Case Report:

A Case Report on Congenital Hyperinsulinism Associated with Heterozygous ABCC8 Missense Mutation

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Abstract

A 6 kg baby boy born via Caesarian section at 39 weeks had the first onset of hypoglycemia at birth. The newborn required a glucose load of 15 mg/kg/min. Insulin level was 45.4 mIU/ml. He responded to diazoxide & octreotide.The boy was found to be heterozygous for an ABCC8 missense mutation.

Key words**:** Congenital Hyperinsulinemic hypolglycemia (CHI), ABCC8 mutation, diazoxide, octreotide, KATP channel

INTRODUCTION

Congenital Hyperinsulinemic hypoglycemia (CHI) is a rare genetic disorder resulting severe hypoglycemia secondary to excessive insulin release from the pancreatic cells. It is the most common etiology for infantile persistent hypoglycemia [1]. It is one of the most serious causes of neonatal hypoglycemia and can cause irreversible brain damage if not treated on time and adequately.

It has an estimated prevalence of 1 in 50000 and almost 1 in 25000 to 1 in 30000 in countries with consanguineous marriage [2]. The mutations in ABBC8 and KCNJ11 are the most commonly found mutations, however several other mutations have beenreported.

CHI can manifest as either focal due to adenomatous islet cell or diffuse lesions secondary to diffuse islet cell hyperplasia [3].

The outcome in the patient primarily depends upon the kind of lesion as the focal lesions benefit from local pancreatectomy whereas the diffuse lesions require extensive pancreatectomy resulting in diabetes in a lot of children in later life [4].

CASE REPORT

The proband is the second child in the family. There was no history of parental consanguinity. He was born at 39 weeks via elective lower segment caesarean section. He had an Apgar score of 8 at 1 minute and 9 at 5 minutes. Antenatal period was supervised and uneventful. There was no history of maternal diabetes or any other illness or drug intake. He was born large for gestation with a birth weight of 6 Kg. Midline defects, such as cleft lip and cleft palate, were absent. There were no neurocutaneous stigmata. He had normal male external genitalia. Other systemic examinations were unremarkable.

He was referred to Indraprastha Apollo hospital (IAH) on day 2 of life for persistent respiratory distress and severe hypoglycemia.

Baby was brought to IAH ventilated. Chest X ray showed bilateral fluid filled fissures. Echocardiogram done on admission showed Non obstructive concentric hypertrophic cardiomyopathy, Fossa Ovalis ASD, 5 mm, L-R shunt, PDA, 2 mm, L-R shunt, Normal ventricular function, No signs of PAH.

He was hypoglycemic at admission with blood glucose of 35 mg/dl, requiring GIR of 15mg/kg/min. A controlled hypoglycaemia screen established the diagnosis of CHI (serum Insulin 45.4 mIU/ml associated with lab glucose of 35 mg/dl and undetectable non-esterified fatty acids and β-hydroxybutyrate). His serum cortisol was 2 µg/dl during the hypoglycaemia screen. The rest of the hypoglycaemic screen including insulin like serum ammonia, lactate, plasma amino acids and urine organic acids was within normal reference range.

Molecular genetic analysis for CHI was performed after informed consent from the parents. He was commenced on diazoxide (5 mg/kg/day in three divided doses) and the dose was gradually increased to 15 mg/kg/day. Chlorothiazide was given along with diazoxide to counteract the side effect of fluid retention. On 15 mg/kg/day of diazoxide and 5 µg/kg/day of Octreotide, he was successfully weaned off intravenous glucose administration. The results of genetic analysis were positive for ABCC8 missense mutation responsible for congenital hyperinsulinemia.

Baby was re-intubated after 48 hours because of stridor & respiratory distress. Chest Xray showed cleared lung fields. Direct laryngoscopy showed normal upper airway and vocal cords but severe macroglossia. He was gradually weaned off from ventilation, nursed in prone position, stridor improved.

Day 16 of hospital admission baby had worsening respiratory distress. Chest X ray showed bilateral ground glass lung fields suggestive of pulmonary venous hypertension, so oral diazoxide was stopped. Review echocardiogram showed biventricular diastolic dysfunction & PAH. In view of worsening respiratory distress and hypoxia, he was re-intubated and mechanically ventilated. Within 24 hrs there was reduction in PAH & cardiac functions improved.

Baby was gradually weaned off from mechanical ventilation. He was on full NG feeds & subcutaneous Octreotide. Mother was trained for giving NG feeds at home.

Baby was discharge at 1 month 11 days of age with weight-6.66 kg on subcutaneous Octreotide injection µg/kg/day and NG feeds.

DISCUSSION

CHI is a heterogeneous genetic disorder of abnormal insulin secretion characterized by hyperinsulinism, hypoketonemia, and hypo-fattyacidemia with severe and persistent hypoglycemia. CHI can occur due to two major defects: channelopathies and metabolopathies. Channelopathies refer to defects in the pancreatic â-cell ATP-sensitive KATP channel that results in unregulated insulin secretion. Metabolopathies cause congenital hyperinsulinemic hypoglycemia either by altering the concentration of intracellular signaling molecules (such as ATP/ADP) or by accumulation of

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intermediary metabolites, triggering the insulin release.The Na K-ATPase pump and the metabolic nutrient state regulate the insulin activity in the body. Genetic mutations render the pump functionally inactive, hence causing the patients to be unresponsive to

diazoxide, while some mutations may cause the pump to be inactive but responsive to pharmacological interventions.

The mutations that increase the nutrient metabolism and increase the ATP/ADP ratio and in in turn increase the insulin secretion are the ones most responsive to diazoxide.

The most common mutations are the inactivating mutations of the β-cell ATP-sensitive K+ channel genes ABCC8 (ATP- binding cassette subfamily C, member 8), which encodes for SUR1 (sulphonylurea receptor) and KCNJ11 (potassium inward rectifying channel, subfamily J, member 11), encoding Kir6.2 [5].

Genetic mutations have been identified in nine genes accounting for CHI resulting in either the diffuse or the focal form. Both autosomal dominant and recessive pattern have been demonstrated mostly in diffuse lesions resulting in the heterogeneity of presentation and severity. Focal ones are more sporadic.

It is hence very important to know the genetic mutations to predict the response to pharmacological interventions and their response in the affected children [6].

The most common mutations are the ABCC8 and KCNJ11, located next to each other on chromosome 11p. Till date there are 3 known Kirk6.2 and over 40 SURI mutations that have been identified [6].

Few other mutations have also been identified and can be useful in predicting the type of pancreatic involvements and responsiveness to diazoxide.

The K- ATP-sensitive potassium channel hyperinsulinism (K-ATP- HI) form caused by mutations in ABCC8 and KCNJ11 on chromosome 11, may cause autosomal recessive inheritance resulting in diffuse lesions and focal lesions due to loss of heterozygosity with paternal mutation. This type of resulting CHI is usually very severe and unresponsive to pharmacological treatment and requires pancreatectomy [7]. These babies are mostly large for gestation due to fetal overgrowth due to excessive insulin.

The dominant K-ATP-HI is inherited as autosomal dominant, it is milder and responsive to diazoxide.

The other common mutations seen are:

- glucokinase (encoded by GCK)
- glutamate dehydrogenase (GDH; encoded by GLUD-1 [glutamate dehydrogenase]
- mitochondrial enzyme short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD); encoded by HADH [hydroxyacyl- coenzyme A dehydrogenase

GDH-HI (glutamate dehydrogenase hyperinsulinism), caused by GLUD-1 mutation o chromosome 10q is autosomal dominant. It is associated with hyperammonemia and responsive to diazoxide. These babies are not born large for gestation and remain asymptomatic at birth, manifest symptoms by several months of age [8].

GK-HI (glucokinase hyperinsulinism), due to GCK mutation on chromosome 7 is autosomal

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dominant and has a variable presentation, but most of them respond to diazoxide. It is relatively rare and has a varied age of presentation and severity of symptoms [9]

SCHAD-HI (short-chain 3-hydroxyacyl-CoA dehydrogenase hyperinsulinis), by HADH mutation on chromosome 4 is inherited as autosomal recessive. It has an abnormal acyl-carnitine profile and is usually diazoxide responsive. The biochemical markers are increased insulin action; increased levels of plasma 3-hydroxybutyryl-carnitine and increased levels of 3-hydroxyglutarate in urine [10]

Mutations in ABCC8 and KCNJ11, both monoallelic and biallelic, account for the majority of CHI patients [11,12]. Although monoallelic ABCC8/KCNJ11 mutations can cause both diazoxide-responsive as well as diazoxide- unresponsive CHI, nearly all biallelic ABCC8/KCNJ11 mutations result in diazoxide unresponsive CHI [13]. In two recent large studies comprising more than 700 patients with CHI, there was no patient reported with diazoxide responsive CHI due to biallelic ABCC8/KCNJ11 mutation.

Conclusion

In conclusion, although the majority of biallelic ABCC8/ KCNJ11 mutations result in diazoxide-unresponsive CHI, occasional biallelic and particularly heterozygous ABCC8 mutations may lead to a diazoxide-responsive phenotype. Also ECHO should be mandatory in a baby on diazoxide as it may cause secondary pulmonary hypertension, hence it should be in mind while treating CHI.

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