

A Newborn with Congenital Hyperinsulinism having a Novel Homozygous Mutation in the ABCC8 Gene

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Abstract: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in newborns and infants. It is characterized by the unregulated secretion of insulin from pancreatic B- cells in relation to blood glucose concentration. We reported the case of full term, appropriate for gestational age newborn suffered from CHI and developed severe and persistent hypoglycemia which unresponsive to medical treatments including diazoxide, octreotide, Nifedipine. Somatostatin receptor PET -CT, Addendum to ⁶⁸Ga Dotatate PET -CT scan showed mild diffuse somatostatin receptor expression is seen in the entire pancreas and focal increased uptake in liver segment IVb and V. The patient was confirmed to have a novel ABCC8 homozygous mutation at c.1335_1364del position.

Keywords: ABCC8, Novel mutation, Refractory hypoglycemia, congenital hyperinsulinism, Octreotide

1. Introduction

Congenital hyperinsulinism (CHI) is a genetic disorder characterized by inappropriately excessive secretion of insulin from pancreatic B- cells in relation to blood glucose concentration [1]. It occurs in sporadic and familial forms. The incidence of sporadic form is 1:40,000 live birth and familial form is 1:2,500 live birth [2]. The clinical manifestations range from life threatening hypoglycemia, presenting on first day of life to only mild symptomatic hypoglycemia. Infant usually presents in the first month of life with hypothermia, hypotonia, seizures and loss of consciousness. The delay in the diagnosis and management is the major cause of permanent brain damage and neurological deficits [3, 4]. Nine genes have been reported to be associated with CHI and most common with autosomal recessive mutation in either ABCC8 or KCNJ11, located on chromosome 11p, encode, sulfonyleurea receptor 1 (SUR 1) and Kir6.2 respectively, which are subunits of adenosine triphosphatase, sensitive potassium channel (K⁺-ATP) [5]. Mutations are found in only 50% of cases while in remaining 50%, the genetic etiology remains unknown [6]. We present the case of a newborn with severe CHI due to novel homozygous recessive mutation in the ABCC8 gene.

2. Case Summary

A 38 week gestational age baby girl (birth weight -3.0 kilogram) was born to 28 year old G₃P₃ A₁L₂ non-consanguinity married, non-diabetic mother by normal vaginal delivery with normal birth events with apgar score 9/10 at 1 and 5 minutes respectively. Baby had no dysmorphic features or congenital anomaly. Maternal history of any chronic disease or medication was negative. Breast feeding was started just after the first evaluation. On 2nd day of life, presented with lethargy, staring look, decreased activity and simultaneous RBS was 31mg/dl. She was treated with dextrose 10% bolus (2ml/kg) followed by Glucose infusion at 6mg/kg/min. Infusion rate was increased upto 12mg/kg/min to keep blood glucose level >45mg/dl. Antibiotics therapy was started with suspected

sepsis and discontinued when blood culture was negative. Laboratory investigations at time of hypoglycemia.

Parameter	measured	parameter	measured
Blood glucose	16 mg/dl	Serum Acetone	Absent
Serum insulin	29 uIU/ml	Urine Acetone	Absent
Serum cortisol	244 ug/dl	U.Reducing substance	Absent
Serum Ammonia	48 umol/L	Urine ketone	Absent
S. growth hormone	19.4ng/ml		

Baby was screened for CHI. Metabolic screen tests including ABGA, serum ammonia, thyroid function test, tandem mass spectrometry were normal. Ultrasonography of brain and abdomen, MRI brain and CT abdomen and pelvis, echocardiography were normal. As per advice by pediatric endocrinologist baby was started diazoxide (10 mg/kg/day) and octreotide (10 ug/kg/day) in addition to high Glucose infusion (12mg/kg/min). Blood glucose levels were transiently increased to 340-480mg/dl range. On 12th day of life octreotide was increased up to 30 ug/kg/day, diazoxide (20mg/kg/day) in addition to high glucose infusion (15mg/kg/min) and started hydrochlorothiazide (2mg/kg/day) because of glucose levels were below 60mg/dl. On 24th day of life Nifedipine (1mg/kg/day) was added to the treatment with high calorie formula. On 35th day of life, long acting octreotide (1ug/kg/dose) 2 doses with 1 month interval was given, which decreased in glucose requirement and weaned to 2 hourly feeding with intermittent glucose infusion at 8-10mg/kg/min. After 6 weeks, maximum tolerated dose of diazoxide (20mg/kg/day), octreotide (20ug/kg/day) and hydrochlorothiazide (2mg/kg/day) needed to keep random blood glucose levels > 70mg/dl with intermittent episode of hypoglycemia. Loading dose followed by maintenance dose of Phenobarbital was continued. On 2 months of life baby was referred to endocrinologist where repeat MRI brain and CT-abdomen were done showed no significant diagnostic pathology was detected. Somatostatin receptor PET-CT and addendum to ⁶⁸Ga dotatate PET-CT showed mild diffuse somatostatin receptor expression seen in entire pancreas (?nesidioblastosis) and focal expression in liver segment IVb,

V. Sequence analysis study showed homozygous for a novel ABCC8 gene at Exon 9 in frame delete mutation c.1335_1364del, results in the deletion of 9 amino acids (p.I446-I455del) which consistent with diagnosis of autosomal recessive CHI. Fourteen days of antibiotics course was completed for Enterobacter aerogenes sepsis. Baby was referred back to parent hospital. After 3 month, IV fluids were discontinued gradually and lengthen the daytime feedings to 3 hourly. However the patient had intermittent hypoglycemic episodes and medical treatment with diazoxide (20mg/kg/day), octreotide (20 ug/kg/day) and hydrochlorothiazide (2mg/kg/day) with blood glucose levels were maintain above >60mg/dl. Patient was discharged home on treatment at 3.5 month of age. She planned to be followed up by pediatric endocrinologist and pediatric department. At 6 month of age follow up MRI brain and EEG was done as patient had intermittent episode of seizure revealed no abnormality so phenobarbiton was stopped. Currently she is 7 month, having weight of 7.4 kg and height of 69cm and on octreotide (15ug/kg/day), diazoxide (10mg/kg/day) and hydrochlorothiazide (2mg/kg/day). Neurological assessment showed minimal delay in development.

3. Discussion

In this report, we present a case of newborn with CHI. Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Hyperinsulinemic hypoglycemia (HH) in newborn period can be transient or persistent. Mostly transient forms of HH are secondary to maternal diabetes, intrauterine growth retardation, birth asphyxia or Rhesus isoimmunization. Persistent HH might be congenital or associated with metabolic disorders such as congenital glycosylation defects and tyrosinemia type 1 and the rare causes such as insulinoma, insulin-receptor gene defects [7]. The absence of ketosis during hypoglycemia rule out fasting or inadequate calorie intake Hypopituitarism, adrenal insufficiency, inborn error of enzyme deficiencies, galactosemia and fructosemia [8]. Serum Ammonia is high in hyperinsulinism hyperammoniasyndrome (HI/HA) [9]. Normal physical examination excluded Beckwith Wiedemansyndrome [10]. Tandem -MS, Urinary organic acid and reducing substance rule out short chain L-3 hydroxyacyl-CoA dehydrogenase (SCHAD) [11]. Diagnostic criteria for CHI are an increased glucose requirement >8 mg/kg/min, detectable serum insulin when blood glucose <45 mg/dl, absence of ketonuria and glycemic response to glucagon [12]. CHI can be caused by mutation in nine different genes, namely ABCC8, KCNJ11, GLUD1, CGK, HADH, LC16A1, HNF 4A and UCP2 gene [5,13]. The most cases of CHI are caused by autosomal recessive mutations in the ABCC8 and KCNJ11 genes that are located on chromosome 11p15.1 encoding the two subunits of the pancreatic B-cell K-ATP channel. The pancreatic K-ATP channel is a functional complex of sulfonylurea receptor 1 (SUR1), encoded by the ABCC8 gene and an inward rectifier potassium channel subunit (Kir6.2), encoded by the KCNJ11 gene. Inactivating mutations in these genes loss of K_{ATP} channel activity resulting in membrane depolarization of the B-cells which opens the voltage-gated calcium channels and raises intracellular calcium concentrations and persistent and unregulated hyper secretion of insulin. These mutations tend to

cause diffuse disease with intractable hypoglycemia, poor response to diazoxide. Autosomal dominant form of CHI is mostly caused by activating mutations in the glucokinase (GCK) gene or regulatory mutations in the glutamate dehydrogenase (GLUD1) gene. Focal pancreatic lesions can be caused by loss of genetic material in the maternal chromosome 11p15 region and paternally inherited mutation in the ABCC8/KCNJ11 genes [14]. Histologically CHI is either diffuse or focal. The diffuse type of CHI is characterized by large β -cells with abnormally large nuclei distributed throughout the whole pancreas, whereas the focal type consists of an adenomatous hyperplasia confined to one region of the pancreas. Preoperative differentiation between focal and diffuse type of CHI is very helpful in the management and should be carried out using positron emission tomography (PET) whenever possible [1]. The most important recent advance in the management of children with CHI over the past 2 decades has been the introduction of 18F-DOPA PET scanning to differentiate focal CHI from diffuse CHI [15]. Early diagnosis and adequate management are very important in order to prevent any subsequent neurological sequelae. Prenatal diagnosis is also possible when the mutation in the index case is known. William H. Peranteau and colleagues reported, for the first time, a prenatal diagnosis of diffuse CHI in a baby with a known family mutation and sibling affected with CHI [3]. To conclude, the diagnosis and management of hyperinsulinemic hypoglycemia in newborns remains a challenge for neonatologists and endocrinologists.

Genetic Analysis of the ABCC8 and KCNJ11 Genes

Blood samples for genetic testing from the baby and both the parents were taken in Jaslok Hospital and research centre, Mumbai. Genomic DNA was extracted from peripheral blood leukocytes by using standard procedures. The genetic sequencing was done at the university of Exeter, Exeter UK.

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