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Persistent Hyperinsulinism - Hyperinsulinemic Hypoglycemia : Follow up and Review of 16 Cases

KEYWORDS: Congenital hyperinsulinism, persistent hypoglycemia, dotanaoc scan

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ABSTRACT *Congenital hyperinsulinism (HI) is a condition characterized by unregulated insulin secretion from the pancreatic beta cells in relation to blood glucose concentration and secondary to various genetic disorders 1. HI is a heterogeneous disorder with two main clinically indistinguishable histo pathological lesions: diffuse and focal 2. HIH severity varies from life-threatening hypoglycemia in neonates within the first days of life, which may require a near-total pancreatectomy, to mildly symptomatic hypoglycemia with initial manifestations in adolescence or adulthood, which may be difficult to identify. The aim of treatment is to achieve normoglycemia without brain damage .We report and discuss the clinical and biochemical characteristics, mode of treatment, and neurodevelopmental outcomes in 16 children who were seen between 2002 and 2013 and diagnosed to have HIH.*

Introduction:
Congenital hyperinsulinism (HI) comprises a group of different genetic disorders with the common finding of recurrent episodes of hyperinsulinemic hypoglycemia due to an inappropriate secretion of insulin by the pancreatic b-cells.

Results :
Retrospective analysis of all babies admitted in institute of child health with clinical features of CHI was analyzed.

The predominant maternal age group was 25-30 years in 68% of neonates. Consanguinity was present in 49% of neonates. Maternal complications of pregnancy was present in 10 patients and respectively were PIH in 2 neonates, GDM in 2, ante partum hemorrhage in 2 ,premature rupture of membranes in 2 and stillbirth of 8 and 9 in 2 cases. PHI was present in II birth order in in 50 % mothers.

Mean Gestational age was 37.1 weeks ± 4.6 weeks (range 25-40 weeks).Male sex was predominant in 52% and 48 % in females. Mean birth weight was 2873 ± 0.69 grams (range 980 grams - 4010 grams).3 neonates were SGA and 1 were LGA. Mean age of hypoglycemia was 15.25 ± 7.28 hours.

Hypoglycemic seizure was the most common presenting symptom and was seen in 12 (75%) neonates. Lethargy in 7(43.5%), refusal of feeds in 3(18%), hypoglycemia in 3(18%) ,apnea in 2 (12.5%) and NNH in 1 (6%) were also among the presenting symptoms.

Insulin (in all patients) and C peptide (available in 13 patients) at the time of hypoglycemia were between 6.2 to 106 mIU/L and between 1.9 to 29 ng/ml respectively .Insulin/glucose ratio ranged from 2.8 to 206.

All patients were treated with GIR 12.5 -14.5mg/kg/min and hydrocortisone 10 mg/kg/day. The mean effective dose of diazoxide was 11.1 ± 2.64 mg/kg/day (range, 5-15 mg/kg/day). Ocreotide was used in 11 patients with mean effective dose of 9.7 ±3.07 mcg/kg/day. Nifedepine was used in 11 patients with mean dose of 0.25-0.5 mg/kg/day. Medical treatment failed to maintain normo glycemia only in 8 patients.

Due to persistent hypoglycemia pet scanning was done in 8 neonates using dotanac in 5,dotatate (figure1) in 3 and gallium 68 in 1 respectively.

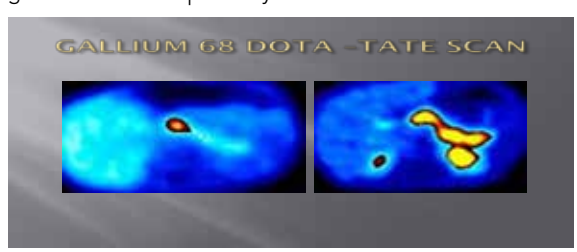

Figure 1: Dota-tate scan reveals increased uptake in head and body of pancreas

Medical unresponsive neonates underwent Near total in 6 and subtotal pancreatectomy in 2 of neonates at mean age of 3.18 ±1.7 months. Histo-pathological examination(figure 2) revealed diffuse hyperplasia in majority of neonates and focal hyperplasia in 1 neonates respectively.

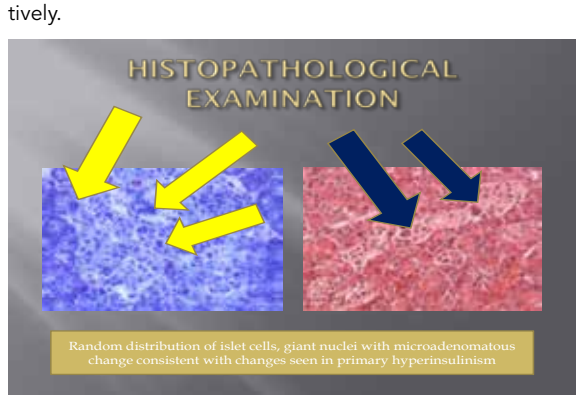

Figure 2: Histo-pathological examination shows random distribution of islet cells, giant nuclei suggestive of hyperinsulinism

Hypoglycemia episodes continued after surgery and was controlled by diazoxide, nifedepine and hydrochlorthiazide in 5 neonates. Of 16 neonates, 3 succumbed of which 2

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were in non operated and 1 in operated group and 13 survived. Major cause of death was sepsis in 2 and persistent seizures in 1 neonates. MRI brain (figure 3) showed bilateral parieto-occipital infarcts in 3 infants with abnormal EEG in 2 infants.

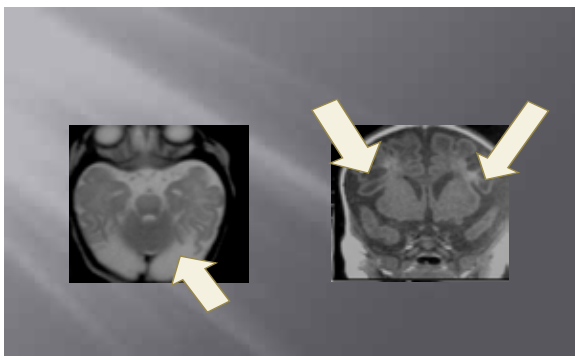

Figure 3: MRI brain depicts bilateral parieto-occipital infarcts

2 patients developed hypertrichosis induced by diazoxide which disappeared after drug withdrawal.

Echocardiography was performed in 1 patient and revealed PDA in 1 neonate. Epilepsy (two patients), developmental delay (three patients), motor-mental retardation (three patients) and visual disturbances (two patients) were the long term complications.

Discussion:

PHHI is characterized by inappropriate insulin secretion and it is important cause of persistent hypoglycemia in neonate. The incidence is estimated at 1/50, 000 live births, but it may be as high as 1/2, 500 in countries with substantial consanguinity.

HI is a heterogeneous disorder with two main clinically indistinguishable histopathological lesions: diffuse and focal. Recessive ABCC8 mutations (encoding SUR1, subunit of a potassium channel) and, more rarely, recessive KCNJ11 (encoding Kir6.2, subunit of the same potassium channel) mutations, are responsible for most severe diazoxide-unresponsive HI [3]. Focal HI, also diazoxide-unresponsive, is due to the combination of a paternally-inherited ABCC8 or KCNJ11 mutation and a paternal isodisomy of the 11p15 region, which is specific to the islets cells within the focal lesion.

Genetics and 18F-fluoro-L-DOPA positron emission tomography (PET) help to diagnose diffuse or focal forms of HI [4]. Dotanac, Dotanate , gallium 68 scans can be used when 18-Flouro Dopa PET is unavailable.

The diagnostic criteria for HI include:

Fasting and/or post-prandial hypoketotic hypoglycemia (< 2.5 - 3 mmol/l)

Inappropriate plasma insulin levels (plasma insulin concentration detectable) and c-peptide concomitant to hypoglycemia

An increase in blood glucose greater than 1.7 mmol/L (30 mg/dL) within 30 - 40 minutes after IM or IV administration of 1 mg glucagon

Inappropriately low ketone bodies in plasma and urines and low free fatty acids in plasma even for fasting hypoglycemia [5].

A glucose infusion rate higher than 10 mg/kg.min in a neonate proves an insulin related hypoglycemia [6].

Recurrent episodes of hyperinsulinemic hypoglycemia may expose to high risk of brain damage. An early and rapid diagnosis as well as initiation of effective treatment is essential for preventing brain damage and intellectual disability in patients with HIH [7]. Diazoxide is the first-line medication for long-term treatment and acts on pancreatic β-cells and opens the KATP channel, thereby inhibiting insulin secretion. Oral diazoxide is used at an initial dose of 5 to 15 mg/kg/day, divided into two or three doses[8] .The mean dose of diazoxide used in our patients was 11.1±2.6 mg/kg/day (5-15 mg/kg/day), and a response to diazoxide was obtained in all patients. The most common side effects of diazoxide are fluid retention, hypertrichosis, hyperuricemia, tachycardia, leukopenia, and feeding problems. Tolerance to diazoxide is usually good. In our group, two patients developed hypertrichosis induced by diazoxide, which disappeared after treatment discontinuation.

Early-onset neonatal HIH is generally severe and progresses with hypoglycemia, which can be recurrent, severe, and treatment-resistant. Meissner et al [9] achieved a response to medical treatment in 29% of patients in the HIH group with a neonatal onset. De Lonlay et al [10] and Touati G et al [11] reported a 16% response rate in their studies. In our study group, the response rate to medical treatment in patients with HIH with a neonatal onset was 50%.

Surgery was required when medical and dietary therapies have failed in severe cases of diffuse HIH[12]. The immediate postsurgical outcome is variable. Hypoglycemia persisted after surgery in five patients, and the requirement for medical treatment continued. Neurologic sequelae, such as psychomotor retardation, cognitive deficits, and epilepsy, are usually due to prolonged and/or recurrent hypoglycemia during the newborn period.

Conclusion:

Congenital hyperinsulinism is the most common cause of persistent neonatal hypoglycemia. Early treatment of hypoglycemia is important to prevent brain damage. Ga 68, Dotanac, Dotanate can be used when 18F-DOPA PET scan is not available. The anatomical details also guide surgery of the lesion. High index of suspicion and early institution of appropriate treatment improves neurological outcome in neonates.

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