Congenital Hyperinsulinism Patient Information Booklet

This booklet is aimed to provide you with both some basic and more detailed information on Congenital Hyperinsulinism (CHI). We hope that by reading this, we will help you understand how this very complex condition occurs, how we diagnose it and what the treatment involves. It will in no way answer all your questions about CHI, so please feel free to ask any member of our Northern Congenital Hyperinsulinism Service (NORCHI) team any questions you might have about CHI, even after you have read it.

Why is my child here? What is NORCHI?

CHI is a rare condition that can have very profound effects on the development of your child. For this reason, the National Commissioning Group (NCG) commissioned two specialist centres in England to treat this condition (Great Ormond Street Hospital and NORCHI). NORCHI is a joint service based between two of the largest specialist children’s hospitals in the North of England, i.e. the Royal Manchester Children's Hospital and the Royal Liverpool Children's Hospital. For this reason, you and your child have been referred to us, to provide your child with the most up to date diagnostic facilities and initiate the best treatment currently available.

What is CHI?

Congenital hyperinsulinism (CHI) is a disorder that causes dangerously low blood sugars in newborn babies and children. This is caused by the uncontrolled release of a hormone in the body called insulin. Insulin is produced by beta-cells located in an organ called the pancreas. It is however very important to note that although CHI involves insulin, it is not the same condition as diabetes.
Since being first recognised in the mid 1930s, CHI has been given many different names. Terms such as nesidioblastosis, idiopathic hypoglycaemia of infancy, leucine-sensitive hypoglycaemia and persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) have all been used to describe this condition in the past.

Worldwide figures suggest that CHI occurs in approximately 1 in 25,000 to 50,000 of children born, with higher rates among specific ethnic populations. This makes CHI a very rare condition. Of those with CHI, more than half are diagnosed in the newborn period, with the remainder diagnosed in the first three years of life.

**Why is diagnosing CHI important?**

Severe low blood sugars can cause many problems. Most commonly, they cause tiredness and reduced feeding. More importantly, are the effects of low blood sugars on the brain. Sugar is a form of fuel for the brain. In normal children, when low blood sugars occur, the body is able to break down fats to form a different type of brain fuel called ketones. This unfortunately cannot happen in CHI, so the brain is starved when low blood sugars occur. This can cause fits and brain damage and if left untreated, lead to coma and even death. Diagnosing CHI is therefore very important so that low blood sugars can be treated effectively and their effects can be avoided.

**How do low blood sugars in CHI occur?**

The hormones, insulin and glucagon, are the most important hormones involved in the control of blood sugars. They are both secreted by an organ in the body called the pancreas. Normally, blood sugars are carefully controlled between 3.3mmol/L and 5mmol/L (60 and 90mg/dl) by the actions of these hormones. For this reason, in patients with CHI, we always try to maintain blood sugars above 3.5mmol/L.

Insulin is secreted when blood sugars rise when food is eaten and it is broken down into sugar. It reduces blood sugar levels by driving sugar (glucose) into cells in the body and storing excess glucose in the liver as glycogen.

When blood sugar levels begin to fall, insulin production is turned off. When insulin has stopped being produced, the body is able to use the hormone glucagon to break down glycogen stores to maintain blood sugar levels in the normal range.

In CHI, the control of insulin secretion in relation to blood sugar levels is lost. This means that insulin production is not turned off even if blood sugar levels are low. This is made worse when the child is fasted.

**What types of CHI exist?**

Some forms of CHI resolve very soon after diagnosis (a few days to several weeks). This is called transient congenital hyperinsulinism. In most cases, this form of hyperinsulinism will never recur in later life to cause problems with low blood sugars.

Transient CHI can be caused by certain effects of a pregnancy on the baby. These include:
- Maternal diabetes
- Babies born small for gestational age (intrauterine growth retardation)
• Maternal pre-eclampsia
• Poor condition at birth with lack of oxygen to the brain (perinatal asphyxia)
• Maternal medications such as diabetes and high blood pressure treatments which include beta blockers and sulphonylureas

Some forms of CHI are life-long and these are called persistent congenital hyperinsulinism. Persistent CHI is most commonly caused by defects in the building blocks that determine how our cells function, called genes.

Persistent CHI can also be linked with particular groups of signs and symptoms called syndromes. The most common association is with certain overgrowth syndromes such as Beckwith-Wiedemann syndrome.

Persistent CHI can be further divided according to where the abnormal beta-cells are located in the pancreas. When all the beta-cells throughout the pancreas are abnormal, this is called diffuse disease. However, in some cases, only a small isolated collection of beta cells are abnormal and this is called focal disease. Even though focal disease does not involve the whole pancreas, nevertheless, this form of CHI can be as severe as diffuse disease. The picture below shows both forms of the disease.

Diffuse disease              Focal disease

How is insulin produced?

Beta-cells in the pancreas are the insulin producing cells in the body. In a normal beta-cell, glucose enters the cell (1) and is processed into energy units called ATP (2).

To function properly, all cells have an electric charge. This is controlled by ‘gate-like’ channels in the lining of the cell. Some of these channels are affected by ATP and are called ATP-sensitive potassium channels ($K_{ATP}$ channels).

When glucose is processed, ATP levels rise within the cell, causing $K_{ATP}$ channels to close (3). This causes calcium to enter the cell through a separate set of channels (4) and triggers insulin containing granules to release insulin into the blood stream (5).
To make all these reactions work, several proteins or enzymes are also involved in this complicated process too – have a look at the picture below.

**How is insulin produced?**

1. Glucose enters the beta-cell.
2. Glucose metabolism increases energy rich ATP.
3. ATP sensitive channel closes.
4. Calcium enters cell.
5. Insulin is released.

Important enzymes (Glucokinase, SCHAD, GDH) involved in glucose processing are labelled in blue.

**What causes persistent CHI?**

More than 60% of cases of persistent CHI are caused by genetic mutations that cause abnormal formation or function of the $K_{ATP}$ channels. This causes the ‘gate-like’ $K_{ATP}$ channels, to remain closed, so that the beta-cells secrete insulin even when blood sugars remain low. The $K_{ATP}$ channels are controlled by two genes. These are the ‘sulphonylurea receptor gene’ (SUR1 now known as ABCC8) and the ‘inward-rectifying potassium channel’ gene (KiR6.2 now known as KCNJ11). Changes or defects in either of these genes can cause CHI or more specifically $K_{ATP}$-HI.

Another 10-15% of CHI is caused by inherited problems in one of the 3 main enzymes involved in glucose metabolism. Problems with the glutamate dehydrogenase (GDH) enzyme cause a form of CHI, in which patients tend to drop their blood sugars after meals that are high in protein. It is therefore associated with raised levels of a by-product of protein metabolism in the blood called ammonia. This is called GDH-HI.

The glucokinase enzyme works as the ‘glucose-sensor’ of the beta-cell. Abnormalities in this enzyme causes beta-cells only turn off insulin secretion at much higher levels of glucose from normal. This is called GK-HI.

Other very rare forms of CHI such as exercise-induced HI also exist but these only tend to present later in life. The remaining persistent cases may be due to causes that have still not been identified.

**How do we inherit CHI?**

All of us have two copies of every gene in our body. We inherit one copy of each gene from each of our parents. Some genetically inherited diseases only require one copy of the gene from either parent to be abnormal to cause the disease (dominant inheritance).
Dominant Inheritance

In dominantly inherited conditions, each child has a 50% (1 in 2) risk of inheriting the disease, because one abnormal gene is enough to cause it. The affected gene is coloured in red.

Father - affected       Mother

Child - affected       Child - unaffected

Some conditions require both copies of the gene to be abnormal (recessive inheritance) before it causes a problem. In these cases, if a person has only one faulty gene, they become carriers of the gene, but do not have the condition itself.

Recessive Inheritance

In recessively inherited conditions, a child has a 50% risk of becoming a carrier of the condition (one abnormal gene) or a 25% (1 in 4) risk of being completely normal or inheriting the disease (2 abnormal genes).

Father - carrier       Mother - carrier

Child - affected       Child - carrier

Most cases of CHI due to $K_{ATP}$ channel defects are recessively inherited (require two abnormal copies of the gene).

$K_{ATP}$-HI can cause diffuse or focal disease. This is dependent on whether the mutation is inherited from a particular parent. When a mutation is confirmed in a child’s mother, diffuse disease occurs. However, mutations
inherited from the father alone may cause focal disease, if the normal copy of the mother’s gene is not working properly (inactivated) in the pancreas.

Genetic mutations in the glucokinase and GDH enzymes cause CHI which is dominantly inherited and diffuse in nature.

**How is CHI diagnosed?**

CHI is usually diagnosed by detectable insulin levels, in the presence of low blood sugars (hypoglycaemia). For this to occur, a blood sample for insulin has to be taken when a child is experiencing a low blood sugar level. This, however, is only the first step toward a more detailed diagnosis of the condition.

As mentioned earlier, most cases of persistent CHI are caused by genetic mutations. Therefore, should your child continue to have problems with low blood sugars, we will take a further sample for DNA analysis to look for faulty genes. This is sent to the genetics laboratory in Exeter. Results usually take several weeks to come back, as this is a complicated test that requires some time to perform.

When the genetic results return, this may give us an idea if your child may have diffuse or focal CHI.

By this time, we will also know if your child is clinically responding to oral medication effectively. If your child is failing to respond to medication and the genetic result is inconclusive or indicative of a focal lesion, we will then plan to carry out a special scan on your child. This scan is called a Positron Emission Tomography (PET) scan, and at this moment in time, this scan has to be undertaken in Germany. Should your child require this, we will provide you with more specific information regarding this procedure then.

**What treatment is available for persistent CHI?**

CHI is usually treated in a stepwise manner. Transient CHI often resolves with a drip (intravenous infusion) of concentrated sugar, until the child is able to feed normally.

We do encourage breast feeding, however, because CHI children require more sugar than is available in breast milk, we would encourage you to express any breast milk you might have and combine that with formula milk, so your child can get the best of both.

A high carbohydrate supplement is sometimes added to the milk, and this is called **Polycal**. It comes in the form of a powder and is measured using a scoop. This is simply mixed into normal milk feeds.

If these mixed feeds are not adequate enough to maintain blood sugar levels, oral medication will then be started. Often before we commence this, we will ask for a heart scan (echocardiogram) to be done to ensure that your child’s heart is in good working condition. The two oral medicines usually used are called diazoxide and chlorothiazide.

**Diazoxide** is usually given three times a day. It is known to cause water retention, which is why we start it at smaller doses and build it up. When used long term, it can also cause increased hairiness, but resolves once medication is stopped.

**Chlorthiazide** is usually given twice a day. It helps prevent water retention and works together with Diazoxide to maintain blood sugars. It can
cause salt loss, so if these medications are started, we will need to check your child’s blood salt levels regularly.

Most children respond to oral medication. However, if your child still has problems maintaining blood sugar levels, the next step is to start an injectable medicine called Octreotide. Octreotide works to stop beta-cells from producing insulin. It can cause several side effects such as nausea and vomiting and accumulation of bile in the gall bladder. When used very long term, it can also affect overall growth. We will therefore be monitoring your child for these effects by plotting his/her growth regularly and performing 3-6 monthly gall bladder ultrasound scans, if this medication is started.

**What other problems are associated with CHI?**

Many children with CHI have very poor access to their veins. This is due to the fact that a lot of them are quite chubby when very young. If your child has moderate to severe CHI, a more permanent form of intravenous access may be required to keep them on a drip of concentrated sugar and to take blood samples regularly. This will require a plastic tube called a central line, to be surgically inserted into one of the larger veins in the neck or leg. This is usually performed under a general anaesthetic. This line can be left there for several months until it is no longer required. However, sometimes it can become blocked or infected and if this happens, it may have to be removed and replaced.

We know that CHI is associated with significant feeding problems and vomiting (reflux) in some children. No one fully understands why this is so, but a lot of CHI babies require their milk to be fed via a nasogastric (NG) tube. This is a soft plastic tube that is inserted directly from the nose into the stomach. We always encourage parents to try to feed their children orally at the start of a feed and to use the NG tube for the remainder of the feed that has been left, to try and encourage them to develop their feeding technique.

In some CHI children, feeding difficulties improve with time (several months); however, if this is not the case, we need a more permanent route for feeding to be established. This is done by inserting a gastrostomy. A gastrostomy is a short plastic tube that connects the outside of the abdomen with the stomach. This requires a small operation and so your child will need to be referred to the paediatric surgeons to have this done under a general anaesthetic.

**Will my child need surgery?**

Most children with CHI respond to oral or injectable forms of medication well. Our aim through therapy is to maintain blood sugar levels above 3.5mmol/L, at all times. If this cannot be achieved with maximum medication, we will then need to proceed to surgery.

The type of surgery performed is dependent on whether only part or the whole of the pancreas is affected. Surgery does not always guarantee a cure, but it will definitely enable better control of blood glucose levels.

**What will I need to learn to do?**

Over the period of your child’s admission, irrespective of the severity of their CHI, there are a few compulsory skills that you will need to learn. These will
include how to mix special feeds, checking blood sugar levels, giving emergency treatment orally and as an injection and how to give NG or gastrostomy feeds. These skills will be taught to you by nurses on the ward and our Specialist CHI Practitioner, Lindsey Rigby.

**What support networks are available for me and my child through NORCHI?**

NORCHI has a parent support group, consisting of some of our parents who have been through this process. If you would like them to contact you, please let us know and we will be more than happy to put them in touch with you.

There is a lot of information in this handbook to try and help you understand this complex condition. Some or all of it will be applicable to you and your child. If you have any questions about anything pertaining to your child or what you have read, please do not hesitate to ask a member of the NORCHI team to explain this to you. We are here to help as best we can.

Thank you.