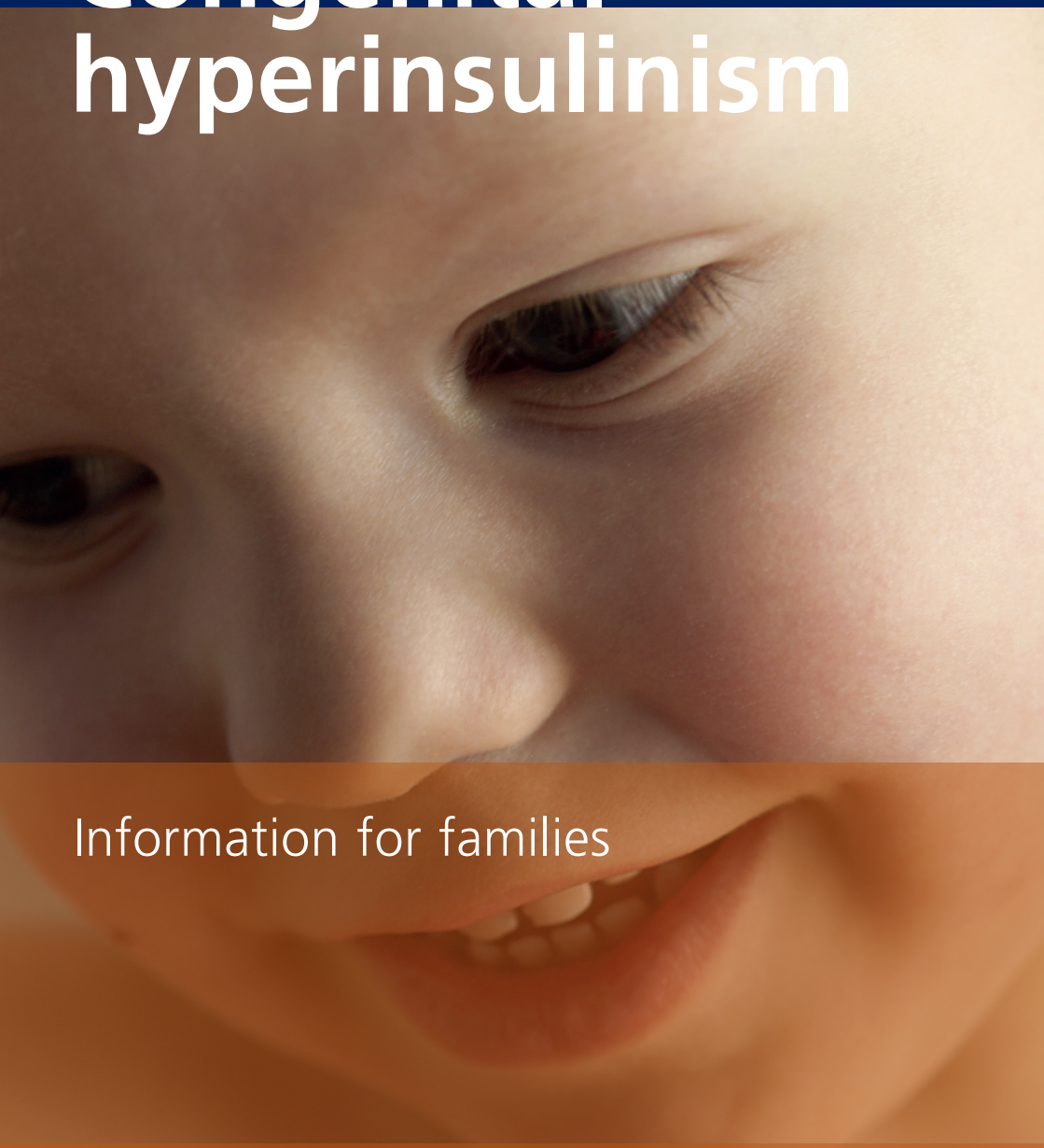
Congenital hyperinsulinism



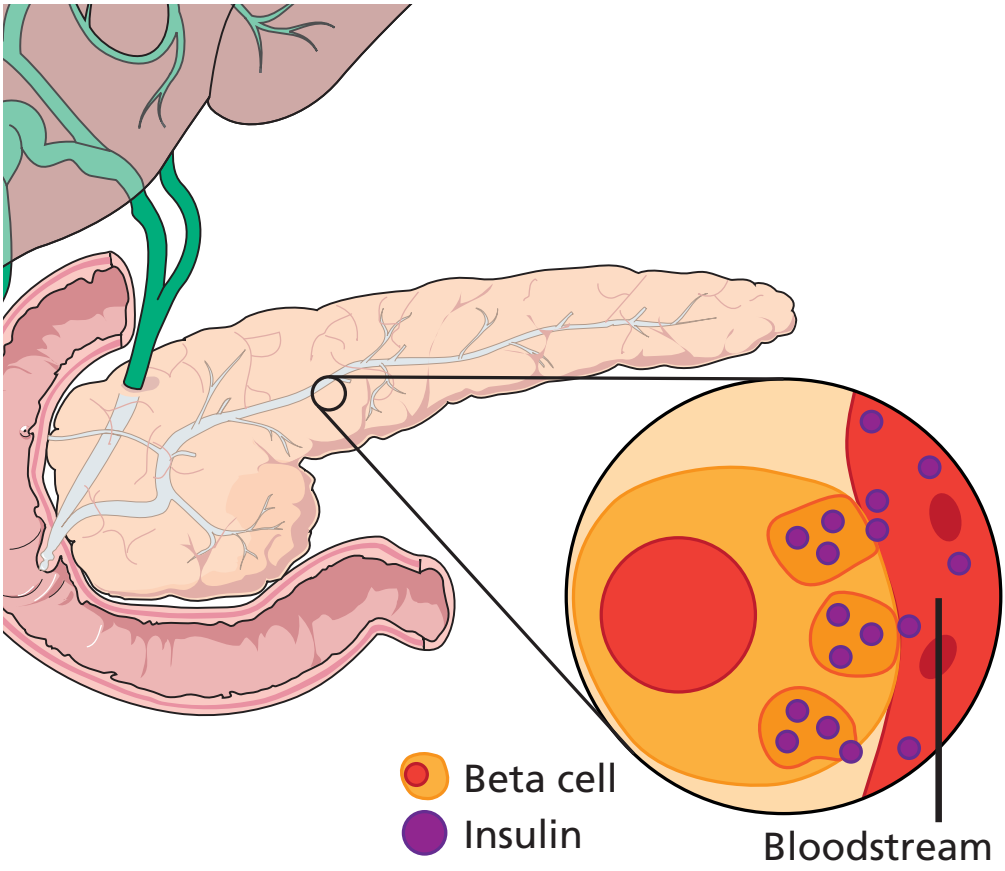
Information for families

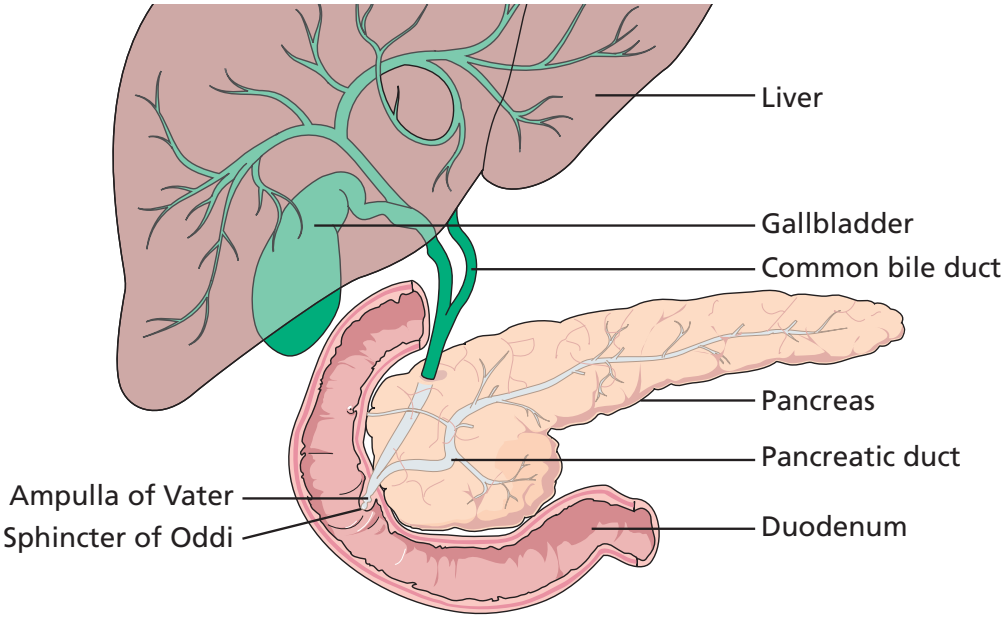
Great Ormond Street Hospital for Children NHS Foundation Trust

This information sheet explains about congenital hyperinsulinism (CHI), which is present at birth and results in high levels of insulin being produced, which in turn can affect all areas of the body.

It explains:

- **What causes CHI**
- **How it can be managed**





What is insulin?

Insulin is a hormone (chemical messenger), which, along with other hormones, controls the level of glucose (sugar) in the blood. Insulin is released by specialised beta-cells spread throughout the pancreas.

Normally, the beta-cells release insulin in response to the level of glucose in the blood. Insulin converts the glucose into a form that can be used by the body. If too much glucose is converted, it is stored in the liver and muscles as glycogen.

Glycogen can be converted back to glucose to be used when glucose is not available.

When there is a high level of blood glucose, 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. This keeps the blood glucose level balanced and at the right level for the rest of the

body to function normally. As well as controlling insulin release, the pancreas also secretes digestive juices called pancreatic enzymes into the first part of the small intestine (duodenum).

What is congenital hyperinsulinism (CHI)?

Congenital hyperinsulinism is characterized by inappropriate and unregulated insulin secretion from the beta-cells of the pancreas. In CHI the beta-cells release insulin inappropriately all the time and insulin secretion is not regulated by the blood glucose level (as occurs normally). The action of insulin causes hyperinsulinaemic hypoglycaemia. High insulin levels prevent ketone bodies being made. This means that the brain is not only deprived of its most important fuel (glucose), but also ketone bodies which are used as alternative fuels.

What is a normal blood glucose level in CHI?

For the purpose of CHI, hypoglycaemia is agreed to be less than 3.5mmol/litre. 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 3.5mmol/litre.

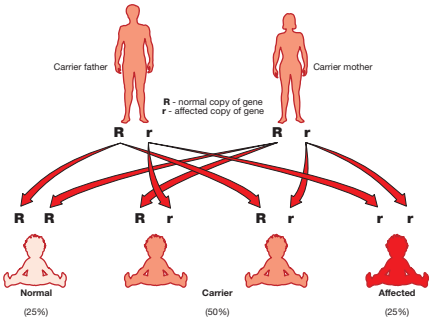
How common is CHI and whom does it affect?

Hypoglycaemia, due to CHI, is a relatively rare but potentially serious condition occurring soon after birth. The estimated incidence of CHI is one in every 40,000 to 50,000. It is much more common in communities where marriage between blood relatives occurs, possibly as frequently as one in every 2500 children.

Genetics of CHI

At present, there are seven known genetic causes of CHI, which can be inherited in an autosomal recessive or dominant manner (see below). Abnormalities in the genes *ABCC8* and *KCNJ11* are the most common cause of severe CHI. Other rare causes are due to abnormalities in genes involved in regulating insulin secretion from the pancreas beta cells.

Autosomal recessive inheritance

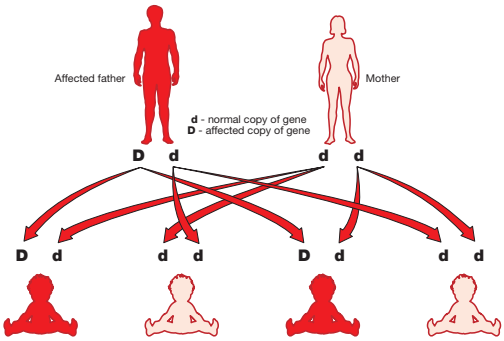


Autosomal recessive inheritance occurs when each parent carries one abnormal gene. The disorder only becomes apparent when both copies of the gene are abnormal. In order for an individual to have two abnormal copies of a gene, an abnormal copy of the gene must be inherited from both parents. (See diagram above.)

Even though both parents are carrying one abnormal gene they are usually healthy. 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. These percentages applied to every conception, regardless of the outcomes of previous conceptions.

Autosomal dominant inheritance

Autosomal dominant inheritance occurs when the abnormal gene that is inherited overrides the normal gene in the pair. Males and females pass on this type of disorder equally. Only one parent has to 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.

CHI sometimes appears in an individual whose parents do not have the disorder. This occurs when a new **mutation** has arisen in a gene. In other words, the alteration occurred for the first time in the sperm or egg that resulted in the conception of the child, rather than being inherited from one of the parents. This happens sporadically, that is, at random.

Secondary causes of hyperinsulinism

Secondary causes of hyperinsulinism can be subdivided into several categories. These categories can often be distinguished by the length of treatment required and the infant's response to medical management. Transient hyperinsulinaemic hypoglycaemia means that the increased insulin production is only present for a short duration and is found in conditions such as:

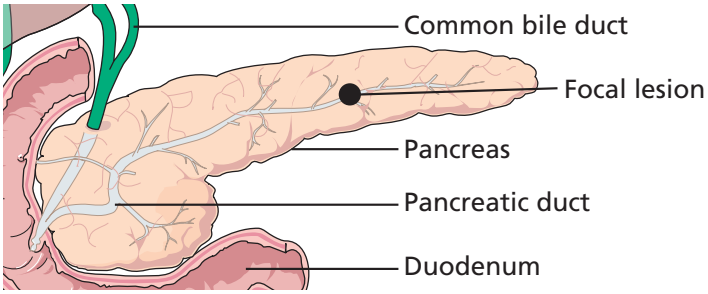
- Intrauterine growth retardation
- Infants of diabetic mothers
- Infants with perinatal asphyxia

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 Weidermann syndrome, an overgrowth syndrome, up to 50 per cent have been observed to develop hyperinsulinaemic hypoglycaemia.

Histology

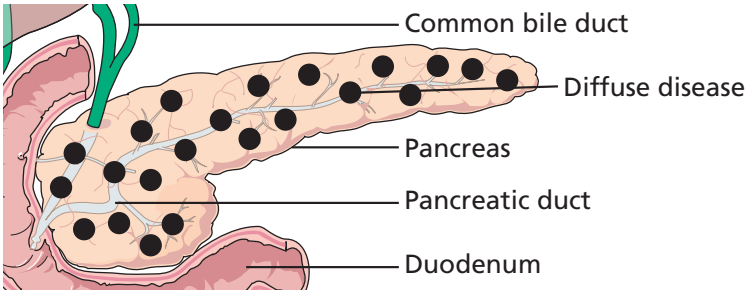
The two main histological forms of persistent CHI are focal and diffuse.

Focal CHI



In focal CHI, a specific area of the pancreas is affected. Focal lesions are usually small, measuring 2mm to 10mm across. Beta-cells in the focal lesion have enlarged nuclei (centre of the cell) surrounded by normal tissue. Around 40 to 50 per cent of infants with persistent CHI will have the focal form.

Diffuse CHI



Diffuse CHI affects the entire pancreas. It can be inherited in a recessive or dominant manner or can occur sporadically.

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.

What are the symptoms of CHI?

As CHI is a congenital condition, a child usually starts to show symptoms within the first few days of life, although very occasionally symptoms may appear later in infancy. Symptoms of hypoglycaemia can include floppiness, shakiness, poor feeding and sleepiness, all of which are due to the low blood glucose levels. Seizures (fits or convulsions) can also occur, again due to 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.

Ideally, children with suspected CHI should be transferred to a specialist centre. Great Ormond Street Hospital (GOSH)and Manchester Children's Hospital are the two centres in the UK that have the expertise to carry out the detailed repeated blood glucose monitoring needed to deliver treatment. During the transfer to the specialist centre, children are monitored closely and regularly to keep the blood glucose level as near normal as possible. If the level drops, the nurse and/or doctor in charge will be able to give glucose, either as a drip or an injection.

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, usually given through a naso-gastric (NG) tube. This tube goes through the nose, down the throat into the stomach. 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. A central venous catheter is often inserted into a vein near the heart during a short operation under general anaesthetic.As central venous catheters offer a direct route into the bloodstream, they need to

be looked after very carefully, but nurses on the ward will teach you all you need to know.

How is CHI diagnosed?

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', that is, all fluids will be gradually reduced for a period of time until the they become hypoglycaemic (3.0mmols/l or less for a very short period of time only). Once the diagnosis has been reached (or the fast has been completed), glucose is given into a vein (intravenously through a drip or central venous device) and/or feed commenced to correct the blood glucose level back to normal.

Once CHI is confirmed, treatment with medicines to stop insulin production is commenced. While we assess the response to medical treatment, we also send blood samples for genetic analysis. The results of the genetic analysis helps in determining whether your child will need an 18-F-DOPA scan.

18-F-dopa Positron Emission Tomography (PET)

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 so you may hear the scan referred to by this name. PET scanning is a relatively new technology. The focal lesion is very tiny and cannot be seen by other X-ray techniques. With this scan, the doctors are trying to identify the area of the pancreas from which excessive insulin is being produced. The treatment recommended by the doctors depends on the results of the scan.

Medical management

This aims to keep a child's blood glucose level stable at 3.5mmol/litre to 10mmol/litre. 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. Information leaflets regarding all these medications will be given to you by the nursing staff or are available from the Pharmacy, Pals Office or our website.

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 sometimes a naso-gastric tube is inserted to deliver continuous feeds. If tube feeding is required long term, a gastrostomy is often needed. Again, the ward nurses will explain this to you in more detail and give you written information.

Even if your child has a naso-gastric tube or gastrostomy, we encourage you to continue to give food orally (by mouth) as this is essential to keep the mouth stimulated reducing the chance of long-term feeding problems.

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. Surgery for focal lesions now often offers a cure to CHI. 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 diabetes or pancreatic insufficiency. Occasionally hypoglycaemia can still happen 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.

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. Brain function in CHI can be normal if hypoglycaemia has been diagnosed and treated quickly, but can be very variable depending on the amount of damage caused before diagnosis and treatment.

When babies and young children are fed through an NG tube, there is a chance that they will 'forget' how to feed so it is important to continue feeding small amounts by mouth in addition to NG feeds. Assessment and support from speech and language specialists can help a child to regain the desire to eat and drink by mouth.

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 food into nutrients, 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.

Ongoing care

Before you return home, the team will always ensure that a manageable regimen of care is established for your child. We will teach you about blood glucose monitoring and giving medications. A plan for what to do if your child develops hypoglycaemia will also be explained. Your child will have regular follow up at your specialist centre, but your local healthcare providers will also be involved. Telephone contact and support is always available.

Further information and support

The Congenital Hyperinsulinism Service at GOSH is one of two National Commissioning Group sites for CHI in the UK. The other site shared between Manchester Children's Hospital and Alder Hey Hospital in Liverpool. By providing services on a national basis, the service is able to develop expertise in rare conditions, improve learning and deliver a safer service. The CHI service was commissioned in 2006.

Rainforest Ward: 020 7829 8824

Clinical Nurse Specialists – CHI: 020 7405 9200 ext 0360/bleep 1016

Clinician's Assistant: 020 7813 8296 or bleep 0896

Out of hours: 020 7405 9200 and ask for the on call doctor for endocrinology

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Compiled by the Endocrinology Department
in collaboration with the Child and Family Information Group.

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www.gosh.nhs.uk