# Neonatal Hypoglycaemia due to ABCC8 Gene Mutation

Sir,

Hypoglycaemia is a common metabolic problem in contemporary neonatal medicine.[1] Most cases of neonatal hypoglycemia are transient and resolve. However, few cases of hypoglycemia persists despite the high glucose infusion rates. Persistent neonatal hypoglycemia caused by congenital hyperinsulinism (CHI) is a rare genetic disorder characterized by inappropriate insulin secretion in spite of severe persistent hypoglycemia. Mutations in the genes ABCC8/KCNJ11, encoding SUR1/Kir6.2 components of the KATP channels, respectively, are the commonest causes of CHI.

## Case Report

A full term large for gestational age (LGA) female infant born out of non-consanguineous marriage with neonatal hypoglycemia from day one of birth was referred to our institute. There was no history of maternal diabetes. Her birth weight was 4,400 gm (>90$^{th}$ percentile), without any dysmorphic features and systemic examination was unremarkable without any clinical evidence of the sepsis or birth asphyxia.

She was having recurrent hypoglycemia and required high glucose infusion rate (GIR) and (>18 mg/kg per min) blood

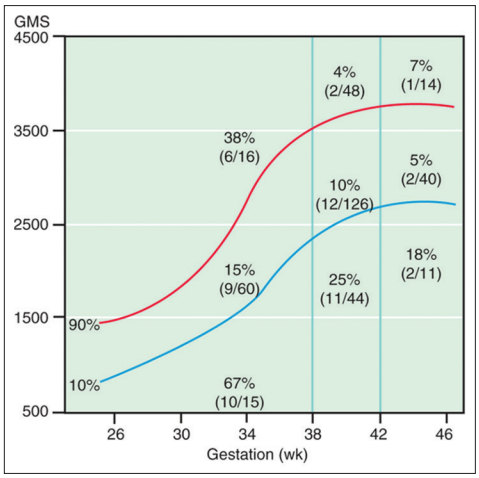


**Figure 1:** Incidence of hypoglycemia by birthweight, gestational age, and intrauterine growth. (From Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birthweight and gestational age. Pediatrics 1971;47:831–838.)

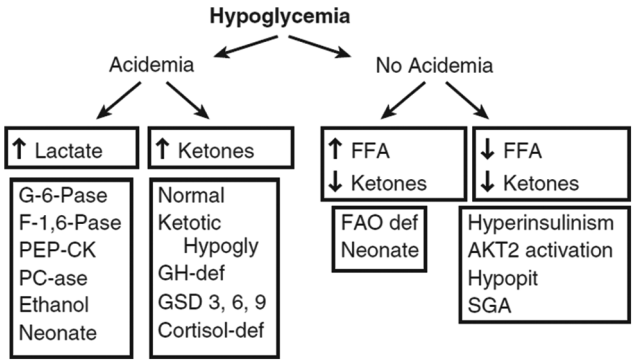


**Figure 2:** Algorithm for diagnosis of hypoglycemia based on "critical" blood tests obtained during a period of hypoglycemia. FFA, free fatty acids; FAO: fatty acid oxidation; GSD, glycogen storage disorder; SGA, small for gestational age. (Stanley CA, Baker L [1978]. Hypoglycemia. In Kaye R, Oski FA, Barness LA (eds.), Core textbook of pediatrics. Philadelphia: JB Lippincott, 280-305.)

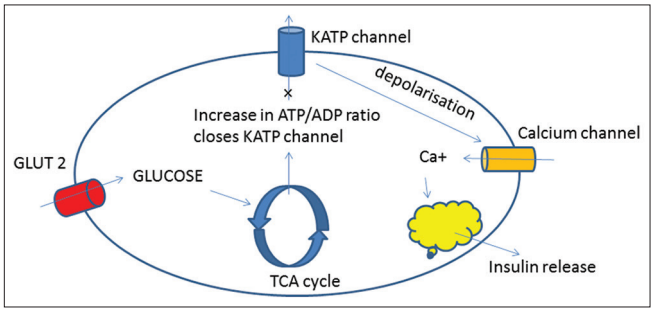


**Figure 3:** Pancreatic beta -cell: entry of glucose in cell increases ATP: ADP ratio this in turn close the KATP channel, resulting in depolarisation of the cell, allowing influx of calcium and finally vesicular exocytosis and release of insulin

**Box 1: Classification of neonatal hypoglycemia**

- Transient (days)
  - Developmental immaturity of fasting adaptation: premature and SGA infant
  - Peripartum stress: glycogen depletion
  - Hyperinsulinemia: infant of mother with poorly controlled diabetes mellitus
- Transient (weeks)
  - Birth asphyxia or SGA infant
  - Hyperinsulinemia
- Persistent
  - Hypopituitarism
  - Inborn errors
    1. Glycogen breakdown or synthesis
    2. Gluconeogenesis
    3. Ketogenesis
  - Congenital hyperinsulinism
  - Other

Adopted from- Sperling MA, Menon RK. Differential diagnosis and management of neonatal hypoglycemia. Pediatr Clin North Am 2004;51:703-723

**Table 1: Difference between focal and diffuse Congenital Hyper Insulinism (CHI) of K-ATP channel mutation**

| Parameter | Diffuse KATP-CHI | Focal KATP-CHI |
|---|---|---|
| Period of gestation at delivery | 38 week | 39 week |
| Birth weight | 3963 g | 3717 g |
| Critical sample insulin | 31.8 µIU/ml | 12 µIU/ml |
| GIR required to maintain blood glucose | 19.2 mg/kg/min | 16.1 mg/kg/min |
| Age of presentation | 0 months | 0.3 months |
| Seizure | 50% | 25% |

Derived from Lord K, Dzata E, Snider KE, Gallagher PR, De Leon DD. Clinical presentation and management of children with diffuse and focal hyperinsulinism: A review of 223 cases. J Clin Endocrinol Metab 2013;98:E1786-9

gas analysis revealed normal pH, bicarbonate. During an episode of documented hypoglycemia (venous plasma glucose <50 mg/dl), her C peptide was 5.36 ng/ml, serum insulin was 9.7 µIU/ml, was negative for blood ketone. Anterior pituitary evaluation revealed normal hormonal profile.

She was started on diazoxide at a dose of 10 mg/kg/day but hypoglycemia persisted. As she was unresponsive to diazoxide, she was started on octreotide, to which she was responsive. Since the patient was unresponsive to diazoxide, genetic study was planned to detect diazoxide unresponsive mutations. As 18F-DOPA-PET/CT was not available in our institute so we planned to proceed with the available HINEC-TOC but results were negative.

## Genetic Studies

Coding region of the ABCC8 and KCNJ11 genes were analyzed using whole genome sequencing with next generation sequencing using illumina chemistry. Patient was found to be homozygous

for the frameshift mutation c.4111delG (p.G1371fs) of the exon 33(NM_000352) in the ABCC8 gene hence the etiological diagnosis of the CHI was clarified.

## Outcome

Patient was not responding to Dizoxide and was on the octreotide injection three times daily in a multidisciplinary medical board discussion resolved with the plan of partial pancretectomy.

## Discussion

Glucose is the main metabolic fuel of fetus. Most of fetal glucose is derived from the maternal circulation. Metabolic changes occur in pregnancy to facilitate nutrient transfer to the foetus and pregnancy-related maternal insulin resistance causes a rise in postprandial glucose concentration which aids glucose transfer to the foetus, a process termed "facilitated anabolism."[2]

The abrupt cessation of the glucose supply from mother after severing of the placenta demands new-born to rapidly respond by glycogenolysis of hepatic stores, inducing gluconeogenesis, and utilizing exogenous nutrients from feeding to maintain adequate glucose levels. During this transition, new-born glucose levels fall to a low point in the first 1 to 2 h of life, and then increases and stabilizes at mean levels of 65--70 mg/dL by the age of 3--4 h.

Birth weights have a significant impact on immediate postnatal glucose status of neonate. it has been estimated that hypoglycemia affects approximately 16% of large-for-gestational-age (LGA) infants and 15% of small-for-gestational-age (SGA) babies [Figure 1]. There is no precise consensus numerical definition of hypoglycemia in new-borns, however an arbitrary level of 40 mg/dL or less has been used as the classic standard for hypoglycemia.

An operational threshold for blood-sugar management as suggested by *Cornblath et al.* is indication for action and is not diagnosis of disease.[3]

When hypoglycemia is refractory and severe or if the need for large glucose infusions lasts more than 1 week, and causes related to the perinatal stress [Box 1] are excluded evaluation of some of the rare causes of hypoglycemia should be considered. A detailed metabolic evaluation should be considered which should include hormonal and metabolic profile (lactate, non-esterified fatty acids (NEFA), β-hydroxybutyrate) at the time of hypoglycemia [Figure 2], neonatal hypoglycemia with suppressed levels of (NEFA) and β-hydroxybutyrate suggest hyperinsulinism.

Clinical features of hypoglycemia with low plasma glucose concentrations and resolution of the symptoms after glucose administration (whipples triad) and inappropriately high levels of plasma insulin and C-peptide coupled with low plasma β-hydroxybutyrate levels and a brisk glycemic response to glucagon characterize congenital hyperinsulinism in neonates and infants.

Normal blood gas analysis and lactate levels with low ketone at time of hypoglycemia in our patient directed us to think in direction of the hyperinsulinemia. Baby was having no body asymmetry or dysmorphia which may suggest hypopituitarism further inappropriately high c peptide and insulin in critical sample confirmed the diagnosis of hyperinsulinemic hypoglycemia.

## Congenital Hyperinsulinism

CHI is the commonest cause of persistent hypoglycemia in neonatal period and infancy. Insulin inhibits gluconeogenesis and glycogenolysis leading to hypoglycemia. Insulin inhibits lipolysis and thereby ketone body synthesis depriving brain of both glucose and ketones as an energy source. The prevalence of CHI is estimated to be between 1/30,000[4] and 1/50,000.[5] A much higher prevalence is higher in some ethnic groups ~1/11,000 in Ashkenazi Jews. CHI has been associated with mutations of six genes: the sulfonylurea receptor-1 SUR1 (*ABCC8 gene*), the potassium inward rectifying channel Kir6.2 (*KCNJ11*), glucokinase (*GCK*), glutamate dehydrogenase (GDH), short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), and ectopic expression of the monocarboxylate transporter 1 (MCT1). Out of these most common mutations are in the *ABCC8* and *KCNJ11* genes.

### ABCC8 or KCNJ11 (congenital hyperinsulinemic hypoglycemia) – KATP-CHI

*ABCC8* and *KCNJ11* encode SUR1 and Kir6.2, respectively, which together form the subunits of the heterooctameric KATP channel in the b-cell membrane. This channel is consist of four inner Kir6.2 subunits, which form the channel's ion pore, and four regulatory SUR1 subunits, which surround the Kir6.2 core.[6]

Normal physiology of insulin secretion is started by GLUT 2-mediated influx of the glucose in beta cells leading to increase in beta cell ATP levels leading to closure of the KATP channel with resultant depolarization of the b-cell membrane and opening of a voltage-gated calcium channel with subsequent Ca2+ influx and subsequent insulin exocytosis [Figure 3]. Inactivating mutations of either SUR1 or Kir6.2 renders the beta cell in state of permanent depolarization and hence consequent constitutive insulin secretion irrespective of serum glucose levels.[7]

Severity of phenotypic expression depends on the type of the mutation and over 300 mutations in *ABCC8* and over 30 mutations in *KCNJ11* have been described spectrum ranging from altered trafficking to membrane surface, density, complete absence of channel activity.[8]

Once diagnosis of CHI established initial treatment plan is to start with Diazoxide in doses of 10--15 mg/kg and if patient is responsive direction is more for the evaluation of the causes other than KATP channel defect (GCK, SCHAD, GDH, MCT1, HNF4A) but if there is no response to the diazoxide which is a potassium channel opener genetic evaluation for the mutation in SUR1 or Kir6.2 should be considered. Our patient was not responding to the diazoxide so was started and continued with the octreotide s/c injections and blood sample was sent for the genetic studies for the mutations of ABCC8 and KCNJ11.

KATP-CHI is divided into two forms: diffuse disease and focal disease. Diffuse KATP-HI is, in most cases, because of autosomal recessive mutations in *ABCC8* or, less commonly, *KCNJ11* whereas children with a paternally inherited heterozygous recessive mutation are more likely to have focal disease.[9-11]

Though there is no stark clinical difference between focal and diffuse CHI still several significant clinical differences are documented by one study [Table 1].[12]

Distinction between focal and diffuse disease is very important as focal disease can be cured by surgical resection of the lesion, whereas diffuse disease requires a near-total pancreatectomy. Among the imaging studies an F-DOPA PET scan can be of help in localization of a focal lesion though limiting factor is the availability of this modality in most developing centre.

Genetic study of our patient revealed that she is having homozygous frameshift mutation c. 4111delG (p.G1371fs) of the exon 33(NM_000352) in the ABCC8 gene since she was having symptoms from day 1 of life and high GIR was needed to maintain the blood glucose levels and imaging (HINEC-TOC) was not showing any lesion so we considered the possibility of the diffuse KATP- CHI and it was finally planned that patient should undergo near total pancretectomy but the parents refused from surgery.

## Conclusion

Hypoglycemia in new-born period is a common entity with variable etiology. Most of the cases respond to routine doses of dextrose and resolve within few days. Some cases fall in the category of the persistent hypoglycemia with congenital hyperinsulinism being most common cause. Mutation of the potassium channel are the most common form of the CHI. Repeated episodes of the hypoglycemia are associated with significant cognitive impairment this demands for a prompt definitive management. Genetic studies and FDOPA-PET are very helpful in decision making in regard to the type of surgery as definitive management of the hypoglycemia.

Work was carried out in Department of Endocrinology and Metabolism and Neonatology, Institute of Post Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital Kolkata West Bengal India and at the time of work author 1 and 2 were post doctoral trainee in the department of endocrinology and author 3 and 4 were consultant in department of endocrinology and neonatology respectively and are still working in the same institute.

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### Conflicts of interest

There are no conflicts of interest.

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