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Persistent Hyperinsulinemic Hypoglycemia of Infancy-Case Report

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ABSTRACT

Persistent hyperinsulinemic hypoglycemia of infancy is rare genetic disorder, occurs due to unregulated insulin secretion instead of hypoglycemia. It results from defects in the pancreatic β-cell ATP-sensitive K_{ATP} channel resulting unregulated insulin secretion. Untreated neonatal-onset hypoglycemia subsequently develops infantile spasms. A three month old female baby of first degree consanguineous parents delivered at term, large for gestational age, developed hypoglycemia soon after birth, and seizure at five day of life. Initially, she had generalized tonic-clonic seizure later developed infantile spasm. She had delayed global milestone, hypotonia and diminished reflexes. Her critical blood sample showed sugar was low, insulin was high, EEG showed epileptiform discharge and CT scan revealed cortical atrophy. We diagnosed the case as Persistent hyperinsulinemic hypoglycemia of infancy with infantile spasm treated with Inj. Octreotide for hypoglycemia and syp sodium valproate and syp levetiracetam for infantile spasm. Early diagnosis and aggressive management of hyperinsulinemic hypoglycemia of infancy is the cornerstone for prevention of hypoglycemia induced neuronal injury.

INTRODUCTION:

Hyperinsulinemic hypoglycemia occurs due to unregulated insulin secretion from β-cells of pancreas in spite of low blood glucose levels. Hyperinsulinism is rare genetic disorder, about 50% of the cases due to persistent hyperinsulinemic hypoglycemia of infancy (PHHI) [1]. Several congenital mutations have been described and half of the cases the adenosine triphosphate (ATP) sensitive K^+ channel in pancreatic β cells play a key role in the uncontrolled insulin secretion [2]. *KCNJ11* and *ABCC8* localized on chromosome 11p15.1 are responsible for coding the 2 subunits of these K-ATP channels [3]. Neonatal hypoglycemia is the most common metabolic disorder during the neonatal period and trigger infantile spasms [4]. Infantile spasms are an age-specific epileptic encephalopathy occurring in early infancy that are characterized by epileptic spasms with neurodevelopmental regression and electroencephalographic (EEG) features of hypsarrhythmia [5]. The main aim of PHHI management is to prevent hypoglycemia, which can lead to complications such as coma, brain damage, seizure and mental retardation [6].

High-dose glucose infusion, diazoxide, octreotide and nifedipine are the major steps in management of PHHI. Total or subtotal pancreatectomy should be considered in case of resistance or treatment failure PHHI patients [7]. The objective of this article is to report the case due to rarity of the disease.

Conclusions: Increased awareness among clinicians about infants with hypoglycemia, and contribution to the diagnosis and management of hyperinsulinism. Analysis of blood samples after collection at the time of hypoglycemic episodes, for intermediary metabolites and hormones, is critical for diagnosis PHHI.

CASE SUMMARY:

A 3 months old girl, only issue of first degree consanguineous parents was born by cesarean section at 38th week at term after an uneventful pregnancy. Birth weight was 4500 g, and Apger scores were 10 at 1 minute and 5 minute. She was admitted at the age of three months with the complaints of repeated seizure since five day of age and persistently low blood sugar soon after birth. During seizure, her blood sugar found low and seizure resolved by glucose administration. Initially, seizure was generalized tonic-clonic in nature and last six weeks she developed flexion of head over trunk and seizures episode were about 100 times a day, and even in sleep. On examination, her weight was on 50th centile, length and occipitofrontal

circumference was on 25th centile. Developmental assessment revealed that her neck control was not achieved yet, she has hand regard, brought hand to mouth, occasional eye to eye contact, no social smiling, vision and hearing were intact, and so she had global developmental delay. CNS examination revealed tone and deep tendon reflexes were diminished. Her random blood sugar was 1.2 mmol/L (N, 4.4 -7.8mmol/L), Critical blood sample showed blood glucosee was1.4 mmol/L (N, 4.4 -7.8mmol/L), concomitant s. insulin was 8.8 µU/mL (N, <2 µU/mL), the insulin-to-glucose ratio was 6.28 (N, < 0.3), growth hormone was 10.7 ng/ml (N,>7-10 ng/ml), TSH was 3.6 mU/L (N, 0.05-5mU/L), FT4 was 20.5 pmol/L(N; 8-26 pmol/L) , s. cortisol was 635 nmol/L (N; 140-690mmol/L). Plasma ammonia and ABG was normal. Urine for ketone body and reducing substance was nil. EEG showed focal epileptiform discharges over left frontal, central and temporal regions and background elctro-physiological function was disturbed. CT scan (Fig 1) showed dilatation of ventricles, increased subarachnoid space and cortical atrophy. Genetic analysis is not available in our country.

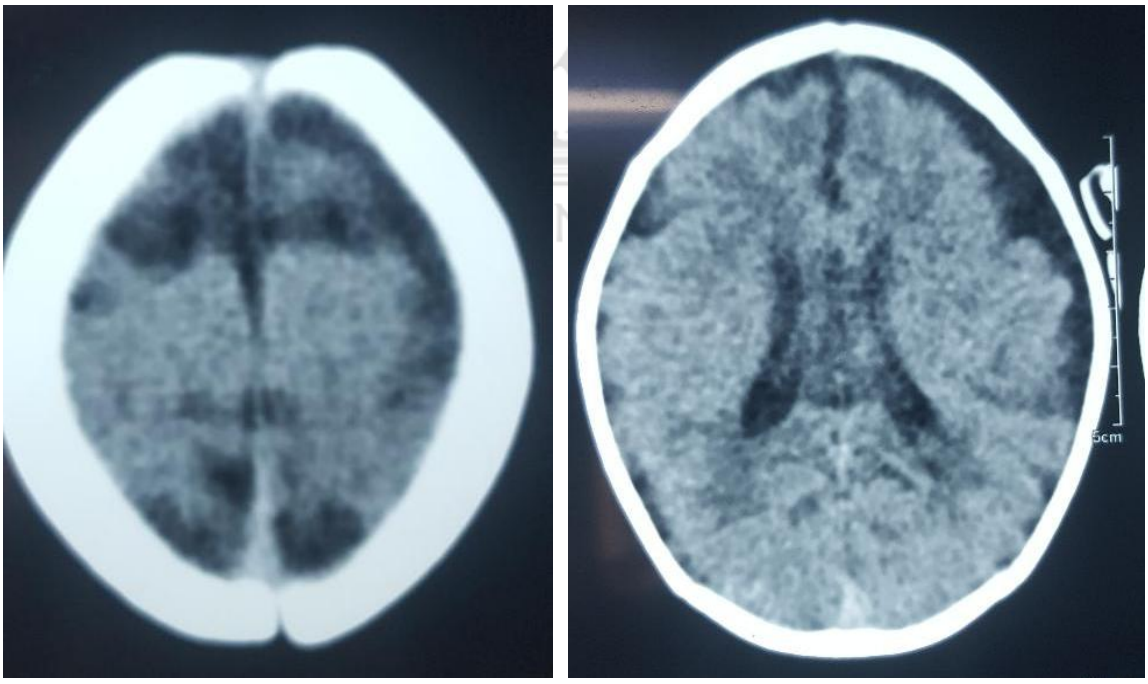

Figure 1. CT scan showing dilatation of ventricles increased subarachnoid space and cortical atrophy

We diagnosed the case as hyperinsulinemic hypoglycemia of infancy with infantile spasm. We treat the patient with S/C inj. octreotide for hypoglycemia, syp sodium valproate and

syrup levetiracetam valproate for infantile spasm as no response to inj ACTH and she was normoglycaemic and achieved 80% control of her seizure.

DISCUSSION

Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI) is the most common cause for severe, persistent neonatal hypoglycemia. PHHI previously termed nesidioblastosis and it was first identify in 1938 by Laidlow [8]. The incidence of PHHI CHI is estimated to be 1:40,000-50,000 in the general population, but in familial forms, it may be as high as 1:2500 in populations with substantial consanguinity [9].

There was first degree consanguinity of marriage in parents of our patients as it an autosomal recessive disorder. Our patient was large for gestational age, these infants are characteristically large due to the growth- promoting action of insulin but they have been reported with normal weight or even small [10].

Symptoms of hypoglycemia appear within 72 h of birth. The presentation includes hunger, jitteriness, lethargy, apnea, and seizures. Seizures are generalized tonic-clonic in nature [11]. Our patient developed hypoglycemia soon after birth and had severe symptom such as recurrent seizure. Severe symptoms are poor prognostic sign and indicates CNS injury. Our patient diagnosed at three months of age and did not get proper treatment during this period, subsequently develop infantile spasm. Glucose is the principal energy source for the neonatal brain and hypoglycemia is known to cause irreversible neuronal injury when it is recurrent and severe, so prompt recognition and treatment of PHHI is necessary [12].

Insulin and C-peptide levels are inappropriately elevated compared to hypoglycemia. In addition, low levels of free fatty acids and ketones can be observed due to inhibition of lipolysis [13]. This increases the risk of brain injury. In our patient insulin level was high in spite of hypoglycemia and there was brain injury evident by presence of seizure, epileptic discharge from EEG and cortical atrophy with dilatation of subarachnoid space in CT scan of brain. Guang Yang observed that 18 patients developed infantile spasms those had neonatal-onset hypoglycemia. This case series suggests that neonatal hypoglycemic brain injury could be an underlying cause of infantile spasms later in the infancy period. The latency period of infantile spasms following the onset of neonatal hypoglycemia was 2-10 months in his case series [14].

The treatment algorithm most widely accepted recommends the K-ATP agonist diazoxide as first-line therapy that keeps the KATP sensitive channels open and the somatostatin analog octreotide as second-line therapy. The calcium channel blocker nifedipine has also been reported as an alternative in unresponsive cases. Our patient was treated with Octreotide as Diazoxide was not available in our country and achieved euglycemia. Histologic presentation may be focal or diffuse based on the spread of affected regions in the pancreas [15]. Differentiation between these subgroups can be made by using 18F 3,4-dihydroxyphenylalanine positron emission tomography scans [16]. Focal lesions need surgical excision, whereas diffuse presentations the only treatment option available is subtotal or total pancreatectomy.[1]A recently published novel treatment option for PHHI of the newborn has been suggested the immunosuppressant sirolimus, an mTOR inhibitor [17].

Prevention of severe hypoglycemia caused by PHHI is of utmost importance as it may lead to severe complications. Sawathiparnich et al. studied 10 patients with PHHI and reported that the majority of cases could be managed with intensive medical interventions [18]. Semiz reported a three-month-old male infant diagnosed as PHHI with symptoms of lethargy, seizure, and blood sugar level low. They observed no response to maximal doses of prednisolone, glucagon, diazoxide, octreotide and glucose, and eventually, pancreatectomy was performed [19]. We managed hypoglycemia in our patient by medical therapy using IV glucose and IV hydrocortisone initially, follow by octreotide. We treated infantile spasm with Inj ACTH and Levotirecitum and achieved partial control of seizure.

CONCLUSION:

Early diagnosis and aggressive management of hyperinsulinemic hypoglycemia is the cornerstone for prevention of hypoglycemia induced neuronal injury. However, the management of hyperinsulinemic hypoglycemia still remains a challenge to the neonatologists and endocrinologists, due to lack of facilities for genetic studies and 18F-DOPA-PET scan. High index of suspicion, early diagnosis and aggressive management is essential to prevent brain injury due to hypoglycemia.

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