric parameters were within normal limits. Baby developed irritable cry on day 2 of life and documented to have hypoglycemia which was symptomatically managed and discharged at day 5 of life. Baby required multiple hospital visits precipitated with irritable cry managed symptomatically for hypoglycemia and discharged. At 3 weeks of age baby had abnormal movements of both upper limbs characterized by clonic movements of both hands with uprolling of eyes. Baby was admitted in a private hospital and diagnosed to have hyperinsulinemic hypoglycemia (Sr. Insulin 24.2 µu/ml and Sr. Cortisol 2.1 µg/dl) for which diazoxide was started and baby was observed for hypoglycemic episodes and discharged home at 1 month of age with diazoxide 10 mg/kg/day in 3 divided doses. Recurrent symptoms of hypoglycemia like irritable cry and abnormal movements appeared inspite of diazoxide therapy, baby was brought to our unit for further management.

On admission baby was 4.16 Kg, had hypoglycemia (RBS: 25 mg/dl) associated with two episodes of seizures. Baby required multiple dextrose boluses and intravenous dextrose infusion with a GIR of 8 mg/kg/min subsequently baby was started on prednisolone (2 mg/kg/day), diazoxide (15 mg/kg/day). Septic markers were unremarkable and serum ketones were negative and high serum insulin was evident from blood workup (Sr. Insulin 12.12 µu/ml, Sr. Cortisol 16.8 µg/dl, Growth hormone 22.99 µg/L, blood ammonia 101 µg/dl, Sr. Lactate 61 mg/dl, TSH 6.39 µu/ml). Since blood glucose levels did not stabilize with diazoxide and IV dextrose infusions, subcutaneous octreotide (5 mg/kg/day every 6 hours (Q6H)) was started in addition to above requirements for maintaining normoglycemia. Intra venous fluids were gradually weaned and breast feeding was restarted as blood sugar started to stabilize with triple therapy. After 24 hours of euglycemia baby had another episode of hypoglycemia, octreotide dose was increased at increments of 5 mcg/kg/day upto 30 mcg/kg/day Q6H. Diazoxide dose was also optimized to 20 mg/kg/day. These measures were not effective and repeated episodes of hypoglycemia were observed 2-3 times a day inspite of combined treatment. Hence baby was also started on sirolimus at 2 mg/m^2/day in two divided doses in addition to diazoxide and octreotide to control erratic blood sugar levels. Her blood sugar levels were controlled thereafter her stay was uneventful. Fluorine 18-L 3,4 Dihydroxy Phenylalanine Positron Emission Tomography (^{18}F DOPA-PET) revealed no pathological focus of Glucagon-Like Peptide-1 (GLP-1) expression in abdominal region. No abnormal focal or diffuse increased tracer uptake noted in the pancreas which ruled out insulinoma. Clinical exome sequencing was done to find out possible pathogenic variant causative of the reported phenotype and turned out to be *ABCC8* mutation at intron 14, Heterozygous suggestive of familial hyperinsulinemic hypoglycemia type 1 autosomal dominant type. She was discharged home with octreotide 30 mg/kg/day and sirolimus 1.5 mcg/m^2/day were continued. In the last neuro-developmental follow up at 11 months she was assessed to be doing well with weight of 8.55 Kg (Table 1).

Table 1: Blood workup done during admission.

Investigation	Report
Serum insulin	12.12 µu/ml
Serum cortisol	16.8 µg/dl
Growth hormone	22.99 µg/L
Serum ammonia	101 µg/dl
Serum lactate	61 mg/dl
TSH	6.39 µu/ml

RESULTS AND DISCUSSION

Congenital hyperinsulinism is a major cause of persistent and recurrent hypoglycemia in neonatal period characterized by inappropriate insulin secretion from pancreatic beta cells in relation to blood glucose concentration [1]. Any patient with recurrent or persistent hypoglycemia can potentially have CHI as this is the only form that persist inspite of glucose infusions [2]. Insulin release from pancreatic beta cell involves a series of events and various metabolic products (glucose, aminoacids and fatty acids) stimulate the release. Branched chain amino acids such as leucine, isoleucine and valine are essential aminoacids which promote protein synthesis and turnover and also involved in the metabolism of glucose. Leucine and glutamine together contribute for insulin release by stimulating Glutamate Dehydrogenase (GDH) which increases polymerization complex of α-ketoglutarate, thus increasing the cellular ATP/ADP ratio [3]. The KATP channel controls the secretion of insulin out of beta cells and this channel open or close in response to blood sugar levels. ATP-Binding Cassette (ABC) transporter proteins transport various molecules across extra and intra cellular membranes and function as a modulator of ATP-sensitive potassium channel and insulin release. Mutation in *ABCC8* gene and deficiency in encoded protein have been observed in patients with HIH of infancy [4]. ABCC8 or *KCNJ11* mutation result in HH familial types 1 and 2. KATP channel depends on pore forming inward rectifier potassium channel subunit (kir 6.2) and regulatory Sulfonyl Urea Receptor (SUR1) encoded by *KCNJ11* and *ABCC8* genes respectively. Increase in ATP/ADP ratio within the cell lead to closure of KATP channel within the beta cell causing depolarization and opening of voltage gated calcium channel with subsequent calcium influx. Increase in intracellular calcium causes insulin degranulation and release. Mutation in either protein encoding gene causes decreased or absent KATP channel activity leading to permanent depolarization, opening of voltage gated calcium channel and insulin secretion irrespective of serum glucose [5-7].

Diagnostic approach of CHI begins with laboratory studies for intermediary metabolites of glucose, ultrasonography, CT, MRI, PET-CT, pathological diagnostic sampling of pancreatic tissue [8] reported ^{18}F DOPA-PET scan to be highly accurate in differentiating the focal and diffuse disease and localizing the lesion in focal type of HH [8]. Early and emergency management of hypoglycemia includes parenteral glucose infusion 2 ml/kg of 10% dextrose as bolus if neonate is unable to take oral feeds, followed by continuous glucose infusion at 6-8 mg/kg/minute, glucagon administration 0.02-0.2 mg/kg/dose IM, IV or SC to and frequent feeding with high calorie carbohydrate feeds. Long term management plan goes individualized for each patient with the aim of achieving euglycemia. To trace the response and side effects to each pharmacological therapy, introduce one at a time [1,9].

Various agents used include Diazoxide-A KATP channel opener, function by binding to SUR1 subunit of KATP channel. Unresponsiveness to diazoxide mandates molecular genetic analysis for mutation in *ABCC8* and *KCNJ11* genes and ^{18}F DOPA-PET/CT scan to find any insulinomas. Diazoxide dose ranges from 5-20 mg/kg/day in three divided doses. Side effects that limits dose or treatment withdrawal includes fluid retention, cardiac failure associated electrolyte imbalance, hypotension and pulmonary hypertension [2,9]. Octreotide a synthetic, long acting somatostatin analogue inhibits insulin secretion by binding with somatostatin receptor (SSTR 2 and 5). SSTR5 activation decreases insulin gene promoter action, decreases calcium mobilization, inhibits KATP channel and decrease insulin secretion. It also activates adenylate cyclase through G-Protein Coupled Receptors to increase glycogenolysis and gluconeogenesis [9]. Octreotide dose ranges from 5-35 mcg/kg/day as subcutaneous injection every 8-6 hour interval. Patient can develop tachyphylaxis following prolonged use of this synthetic octapeptide. Sirolimus immunosuppressant with antiproliferative ability inhibit mammalian target of rapamycin, a serine/threonine kinase which regulates cell growth by protein synthesis and increased mRNA translation process. Sirolimus decreases calcium stores and alter mitochondrial activity decreasing insulin release. MTOR inhibition with sirolimus decreases insulin secretion as well as beta cell growth, islet cell mass, insulin sensitivity. Side effects include stomatitis, increased risk of infection, immunosuppression, renal dysfunction, fatigue. Sirolimus dose ranges from 1-3 mg/m^2/ day.

Apart from these treatment options there are other drugs that could be of use in HH as nifedipine (calcium channel blocker), glucagon like peptide 1 antagonists (Exendin) and surgical therapy is also recommended in insulin secreting tumors [3,9].

CONCLUSION

CHI has been a known cause of persistent hypoglycemia during infancy due to dysregulated insulin secretion. GIR above 8 mg/kg/minute to maintain euglycemia is typical of this condition. In infants with HH diazoxide unresponsiveness is an absolute indication for performing genetic studies as reported in our case. Appropriate investigation for intermediary metabolite like serum insulin, cortisol, growth hormone, ketone bodies, FFA, amino acids, lactate, ammonia, bicarbonate, and blood gas analysis are considered as cornerstone for diagnosis and management of HH. Screening for genetic mutation (*KCNJ11* and *ABCC8*) and F-DOPA PET scan to rule out congenital causes and insulin secreting tumors has streamlined the management of CHI. Although there are many risk factors for hypoglycemia in neonates commonest were Small for Gestational Age (SGA) and macrosomic infants born to diabetic mother. Early diagnosis and aggressive management is considered highly essential to have better neurodevelopmental outcomes.

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CONFLICT OF INTEREST

The authors had no conflict of interest.

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