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Case Report

Paediatrics Section

Refractory Hypoglycaemia- The Need for Genetic Work Up

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ABSTRACT

Congenital Hyperinsulinism of Infancy (CHI) is a rare condition that causes of persistent hypoglycemia refractory to treatment. Neonatal hypoglycaemia is caused by numerous clinical conditions, such as birth asphyxia, Small for Gestation Age (SGA), premature birth, infant of diabetic mother, systemic disorders and hormonal disorders of fatty acid oxidation disorders. Of them infants that experience birth asphyxia, SGA, premature birth and born to diabetic mother that usually have transient hyperinsulinism resolves quickly, even though it may be quite severe. Hypoglycaemia in CHI occurs secondary to the dysregulation of insulin secretion. CHI has been established as a genetic disorder of islet cell hyperplasia, associated with a mutation of *ABCC8* or *KCNJ11* genes, which encode the sulfonylurea receptor 1 and inward rectifying potassium channel (kir6.2) subunit of the ATP-sensitive potassium channel, respectively. A case report of a neonatal persistent refractory hypoglycaemia born to primigravida mother as a result of CHI caused by mutation of *ABCC8* gene at a secondary care centre was presented.

Keywords: *ABCC8* mutation, Congenital hyperinsulinemia of infancy, Neonatal hypoglycaemia

CASE REPORT

A girl child, born of a non-consanguineous marriage to a mother of 29 years of age primigravida, was admitted to Neonatal Intensive Care Unit (NICU) for post resuscitation care, with respiratory distress and sugar monitoring. She was large for gestation age. The mother had no history of diabetes, hypothyroidism or hypertension. She was born at 38 weeks of gestation with a birth weight of 4.5 kilograms (90^{th}-97^{th} percentiles). Patient delivered by caesarean section delayed cry was there and her APGAR score was 4 at 1 minute, 6 at 5 minutes and 7 at 10 minutes [Table/Fig-1].

[Table/Fig-1]: Clinical picture of patient.

On examination, she was euthermic with a heart rate of 149 beats per minute, respiratory rate was 60 per minute and required nasal continuous positive airway pressure. Weight was 4.5 kg, length 48 cm, head circumference was 34 cm, chest circumference was 34.5 cm, no congenital anomalies were apparently visible.

She was lethargic and presented with hypotonic posture. Respiratory findings were normal, with systolic murmur suggestive of Patent Ductus Arteriosus (PDA). At 46 hours of life, she developed hypoglycaemic convulsions. Glucose Infusion Rate (GIR) was started at 4 mg/kg/min and gradually stepped up to 12 mg/kg/min, after that blood sugars level were momentarily normal and again patient developed hypoglycemia with random blood sugar of 30 g/dL.

Blood glucose levels were fluctuating under high intravenous GIR. Patient was started on short course of hydrocortisone (2 mg/kg/d) but no effect was there on blood sugar levels. Oral diazoxide was started with a dose of 5 mg/kg/day ,intermittently injection glucagon was also given when hypoglycemia reached below 30 g/dL, but still the levels were fluctuating so octreotide was added subcutaneously (5 µg/kg/dose) along with glucagon infusion on day of life 25, the patient thus had refractory hypoglycemia with levels in between 25-40 g/dL.

Because there was refractory hypoglycemia and all investigations done were suggesting hyperinsulinemia, after excluding all causes for it full sequencing of the *ABCC8*

gene was performed. Genetic analysis revealed a new heterozygous variation of c.4307G>C on exon 35 of *ABCC8* gene chromosome 11. This was the reason for congenital hyperinsulinism in the baby [Table/Fig-2].

Investigations	Values
HB	17.5 gm/dL (19.3-22)
PCV	52%
WBC	4400/mcL (4000-11000)
Platelets	254000/mcL (150000-450000)
CRP	3.2 (<3 mg/L)
Insulin	39.4 (<25 mIU/L)
Cortisol	8.51 mcg/dL (10-20)
Ketone bodies in blood	0.04 mmol/L (<0.6 mmol/L)
PET scan	Normal
TSH	Normal (0.4-4.0 Miu/L)
Na	136 mmol/L (135-145)
K	4.5 mmol/L (3.5-5)
Ca	9.1 mg/dL (8.5-10.5)

[Table/Fig-2]: Lab investigations of child.
HB- Hemoglobin; PCV- Packed Cell Volume; WBC- White Blood Cells; CRP- C Reactive Protein; PET- Positron Emission Tomography; TSH- Thyroid Stimulating Hormone; Na- Sodium; K- Potassium; Ca-Calcium

Being a secondary care centre with limited laboratory facilities, the patient was diagnosed as congenital hyperinsulinism of infancy and then she was transferred to tertiary care centre where pancreactomy was planned for the baby.

DISCUSSION

Persistent hypoglycemia can be caused by hyperinsulinism, even if there is no history of biochemical evidence of maternal diabetes, birth asphyxia, premature birth or SGA. Non-ketotic persistent severe hypoglycaemia in neonates and inappropriate insulin secretion from pancreatic beta cells leads to CHI. Inherited or sporadic mutations in the regulation of the potassium channel involved in insulin secretion by the pancreatic cells can lead to CHI [1]. Worldwide the incidence of CHI is 1 in 30000 to 1 in 50000 live births. A particular high incidence of 1 in 2500 has been reported from Arabian countries due to high rates of consanguinity [1].

Most common causes of CHI are mutations that inactivate the *ABCC8* and *KCNJ11* genes encoding the sulfonylurea receptor 1 and the inward rectifying potassium channel (kir6.5) subunit of the ATP- sensitive potassium channel [2]. Persistent hypoglycaemia is the major risk factor for intellectual deficit, therefore early diagnosis and treatment is very important. CHI is an inappropriate for insulin secretion by the pancreatic β-cells secondary to various genetic disorders. Approximately 1/50, 000 live births incidence is estimated overall, but it may be high in countries with consanguinity to 1/2,500 [3]. Recurrent episodes of hyperinsulinemic hypoglycaemia may expose to high risk of brain damage. There are two main clinically indistinguishable histopathological lesions: diffuse and focal in CHI. Recessive *ABCC8* mutations code for SUR1 and *KCNJ11* code for Kir6.2, both are subunits of the potassium channel, responsible for most severe diazoxide-unresponsive HI [4].

Pathogenesis consists of channelopathies, affect the subunits of a KATP channel set through the plasma membrane of the β-cells. Both subunits can be affected: the Sulfonylurea Receptor (SUR1) encoded by the *ABCC8* gene and the inward-rectifying potassium channel (Kir6.2) encoded by the *KCNJ11* gene. Enzymes anomalies or other metabolic defects involve glucokinase encoded by the *GCK* gene, glutamate dehydrogenase or GDH encoded by *GLUD1* gene (HI/HA syndrome), Short-Chain L-3-Hydroxyacyl-coa Dehydrogenase (SCHAD) encoded by *HADH* gene. A transcription factor defect, involving the Hepatocyte Nuclear Factor 4 Alpha genes (HNF4A), is also responsible of HI [5].

Congenital conditions such as Beckwith-Wiedemann, Mosaic Turner syndrome and Costello syndromes have also been linked to hyperinsulinemia and subsequent hypoglycemia [6]. The diagnostic criteria for hyperinsulinism based on laboratory analysis of a critical blood sample are: plasma insulin >2 μU/mL, plasma free fatty acids <1.5 mmol/L, plasma beta-hydroxybutyrate <2.0 μmol/L, glycemic response to 0.1 mg/kg intravenous glucagon >30 mg/dL. Other tests such as serum ammonia, plasma acylcanitine profile and urinary organic acids for CHI caused by mutation in SCHAD enzyme and lastly the genetic testing [7]. Recurrent hypoglycaemia can be avoided by stimulation of neonatal gluconeogenesis which is limited by glucose infusion and/or insulin secretion. Lipid administration induces a hyperglycaemic response which is explained by a stimulation of gluconeogenesis. It also results in ketogenesis which provides the compensatory factors of hypoglycaemia and which seems to be linked to gluconeogenesis [8].

Among the syndromics, metabolic and milder form of KATP channel defects usually responds to diazoxide, which is the first line of treatment. In those infants who fail to respond, octreotide is the second line drug. Nifedipine, a calcium channel antagonist and chlorthiazide has synergistic response to diazoxide have been reported to be effective in some cases. Glucagon is useful in short term management of infants awaiting surgery. Surgical therapy like pancreactomy partial or complete is required in those infants who fail to respond to medical management and in cases of nesioblastosis [9].

CONCLUSION(S)

Neonatal hypoglycaemia management is controversial due to inconsistent definitions and a lack of trials. But the serious consequences of hypoglycaemia, especially due to

hyperinsulinism, have been confirmed and advances made in the diagnosis and management of the patients, so to prevent all these poor outcomes there should be high index of suspicion kept for genetic disorder in case of persistent refractory hypoglycaemia.

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