Introduction

This leaflet aims to provide parents and carers information on the causes, diagnosis and management of congenital hyperinsulinism in babies and children.

What is Congenital Hyperinsulinism (CHI)?

Congenital hyperinsulinism (CHI) is the inappropriate secretion of high levels of insulin from the pancreas. This leads to persistently low blood glucose levels in the body. CHI is the most frequent cause of severe and persistent hypoglycaemia (low blood glucose) in new born babies and children.

How does insulin work?

Insulin is a hormone, which controls the level of glucose (sugar) in the blood. Insulin is released by specialised cells in the pancreas. When food is eaten blood glucose levels rise and the pancreas releases insulin to keep the blood glucose in the normal range.

Insulin acts by driving glucose into the cells of the body. This has two effects:

- Maintaining blood glucose levels
- Storing glucose as glycogen in the liver

During fasting (for example when asleep) insulin secretion is turned off. This allows stores of glycogen to be released into the bloodstream to keep blood glucose level normal. When insulin secretion is switched off, protein and fat stores can be used instead of glucose as sources of fuel. In this way blood glucose levels remain in the normal range and the body has access to energy at all times.
What goes wrong in CHI?

In CHI, the close regulation of blood glucose and insulin secretion is lost. The pancreas continues to release insulin despite the low blood glucose level. As a result, a baby or child with CHI develops severe hypoglycaemia and needs large amounts of glucose to maintain normal blood glucose levels.

Why is it important to maintain normal blood glucose?

Babies with CHI rely on a normal circulating blood glucose concentration for normal neurological function. A blood glucose level less than 3.5mmol/l is considered as hypoglycaemia in babies and children with CHI. This is why it is important to maintain blood glucose level above 3.5mmol/litre.

Insulin also suppresses the release of alternative fuels like ketones (chemicals produced by the body from the fat for energy), and so the brain is deprived of both glucose and ketones. If brain cells are deprived of these fuels, they cannot make the energy they need to work and this may result in seizures and coma. The cell damage can manifest (as a permanent seizure disorder, learning disabilities, cerebral palsy and blindness).

How common is CHI?

Hypoglycaemia due to CHI is relatively rare but potentially a serious condition occurring soon after birth. The estimated incidence of CHI is 1 in every 40,000 - 50,000 children although it is likely that the incidence is higher (no need for reference).

What causes CHI?

There are different forms of CHI. Some forms are considered transient (temporary). Others arise from genetic defects and persist for life. In some of those cases, CHI may become easier to treat as the child gets much older.

Genetics of CHI

At present, there are nine known genetic causes of CHI. The defects in the genes (basic unit of heredity that gives instructions to all parts of the body) can lead to abnormalities in the insulin secretion from the pancreas, thereby causing CHI. The two most common gene defects associated with CHI are abnormalities in ABCC8 and KCNJ11. Genetic testing will be needed in babies who have persistent and severe CHI and who do not respond to first line medical therapy. Your doctor will explain this more depending on the course of the illness.

Transient CHI

Transient CHI means that the increased insulin production is only present for a short period of time. It is found in conditions such as:

- Intrauterine growth retardation (babies born with low birth weight)
- Prematurity (babies born earlier than their due date)
- Infants of diabetic mother
- Infants with perinatal asphyxia (babies deprived of oxygen at the time of birth)
Transient hyperinsulinism can occur in infants with no predisposing risk factors, the reasons causing this is currently unclear. Some of the transient forms of CHI will need treatment with medications for a few weeks to a few months.

Generally infants and children will be able to come off treatment at a later date. They will be assessed with a fasting study when all their medications are stopped to prove that the CHI has completely resolved.

**Types of persistent CHI**

In children with persistent CHI, two main histological (seen under a microscope) forms are noted: focal and diffuse. Children with either form are identical in their presentation and behaviour. They tend to have significant hypoglycaemia within the first few days of life and require large amounts of glucose to keep their blood glucose normal. They may have seizures due to hypoglycaemia.

**Focal CHI:** A focal (occurring in one particular site) area of the pancreas is affected. Focal lesions are small, measuring 2-10mm.

**Diffuse CHI:** Diffuse CHI affects the whole of the pancreas.
What are the symptoms of CHI?

Infants with CHI usually show symptoms within the first few days of life, although symptoms may appear later in infancy. Symptoms of hypoglycaemia can include:

- floppiness,
- shakiness,
- poor feeding
- sleepiness,

all of which are due to low blood glucose levels.

Seizures (fits or convulsions) can also occur due to hypoglycaemia.

If CHI is not diagnosed and treated early, a child could develop brain damage. Ideally, children with suspected CHI should be transferred to a specialist centre. Alder Hey Children’s Hospital is one of the three specialist centres in the UK. These specialist centres have the expertise to carry out the detailed or repeated blood glucose monitoring needed to provide the appropriate treatment.

How is CHI diagnosed?

Once at the specialist centre, the initial task is to stabilise the child.

This involves an intravenous drip (IV) of glucose and sometimes an infusion of glucagon. A central venous access device (central line) may be required to:

- administer high concentration of glucose,
- obtaining crucial blood samples and
- rapid correction of hypoglycaemic episodes.

A central venous catheter (small thin tube) is inserted into a large vein during a short operation under general anaesthetic.

Once a child is stable, the team will confirm or rule out a diagnosis of CHI. This is usually done through detailed blood and urine tests taken while a child’s blood glucose level is low. If their blood glucose level does not fall sufficiently low during the initial period, they may have a ‘diagnostic fast’.

As part of the fast, all feeds and fluids are gradually reduced and then stopped for a period of time until the child becomes hypoglycaemic (glucose level of 3.0mmol/l or less for a very short period of time). Once the fast has been completed, glucose is given into a vein to correct the blood glucose level.

In children with persistent CHI, genetic tests and a special scan (DOPA – PET scan) will be required. These tests are to help us tell the difference between focal CHI from diffuse CHI.
How is CHI treated?

The aim is to keep the child’s blood glucose level stable (3.5 – 10mmol/litre). Initially a child is managed with high concentration of intravenous glucose containing fluids (infusion of glucose containing liquid substances directly into a vein). Sometimes, glucagon infusion (a medicine is used to release stored glucose in the body) may be needed.

The child is then established on feeds and started on the first line medications (diazoxide and chlorothiazide). Before starting on diazoxide a child will have heart scan (echo) to rule out any underlying heart defect.

Diazoxide is an oral medication (given three times a day) that aims to suppress the insulin secretion. The side effects include fluid retention and so it is always used with chlorothiazide (a diuretic) twice a day. In the long run, diazoxide can lead to excessive hair growth. This hair growth resolves several months after diazoxide therapy is stopped.

Once a child responds to diazoxide, they will be gradually weaned off their intravenous fluids and glucagon infusion.

Once the blood glucose is stable and the child is off all intravenous infusions they will have a fasting test. This is to ensure that the glucose control is optimal before discharge from hospital. The central line is usually removed in the ward or in the theatre before discharge.

What if babies do not respond to diazoxide?

In children, who do not respond to the first line medication, further investigations (genetic tests and or DOPA PET scan) will be needed to identify diffuse versus focal disease. In patients with diffuse disease, octreotide (which is given as six hourly injections) can be tried.

Diffuse patients who do not respond to medical therapy will need surgery to remove the majority of their pancreas. Children with focal CHI will undergo surgical removal of the focal lesion.

What is the prognosis for children with CHI?

Prognosis is greatly influenced by the form (severity) of CHI. The most severe long term complication is neurological impairment. Brain function in CHI can be normal if hypoglycaemia has been diagnosed and treated quickly. However it can be very variable depending on the amount of damage caused before diagnosis and treatment. With increased knowledge and research, the outcomes for these children are continually improving.

What happens after discharge from hospital?

It is important to monitor blood glucose regularly at home. Our nurse specialist will provide training to parents and carers on checking blood glucose levels. Telephone contact and support will be available. A detailed plan will be provided so parents can deal with any hypoglycaemic episode at home.
Children will be followed up in our outpatient clinic on a regular basis. Children who are on small doses of diazoxide will be admitted to hospital at a later stage to trial coming off diazoxide. The children with transient CHI are usually able to come off treatment after several weeks or months.

**Who to contact for further information**

**Endocrine Nurse Specialist**

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**Consultant Endocrinologists**

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The Congenital Hyperinsulinism Service at Alder Hey is one of three nationally commissioned sites for CHI in the UK. The other sites are Royal Manchester Children's Hospital and Great Ormond Street Hospital.

**Where can I get more information on CHI?**

Congenital Hyperinsulinism International: [http://congenitalhi.org/congenital-hyperinsulinism/](http://congenitalhi.org/congenital-hyperinsulinism/)

This leaflet only gives general information. You must always discuss the individual treatment of your child with the appropriate member of staff. Do not rely on this leaflet alone for information about your child's treatment. This information can be made available in other languages and formats if requested.

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