congenital hyperinsulinism (CHI)

What is congenital hyperinsulinism (CHI)?

Congenital hyperinsulinism (CHI) is a rare genetic disorder characterized by dysregulation of insulin secretion from the pancreas, leading to excessive production and release of insulin. This results in persistent hypoglycemia (low blood sugar levels), which can cause serious complications if left untreated.

In individuals with congenital hyperinsulinism, the pancreas produces and secretes insulin inappropriately, even in the absence of high blood glucose levels. This dysregulation can occur due to mutations in genes that play a role in regulating insulin secretion.

What is a normal blood glucose level in CHI?

For the purpose of CHI, hypoglycaemia is agreed to be less than 63mg/dl. In the absence of ketone bodies, infants with CHI are constantly reliant on the circulating blood glucose as the fuel for normal neurological functioning, hence the importance of maintaining the blood glucose concentration above 63mg/dl.

How common is CHI and whom does it affect?

Congenital hyperinsulinism (CHI) is a rare disorder, with an estimated incidence of approximately 1 in 25,000 to 50,000 live births worldwide. However, the prevalence of CHI may vary across different populations and geographic regions.

Genetics of CHI

At present, there are up to 14 known genetic causes of CHI and others where CHI is a feature of a syndrome (collection of symptoms often seen together). There are several genetic causes of CHI, with mutations in different genes implicated in its development. Here are some key genetic aspects:

1. **ABCC8 and KCNJ11 Genes**: Mutations in the ABCC8 and KCNJ11 genes are the most common cause of CHI, accounting for around 60-70% of cases. These genes encode subunits of the ATP-sensitive potassium channel (KATP channel) in pancreatic beta cells.

Mutations in these genes result in overactivity of the KATP channel, leading to excessive insulin secretion and hypoglycemia.

2. **GLUD1 Gene**: Mutations in the GLUD1 gene, which encodes the enzyme glutamate dehydrogenase, can also cause CHI. These mutations lead to increased activity of glutamate dehydrogenase, resulting in excessive insulin secretion.

3. **HNF4A, HADH, GCK, and UCP2 Genes**: Mutations in other genes such as HNF4A, HADH, GCK, and UCP2 have also been implicated in rare cases of CHI. These genes play roles in pancreatic beta cell function, glucose metabolism, or insulin secretion.

4. **Genetic Heterogeneity**: CHI exhibits genetic heterogeneity, meaning that different genetic mutations can lead to similar clinical manifestations. Additionally, the severity of CHI can vary depending on the specific genetic mutation and its effects on insulin secretion.

5. **Inheritance Patterns**: The inheritance pattern of CHI varies depending on the underlying genetic cause. In some cases, CHI is inherited in an autosomal recessive manner, where two copies of the mutated gene are needed to cause the disorder. In other cases, it may be inherited in an autosomal dominant manner, where only one copy of the mutated gene is sufficient to cause the disorder.

Transient hyperinsulinaemic hypoglycaemia means that the increased insulin production is only present for a short duration and is found in conditions such as:

- Intrauterine growth retardation
- Infants of diabetic mothers
- Infants with perinatal asphyxia

Transient hyperinsulinism can occur in infants with no predisposing factors such as those listed above. More research is needed to understand why transient hyperinsulinism occurs. Some syndromes also present in the newborn period with hyperinsulinaemic hypoglycaemia. In infants with Beckwith Weidemann syndrome, up to 50 per cent have been observed to develop hyperinsulinaemic hypoglycaemia. Other syndromes were CHI could be a feature include Turner Syndrome and Kabuki Syndrome.

Histology

Congenital hyperinsulinism (CHI) can present in two main forms: focal and diffuse. These subtypes have distinct characteristics in terms of pathology, genetic basis, and clinical management:

1. **Focal CHI**: Focal CHI is characterized by the presence of a discrete focal lesion or adenomatous hyperplasia within the pancreas. This focal lesion contains abnormal beta cells that continuously secrete insulin, leading to hypoglycemia.

2. **Diffuse CHI**: Diffuse CHI is characterized by diffuse hyperplasia of the pancreatic beta cells throughout the pancreas. There is no discrete focal lesion, and the abnormal beta cells are distributed diffusely within the pancreatic tissue.

In summary, focal and diffuse CHI are two distinct subtypes of the disorder with different pathological and clinical characteristics. Diagnosis and management strategies differ between the two subtypes, with surgical resection being the primary treatment for focal CHI and medical therapy being the mainstay for diffuse CHI.

What are the symptoms of CHI?

CHI manifests as hypoglycemia in neonates, Hypoglycemia, especially in neonates, can manifest differently compared to adults due to various physiological differences. Symptoms can range from subtle signs to more severe manifestations. Here are common symptoms of hypoglycemia in neonates:

1. **Jitteriness or Tremors**: Neonates experiencing hypoglycemia may exhibit jitteriness or tremors, which can be observed as fine, rapid movements of the extremities or the entire body.

2. **Irritability and High-Pitched Crying**: Hypoglycemic neonates may become irritable and have episodes of high-pitched crying, which may be difficult to console.

3. **Poor Feeding**: Neonates may show reluctance to feed, have decreased suckling ability, or feed less frequently than expected.

4. **Lethargy or Weakness**: Hypoglycemia can cause neonates to become lethargic, sleepy, or unusually weak. They may have decreased responsiveness to stimuli.

5. **Apnea or Respiratory Distress**: In severe cases, hypoglycemia can lead to episodes of apnea (temporary cessation of breathing) or respiratory distress, characterized by rapid or shallow breathing.

6. **Hypothermia or Temperature Instability**: Neonates with hypoglycemia may exhibit hypothermia (low body temperature) or temperature instability, with fluctuations between hypothermia and hyperthermia.

7. **Cyanosis or Pallor**: Cyanosis (bluish discoloration of the skin) or pallor (pale skin) may occur in hypoglycemic neonates, particularly around the lips, mouth, or extremities.

8. **Seizures**: Severe or prolonged hypoglycemia can lead to seizures in neonates, which may present as jerking movements, staring spells, or loss of consciousness.

9. **Hypotonia or Floppiness**: Neonates with hypoglycemia may exhibit hypotonia (decreased muscle tone) or floppiness, where they appear limp or floppy when held.

10. **Altered Level of Consciousness**: In severe cases, hypoglycemia can lead to altered levels of consciousness, including coma or unresponsiveness.

Immediate care

Once at the specialist centre, the initial task is to stabilise the child, usually with an intravenous drip of glucose. Sometimes a high carbohydrate feed is given as well. Intravenous glucose is often the quickest way of returning a child's blood glucose level to normal.

A central venous access device may be required to give a high concentration of glucose for the rapid correction of hypoglycaemic episodes and for obtaining crucial blood samples.

How is CHI diagnosed?

Diagnosing congenital hyperinsulinism (CHI) involves a comprehensive approach, including clinical evaluation, biochemical testing, genetic analysis, and sometimes imaging studies. Here's an overview of the diagnostic process for CHI:

Biochemical Testing:

- Blood tests are performed to measure glucose and insulin levels during episodes of hypoglycemia. The diagnosis of CHI is confirmed by demonstrating inappropriately elevated

insulin levels in the presence of low blood glucose (<55 mg/dL or <3.0 mmol/L). It is performed under monitoring and referred to as critical sampling.

- Additional tests may include measuring other hormones such as cortisol, growth hormone, and ketones to rule out other causes of hypoglycemia.

Genetic Analysis: - Genetic testing is essential for confirming the diagnosis of CHI and identifying the underlying genetic mutations responsible for the condition The most common genetic mutations associated with CHI are found in the ABCC8 and KCNJ11 genes, which encode subunits of the ATP-sensitive potassium channel (KATP channel) in pancreatic beta cells. Next-generation sequencing (NGS) techniques can be used to analyze multiple genes associated with CHI simultaneously.

Imaging Studies:

In cases of suspected focal CHI, 18F-DOPA PET/CT scan may be used to identify the focal lesion within the pancreas as it is a very small lesion requiring specialized investigation.

Once a diagnosis of CHI is confirmed, ongoing monitoring and management are necessary to prevent hypoglycemic episodes and minimize the risk of complications.

Medical management

This aims to keep a child's blood glucose level stable at 63 to 180 mg/dl. This can be managed by regular high carbohydrate feeds alongside medicines to reduce insulin secretion.

There are various drugs and each one will be tried in turn until the one that offers the best result is found. Drugs used to reduce insulin secretion include: diazoxide, chlorothiazide, nifedipine (this is rarely used as it is not as effective as the other medications), glucagon and octreotide.

Children with CHI often appear to have feeding problems, particularly affecting the movement of food through the digestive system and gastro-oesophageal reflux. This can be treated with medicines, however a naso-gastric tube can be inserted to deliver continuous feeds, although this is rarely needed.

Surgical treatment

This may be an option if medical management does not keep a child's blood glucose levels at an acceptable level. If a child has been diagnosed with focal CHI, usually following a PET scan, the area of the pancreas containing the defective beta cells can be removed in an operation under general anaesthetic.

What is the outlook for children with CHI?

Sometimes the management of CHI can be complicated. However, once CHI is stable, a degree of normal life can be achieved. Children and young people can have issues with brain development causing problems with memory and processing information so may need additional support in school and the workplace.

In children who have had some or the majority of their pancreas removed, there is a chance of developing insulin dependent diabetes. This is a condition where the remaining portion of the pancreas does not make enough insulin, so insulin has to be injected several times a day. Many children with this type of diabetes cope well with treatment and have a near normal childhood. Pancreatic insufficiency, where the pancreas cannot release the enzymes needed to break down fats, can also occur, but oral enzyme replacement therapy with meals is an option. With increased knowledge and research, the outcomes for these children are continually improving.

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