CONGENITAL HYPERINSULINISM

1. What is Congenital Hyperinsulinism (CHI)?

Congenital hyperinsulinism (CHI) is characterised by inappropriate and dysregulated insulin secretion from the beta-cells of the pancreas. The pancreas, which is responsible for insulin secretion, is blind to the blood glucose levels and produces insulin independently of the blood glucose concentrations, leading to hyperinsulinemic hypoglycaemia. For CHI, hypoglycaemia is defined as blood glucose concentrations less than 60 mg/dl.

2. How often is CHI and when is it diagnosed?

Congenital hyperinsulinism (CHI) is the most frequent cause of severe, persistent hypoglycaemia in newborns and children. In most countries it occurs in approximately 1/25,000 to 1/50,000 births. About 60% of babies with CHI develop hypoglycaemia during the first month of life. An additional 30% will be diagnosed later in the first year and the rest of them afterwards.

3. What is the role of insulin?

The main role of insulin is to regulate blood glucose levels. Normally, the pancreatic beta-cells release insulin in response to the level of glucose in the blood so it can be used and stored. Insulin converts the glucose into a form that can be used as energy substrate by the body. Excess glucose in converted into glycogen and stored in the muscles and the liver, so that it can be reconverted back to glucose in case glucose is not available. Moreover, insulin prevents the conversion of protein to glucose (gluconeogenesis), as well as the conversion of fat into ketones (fatty acid oxidation and ketogenesis), which are both protective reactions to hypoglycaemia.

When there is a high level of blood glucose (such as after a meal), the beta-cells release more insulin to allow the glucose to be absorbed from the blood. If there is a low level of glucose, the beta-cells release much smaller amount of insulin or even switch off insulin production

4. What are the symptoms of CHI?

As CHI is a congenital condition (meaning that the patient is born with it), symptoms begin within the first few days of life, although rarely symptoms may appear later in infancy. Symptoms of hypoglycaemia can include irritability, excessive hunger, lethargy, floppiness, shakiness, rapid heart rate, poor feeding and sleepiness. Seizures (fits or convulsions) may also occur because of the low blood glucose levels. If the child's blood glucose level is not corrected, it can lead to loss of consciousness and potential brain injury.

CONGENITAL HYPERINSULINISM

5. What is the cause of CHI?

CHI is caused by genetic mutations that result in disproportionate, inappropriate and excessive insulin secretion from the beta cells of the pancreas. A genetic basis can be identified in about 50 percent of cases, attributed to defects in at least 11 genes, ABCC8, KCNJ11, GLUD1, GCK, HK1, HNF1A, HNF4A, SLC16A1, UCP2, PGM1. The two first genes encode the SUR1 and the Kir6.2 subunits of the K_{ATP} channel that is an important structure on the surface of the beta cell that allows the secretion of insulin. They account for 45% and 5% of CHI cases with an identified genetic cause.

The mutations may be inherited in an

1. Autosomal recessive pattern

The disorder only becomes apparent when both copies of the gene are abnormal, that is when each parent carries one abnormal gene and the child inherits the abnormal copy from both parents. Couples who have had a child affected with a recessive disorder (or who are both known to be carriers of a recessive gene) have a 25 per cent chance that any future child will have the disorder and a 25 per cent chance that the child will inherit both normal copies of the gene.

There is a 50 per cent chance that the child will inherit a normal copy of the gene from one parent, and an abnormal copy of the gene from the other, which means they will be a carrier, just as his/her parents. These percentages applied to every conception, regardless of the outcomes of previous conceptions.

2. Autosomal dominant pattern

The disorder becomes apparent even if one abnormal copy of the gene is present. Only one parent must have the affected gene to pass it on to the child, who then has a 50 per cent chance of inheriting the gene and therefore the disorder. The same risk applies to each conception, regardless of the outcome of previous conceptions.

3. New mutation

None of the parents has an abnormal copy of the gene and the mutation occurred for the first time in the affected child.

The origin of the defective gene (maternal or paternal) may be of importance regarding the type of CHI

6. Are there different types of CHI?

The two main types of CHI are based on the extent of the histological pancreatic lesion, namely the diffuse and focal subtype. The diffuse type affects the whole pancreas, whereas the focal form is confined to a specific region of the pancreas. The remaining pancreas is anatomically and functionally normal. The management of diffuse and focal disease is different. Focal disease can now be cured if the lesions are located accurately and removed completely. However, diffuse disease will require removal of almost the entire pancreas, if it does not respond to medical management.

CONGENITAL HYPERINSULINISM

7. How is CHI diagnosed?

When CHI is suspected, due to the occurrence of hypoglycaemic episodes, the diagnosis may be confirmed through detailed blood and urine tests drawn while a child's blood glucose level is low. If the blood glucose levels do not fall sufficiently low during the initial diagnostic period, a fasting test is performed to provoke a hypoglycaemic episode. Blood tests drawn when plasma sugar is less than 50 mg/dL are essential for the diagnosis of CHI. In congenital HI, with a plasma sugar < 50, you will see suppressed ketones and free fatty acids, an elevated (or inappropriately normal) insulin level, and a glycaemic response to glucagon, with the plasma sugar rising more than 30 mg/dL when glucagon is administered. Once CHI is confirmed, treatment with medications that stop insulin production is commenced. While we assess the response to medical treatment, blood samples are sent for genetic analysis. The results of the genetic analysis help in determining whether your child will need an 18-F-DOPA scan, that will differentiate focal from diffuse disease. A PET scan gives very detailed, three-dimensional images of the body. It works by injecting an isotope. The isotope used is called 18-F-DOPA. PET scanning is a relatively new technology that allows the imaging of otherwise undetectable tiny focal lesions.

8. How is CHI treated?

Medications used to treat CHI include diazoxide, octreotide, and glucagon.

Diazoxide is given by mouth 2-3 times per day. The dose varies from 5 to 20mg/kg/day. Usually, if 15 mg/kg/day does not work, higher doses will not work. Diazoxide acts on the K_{ATP} channel to prevent insulin secretion. This may explain why this medicine is not effective in cases with K_{ATP} channel mutations. Side effects of diazoxide include fluid retention and excessive hair growth of the eyebrows, forehead, and back (referred to as hypertrichosis). A diuretic such as hydrochlorothiazide is often used to prevent oedemas from fluid retention.

Octreotide is a drug that also inhibits insulin secretion. It is administered by injection. Long-acting analogues are commercially available so as to prolong the time between injections. Octreotide is often very effective initially, but its initial effectiveness may wane with time and it can become less effective. In addition, more is not always better as the higher the dose (higher than 20-40 micrograms/kg/day) the less effective it may become. Side effects include alteration of gut motility, which may cause poor feeding. It may also cause gallstones and very rarely may produce hypothyroidism, and short stature. As with any injection, risks of pain, infection, and bruising exist. Additionally, octreotide is not currently recommended in neonates already at risk for NEC (necrotizing enterocolitis).

Glucagon stimulates release of glucose from the liver. It is given through a vein or by injection under the skin or into the muscle. Glucagon can be used in cases of emergency or in the hospital as a continuous intravenous infusion.

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 medications, however sometimes a nasogastric (NG) tube is inserted to deliver and ensure continuous feeding. If a tube feeding is required long term, a gastrostomy is often needed. Even in the presence of a naso-gastric tube or gastrostomy, oral feeding is essential to keep the mouth stimulated reducing the chance of long-term feeding problems.

CONGENITAL HYPERINSULINISM

Surgical treatment may be an option if medical management is not effective in preventing hypoglycaemias. 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 anaesthesia. Surgery for focal lesions offers a cure in 96.9 % of cases. Surgery to remove all or most of the pancreas is only an option for diffuse disease if medical management fails, but has a greater risk of long-term effects, such as insulin-dependent diabetes or pancreatic insufficiency (insufficiency of enzymes produced by the pancreas that help nutrient absorption). Occasionally, hypoglycaemia may still occur after surgery for diffuse disease, but it is usually in a milder form which is then more responsive to medical management, allowing the child to be managed at home.

Although the genetic forms of CHI persist through life, some may become easier to treat as the child grows up. Spontaneous resolution of CHI after a period of treatment has also been reported in patients with well-defined genetic mutations. In particular, some patients with mutations of ABCC8/KCNJ11 genes and many with HNF4A mutations have spontaneous resolution of clinical disease over time. The causes of the spontaneous remission of hyperinsulinemia in these patients remains to be determined but maybe influenced by other genetic factors that have not yet been identified.

9. What are the consequences of uncontrolled CHI?

CHI causes a particularly damaging form of hypoglycaemia because the brain cannot use all the fuels on which it is critically dependent. These fuels are glucose, ketones, and lactate. The lack of appropriate fuel for the brain may result in seizures and coma and if prolonged may result in brain damage. For all children, the development of learning disabilities is difficult to predict and depends not only on the frequency of low blood glucose but also on the duration of a hypoglycaemic episode. In addition to learning disabilities, other neurological problems sometimes occur such as poor motor coordination, cognitive delays, seizures or cerebral palsy. Strabismus (turned in eye), nystagmus (involuntary motions of the eye), or blindness may also be caused by hypoglycaemia.

Nevertheless, with early treatment and aggressive prevention of hypoglycaemia, brain damage can be prevented. However, brain damage can occur in children with CHI if their condition is not diagnosed or if treatment is ineffective.