# Persistent Hyperinsulinemic Hypoglycaemia Of Infancy (PHHI)

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## Introduction

PHHI is the most common and severe forms of hyperinsulinemic hypoglycemia in neonates and infants . PHHI is a genetic disorder with familial and sporadic forms , both of which are characterized by dysregulation of insulin secretion occur in the neonates .In recent study described genetic abnormalities in nine genes (*ABCC8, KCNJ11, GCK, SCHAD, GLUD1, SLC16A1, HNF1A, HNF4A*, and *UCP2* ) that lead to the congenital forms of HH (1). The most severe forms of CHH are due to defects in the genes (*ABCC8* and *KCNJ11*) (2,3). In PHHI the histological abnormalities in pancreatic structure grouped into 2 categories: The focal lesion has abnormal islet cells , the majority of focal CHH due to heterozygous paternally inherited mutation in the *ABCC8* or *KCNJ11* gene , gene account for almost 30–40% of all CHH cases . Focal CHH is usually confirmed by a fluorine-18 dihydroxyphenylalanine-positron emission tomography (18F-DOPA-PET) scanning. Surgical resection of the lesion usually resolves HH. Diffuse CHH , the diffuse pancreas affects all the pancreatic β-cells, Patients with diffuse CHH either have a homozygous recessive or a compound heterozygous mutation in their $K_{ATP}$ channel genes. This form of CHH accounts for 60–70% of all CHH cases , require a near total pancreatectomy (4).

## METHODS

We have reviewed 14 infants (9 male & 5 female) who presented with severe recurrent non ketotic hypoglycaemia , in the period between (1996-2013), the mean age of presentation 3 weeks ( 1 days- 3 months) except one patient was diagnosed at 6 years of his age. The diagnosis of primary form of congenital hyperinsulinemic hypoglycaemia was confirmed by laboratory investigations. Analysis of data regarding the time & mode of presentation , birth history ,family history ,consanguinity , Initial blood sugar levels , Insulin levels ,Insulin to glucose ratio, genetic analysis ,management ,histopathology & outcome of the patients were studied.

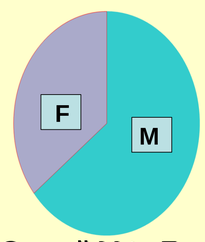
## Genetic Study

Genetic testing was done in one patient and the result reveals that homozygous mutation was identified
SUR (ABCC8) gene which confirms a diagnosis of autosomal recessive congenital hyperinsulinism, the heterozygous mutation detected gene ABCC8 location axzon 3 consequence

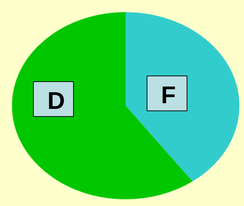
## Results of data analysis

| PT NO | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | F | F | M | M | M | F | F | M | M | M | M | M | F | M |
| BW(kg) | 3.9 | 3.8 | 4 | 5.7 | 4 | 2.9 | 3.1 | 4.5 | 5.6 | 4.1 | 3.6 | 5.7 | 3 | 1.9 |
| Age at onset | 6yr | 3 D | 4 D | 1 D | 3 M | 2 M | 50 D | 7D | 1 D | 7 D | 14 M | 4 D | 1 M | 3 D |
| Current age | 21yr | 12 yr | 7.5 yr | 8.5 yr | 8.6yr | 6 yr | died | died | 4 yr | 3.6 yr | 27 yr | 6 yr | 5.6yr | 3.6yr |
| Insulin µU/ml | 26 | 26 | 17 | 21 | 17 | 18 | 20 | 24 | 20 | 16.6 | 17 | 32 | 26 | 22 |
| Initial BS mg% | 14 | 8 | 12 | 2 | 18 | 12 | 22 | 4 | 4 | 22 | 17 | 4 | 10 | 18 |
| Insulin/glucose ratio | 1.85 | 3.25 | 1.42 | 5 | 0.94 | 1.5 | 1 | 6 | 5 | 0.75 | 0.94 | 8 | 2.6 | 2.1 |
| Age at operation | 7 yr | 9 M | 3 M | 45 D | 2.5yr | 6 M | 3 M | 34 D | 30 D | 48 D | Octero | 30D | 4 M | 2M |
| Histopathology %resection | Fo 95% | Fo 95% | Di 98% | MF 98% | Di 95% | Di 95% | Di 95% | MF 98% | Fo 98% | Di 98% | Di (PET S) | Di 95% | Fo 95% | Di 98% |
| Out come | EG | EG | DM | DM | EG | EG | EG | EG | EG | EG | EG | EG | EG | EG |
| Mental status | MR | MR | Normal | ADHD | MR | normal | Died | Died | normal | normal | MR | normal | normal | normal |

Table : clinical evaluation of the patients
Octer= octerotide ,FO=Focal ,DI=diffuse , MF=multifocal , EG=euglycemia, , MR= mental retardation, ADHD=attention deficit hyperactivity disorder




Overall M to F ratio
1.8:1




Focal to diffuse
2:3

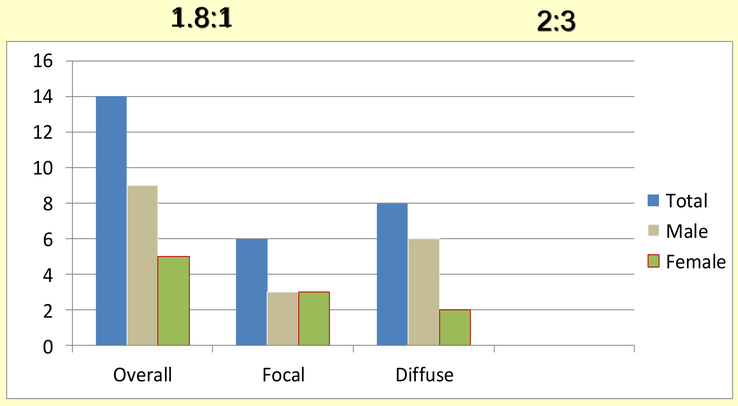
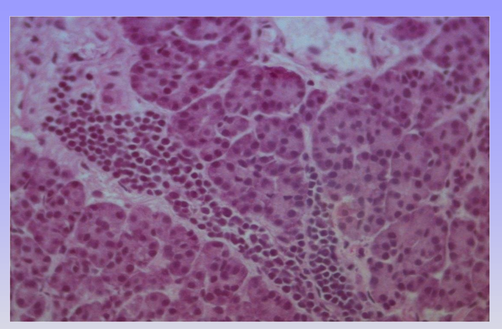


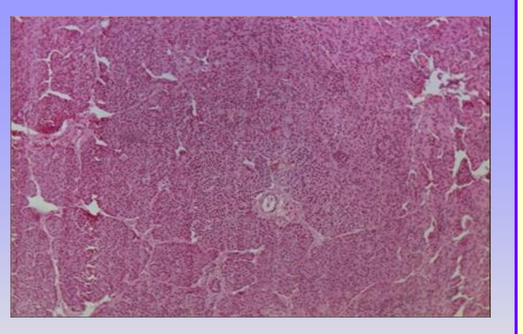

Figure s: male to female,focal to diffuse & over all ratios

## RESULTS

- **Mean birth weight 4 kg .**
- **Mean age of presentation 3 weeks except one patient was presented at 6 year.**
- **10 pts (71%) having first cousin of consanguinity .**
- **3 patients have had family history of siblings died from neonatal hypoglycemia.**
- **Initial Blood sugar 2mg-22mg% with mean 12 mg/dl .**
- **Mean insulin levels 21.6 µU/ml in presence of hypoglycemia.**
- **Insulin: glucose ratio was 0.75 – 8 .**
- **All patients underwent sub-total to near- total pancreatectomy except one patient .**
- **Histological Findings:**
  - **Focal form in 6 patients (43%) with Insulin level > 20 µU/ml ,Blood sugar ≤12mg%**
  - **Diffuse form in 8 patients (57%) with Insulin level ≤ 20 µU/ml and Blood sugar > 12mg%**
- **Focal (3 M,3 F), Ratio 1 : 1. Diffuse(6 M,2 F), Ratio 3 : 1. Overall (9 M,5 F) with male to female ratio was ( 1.8 : 1).**
- **Large size baby with focal lesion and small or average sized baby with diffuse hyperplasia .**
- **Focal lesion is more severe than the diffuse one.**
- **Two male infants presented with severe form of hypoglycemia earlier age 1-7 days of life with blood sugar 2-4 mg%, and had greater birth weight (4.5 kg & 5,7kg) their mothers were not suffering from gestational diabetes, they didn't respond to medical therapy they found to have had multifocal adenomatosis in their pancreases .**
- **Diabetes Mellitus developed in 2 cases (14%). 1 multifocal and other one diffuse, with mean age 5 year.**
- ***Unfavourable neurological outcome in 2 pts due to late intervention, because their family rejected operation,***
- ***Neurologic & Psychomotor retardation in 4 patients (29%) & ADHD in one patient .***



Histopathology
Focal 43 %



Histopathology
Diffuse 57%

## CONCLUSIONS

- Early recognition , diagnosis & treatment to prevent or minimize neurologic damage
- Family education & long term Follow-up to detect recurrence and detection of DM.
- A genetic studies considered as a useful parameter to determine cause and for genetic counseling.
- New drugs should be available.
- Preoperative investigations will limit pancreatectomy & prevent post operative diabetes .

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