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Persistent Hyperinsulinemic Hypoglycemia

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- **Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is is the most important cause of hypoglycemia in early infancy.**
- **The excessive secretion of insulin is responsible for profound hypoglycemia and requires aggressive treatment to prevent severe and irreversible brain damage.**
- **the severity of hypoglycemia decreasing with age.**

- **PHHI is a heterogeneous disorder with two histopathological lesions, diffuse (DiPHHI) and focal (FoPHHI), which are clinically indistinguishable.**
- **FoPHHI is sporadic and characterized by somatic islet-cell hyperplasia.**
- **DiPHHI corresponds to a functional abnormality of insulin secretion in the whole pancreas and is most often recessive although rare dominant forms can occur, usually outside the newborn period.**
- **Persistent hyperinsulinism in older children is most commonly caused by pancreatic adenoma**

Genetics

- **The estimated incidence of PHHI is 1/50,000 live births but in countries with substantial consanguinity, such as Saudi Arabia, it may be as high as 1/2500.**
- **Focal islet-cell hyperplasia is associated with hemi or homozygosity of a paternally inherited mutations of the sulfonylurea-receptor (SUR1) or the inward rectifying potassium channel genes (Kir6.2) on chromosome 11p15, and loss of the maternal allele in the hyperplastic islets.**

- **Recessive SUR1 mutations, and more rarely recessive Kir6.2 mutations, are responsible for the majority of diffuse and severe neonatal HI resistant to medical treatment.**
- **Dominant SUR1 mutations are responsible for less severe HI occurring in the first year of age and are sensitive to diazoxide.**

- **Dominantly expressed missense mutations of the mitochondrial matrix enzyme, GDH, cause hyperinsulism/hyperammonemia HI/HA syndrome, the second most common form of HI.**
- **Dominantly expressed GK mutations are a rare cause of HI. They result in a gain of function by increased affinity of GK for glucose leading to inappropriate insulin secretion.**

- **Adenoma related to the MEN1 syndrome by dominant mutation on the MEN1 gene following menine protein deficiency. A loss of the 11p13 region has been described in some adenomas and one adenoma has been described in Bourneville's tuberous sclerosis.**

Metabolic Defects

- **Hyperinsulinemic hypoglycemia is due to either focal or general insulin hypersecretion by the pancreas. Insulin decreases plasma glucose both by inhibiting hepatic glucose release from glycogen and gluconeogenesis, and by increasing glucose uptake in muscle and fat.**
- **PHHI is a heterogeneous disorder which can be caused by various defects in the regulation of insulin secretion by the pancreatic B-cell.**

- **These include i) Channelopathies affecting either the SUR1 or the KIR channel; ii) enzyme deficiencies including glucokinase (GK), glutamate dehydrogenase (GDH) and short chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD); iii) modifications of the insulin receptor.**