Abstract

Insulin is a powerful hormone produced by the beta-cells in the pancreas. Its major function is to regulate blood glucose levels, facilitating the transport of glucose into the body’s cells. Congenital hyperinsulinism is characterized by the presence of insulin that is inappropriately high for the concentration of blood glucose. Because high levels of insulin also switch off all alternative fuels for the brain to use, this condition can cause brain injury if not detected quickly. Nurses are in a unique position by the bedside to identify the symptoms and treat the hypoglycaemia through very simple nursing interventions, such as safe administration of glucose and frequent blood glucose monitoring. Congenital hyperinsulinism can be transient or persistent. Persistent congenital hyperinsulinism can be further divided into focal or diffuse disease. Focal congenital hyperinsulinism can now be cured, and the management of congenital hyperinsulinism has radically changed with the help of genetics and research. Now pancreatectomy surgery is only used as the last resort.

Key words: Congenital hyperinsulinism ▪ Diffuse and focal disease ▪ Nursing interventions ▪ Persistent hypoglycaemia ▪ Potential brain damage ▪ Transient hypoglycaemia

Congenital hyperinsulinism is a rare but serious disorder. If diagnosed late and inappropriately managed, it can have lifelong consequences in terms of brain injury and the risk of developmental delay (Steinkrauss et al, 2005). It is a cause of severe and persistent hypoglycaemia in the neonatal period (Hussain, 2005). The incidence of sporadic forms of congenital hyperinsulinism is about 1 in 40–50 000, with familial forms being more common (Kapoor et al, 2009a). In some communities, where there is a high rate of consanguinity (quality of being descended from the same ancestor as another person), the incidence of familial congenital hyperinsulinism can be as high as 1 in 2500 (Otonkoski et al, 1999).

It is important for nurses to be knowledgeable on the subject of congenital hyperinsulinism as they are usually the first to identify the infant’s low blood glucose levels accompanying often non-specific symptoms, such as floppiness, twitching, jitteriness, fitting, lethargy or poor feeding. Simple nursing interventions of frequent blood glucose monitoring and maintaining normal blood glucose levels can be transient or persistent. Persistent congenital hyperinsulinism can be further divided into focal or diffuse disease. Focal congenital hyperinsulinism can now be cured, and the management of congenital hyperinsulinism has radically changed with the help of genetics and research. Now pancreatectomy surgery is only used as the last resort.

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Investigation and management of congenital hyperinsulinism

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Normal physiology of insulin secretion

In normal pancreatic beta-cells, insulin production is regulated to maintain blood glucose concentrations within a narrow range (4–7 mmol/litre) (Hill, 2009). To release insulin, beta-cells have to metabolize glucose. In normal physiology the rate of glucose metabolism determines insulin secretion (Hussain, 2005). In pancreatic beta-cells, insulin secretion is regulated by special channels called the adenosine triphosphate-sensitive potassium (K\text{ATP}) channels. Figure 1 provides an outline of the role of pancreatic beta-cell K\text{ATP} channels.

The K\text{ATP} channel in the beta-cell plays an important role in linking glucose metabolism to the production of insulin and is thought to be an on–off switch for triggering insulin secretion. The K\text{ATP} channel consists of two proteins, SUR1 and K\text{IR}6.2 (encoded by genes ABCC8 and KCNJ11), and is responsible for maintaining the electrical potential of the beta-cell membrane (Hussain, 2005). When glucose is mobilized in the beta-cell, this increases the ratio of the adenosine triphosphate/diphosphate (metabolites involved in the exchange of energy within the mitochondria of each cell), which results in the closure of the K\text{ATP} channel. When this channel is closed the calcium channels open, which allows calcium into the beta-cells; this is thought to be the stimulus for the release of insulin (insulin exocytosis).

What is congenital hyperinsulinism?

Insulin is a powerful hormone produced by the beta-cells in the pancreas. Its major function is to regulate blood glucose
levels, facilitating the transport of glucose into the body’s cells (Fain, 2009). Congenital hyperinsulinism is a major cause of persistent hypoglycaemia in the newborn and infancy periods (Hussain, 2008). It is characterized by the presence of insulin concentrations that are inappropriately high for the concentration of blood glucose (Aynsley-Green et al, 2000). This means that insulin production is not switched off, even when the blood glucose level is low. As congenital hyperinsulinism is associated with potential brain injury, rapid diagnosis and appropriate management of these patients is essential (Hussain, 2008).

**Biochemical basis of congenital hyperinsulinism**

Congenital hyperinsulinism is characterized by inappropriate and unregulated insulin secretion from the beta-cells of the pancreas (Kapoor et al, 2009a). In congenital hyperinsulinism the beta-cells release insulin inappropriately all the time and the insulin secretion is not regulated by the blood glucose level (as occurs normally) (Hussain, 2005). Biochemically, this inappropriate insulin secretion causes glucose to be taken up by insulin-sensitive tissues (such as skeletal muscle, adipose tissue and the liver) and at the same time insulin reduces glucose production in the liver (via glycolysis and gluconeogenesis), as well as suppressing fatty acid release and ketone body synthesis (inhibition of lipolysis and ketogenesis) (Kapoor et al, 2009a). The action of insulin causes hyperinsulinaemic hypoglycaemia, with inappropriately low fatty acids and ketone body formation. This forms the biochemical basis for why patients with congenital hyperinsulinism have an increased risk of brain injury (Kapoor et al, 2009b). This means that the brain is not only deprived of its most important fuel (i.e. glucose), but also ketone bodies which are normally used as alternative fuels.

**What is a normal blood glucose level in congenital hyperinsulinism?**

Cornblath et al (1990) debated what normal blood glucose levels should be. However, for the purpose of congenital hyperinsulinism, hypoglycaemia is agreed to be less than 3.5 mmol/litre (Hussain et al, 2007). Steinkrass et al (2005) suggest that for treatment purposes the goal is to keep blood glucose levels above 3.8 mmol/litre (70 mg/dl). Based on the neurophysiological changes associated with hypoglycaemia, Koh et al (1988) suggested a blood glucose level of 2.6 mmol/litre. However, the infants in this study did not have congenital hyperinsulinism and were able to mobilize ketone bodies as alternative fuels. Hussain et al (2007) studied seven infants with congenital hyperinsulinism and concluded that these infants are not able to generate alternative fuels, such as ketone bodies and fatty acids, in response to hypoglycaemia. Infants with congenital hyperinsulinism are consistently reliant on a normal circulating blood glucose concentration as the oxidative fuel for normal neurological functioning, hence the importance of maintaining blood glucose levels above 3.5 mmol/litre (Hussain et al, 2007).

**Genetics of congenital hyperinsulinism**

At present, there are seven known genetic causes of congenital hyperinsulinism, which can be inherited in an autosomal recessive or dominant manner. Congenital hyperinsulinism is an extremely heterogeneous condition in relation to clinical presentation and underlying molecular biology. Abnormalities in the genes ABCC8 and KCNJ11, which control the function of the proteins (SUR1 and Kir6.2) of the KATP channels are the most common cause of severe congenital hyperinsulinism (Kapoor et al, 2009a). Other rare causes are due to abnormalities in genes which are involved in regulating insulin secretion from the pancreatic beta-cell. Box 1 summarizes the known genetic defects that lead to congenital hyperinsulinism.

**Secondary causes of hyperinsulinaemic hypoglycaemia**

Congenital 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 present for only a short duration and is found in conditions such as:

- Intrauterine growth retardation

**Box 1. Known genetic causes of congenital hyperinsulinism**

- ATP-binding cassette, subfamily C (membrane 8 sulfonylurea receptor) (ABCC8): autosomal – recessive and dominant
- Potassium inwardly-rectifying channel (KCNJ11) autosomal – recessive and dominant
- Glutamate dehydrogenase 1 (GLUD1) – dominant
- Glucokinase (hexokinase-4) (GCK) – dominant
- Short chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) – recessive
- Hepatocyte nuclear factor 4 (HNF4A) – dominant
- Monocarboxylate transporter 1 (SLC16A1) (exercise induced) – dominant

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Figure 1. Insulin secretion pathway via the KATP channels.
Infants of diabetic mother
Infants with perinatal asphyxia.
Transient hyperinsulinism can occur in infants with no predisposing factors; the mechanisms causing this is currently unclear (Hussain, 2005). This group of infants have been shown to be fully responsive to medical management with a medication called diazoxide, which eventually can be weaned and stopped.

Some syndromes also present in the newborn period with hyperinsulinaemic hypoglycaemia. In infants with Beckwith-Wiedemann syndrome, which is an overgrowth syndrome, up to 50% have been observed to have hyperinsulinaemic hypoglycaemia (Munns and Batch, 2001).

Histology
There are two main histological forms of congenital hyperinsulinism, which are both characterized by persistent hyperinsulinaemic hypoglycaemia. In infants with Beckwith-Wiedemann syndrome, which is an overgrowth syndrome, up to 50% have been observed to have hyperinsulinaemic hypoglycaemia (Munns and Batch, 2001).

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Diffuse congenital hyperinsulinism affects the whole of the pancreas and is characterized by beta-cell hypertrophy and hyperplasia of the pancreas (Hussain, 2005). Diffuse disease can be familial or sporadic and can result from recessively-inherited or dominantly-acting mutations, while focal disease is always sporadic (de Lonlay et al, 1997).

The management of diffuse and focal disease is different. If accurately located and completely removed, focal disease can now be cured. Diffuse disease, if medically unresponsive, will require a 98% pancreatectomy (Steinkrauss et al, 2005).

Brain damage
Hussain and Aynsley-Green (2004) outline how some infants with congenital hyperinsulinism do develop brain injuries as a result of either prolonged or repeated hypoglycaemic episodes. The degree of brain injury is variable, with some infants developing seizures and global developmental delay. However, some may have very subtle problems with memory, which often manifests itself when the children are of school age. Skeinkrass et al (2005) found that one-third of infants with congenital hyperinsulinism develop some form of developmental delay. The rationale for early diagnosis and maintaining the blood glucose above 3.5 mmol/litre is to avoid brain injury.

Diagnosis of congenital hyperinsulinism
Any infant with persistent or frequent hypoglycaemia can potentially have congenital hyperinsulinism. Typically, newborns with congenital hyperinsulinism are unable to fast for long periods; however, some infants develop hypoglycaemic episodes which are precipitated by feeds (Kapoor et al, 2009b). To ascertain the diagnosis and the cause of the congenital hyperinsulinism, vital blood samples are needed during a controlled hypoglycaemia screen (Steinkrauss et al, 2005).

A central venous access device is required to administer high concentrations of glucose, for obtaining crucial blood samples and for the rapid correction of the hypoglycaemic episode. At all times the true glucose sample should be a capillary sample in order to prevent it from being falsely contaminated with intravenous glucose solution. At the time of hypoglycaemia vital blood samples are taken, these include true glucose, insulin, ketones and fatty acids. Other blood samples are also taken at this time to exclude other endocrine and metabolic causes of hypoglycaemia. Genetic blood samples are taken, however these do not need to be at the time of hypoglycaemia. The calculation of the intravenous glucose infusion rate required to maintain normal blood glucose levels is a clue to diagnosing congenital hyperinsulinism. An intravenous glucose infusion rate greater than 8 mg/kg/minute (normal is 4–6 mg/kg/minute) is virtually diagnostic of hyperinsulinism (Kapoor et al, 2009b).

Once the diagnosis of congenital hyperinsulinism has been established, medical management is trialed. The first-line medication is diazoxide which opens the K<sub>ATP</sub> channel in order to reduce insulin secretion (Hussain, 2005). Diazoxide has a fluid-retaining action (especially in newborns) and hence it is used with care (Hussain, 2005). It is used with chlorothiazide, a diuretic, to treat any possible fluid retention.
Subcutaneous octreotide can also be used, an analogue of somatostatin, as it inhibits insulin secretion (Hussain, 2005). The genetic results are essential for establishing if an $^{18}$F-dopa PET (positron emission tomography) scan is required. Currently, only those infants with suspected focal lesions on genetic analysis have PET scans to locate the exact location of the lesion. The precise preoperative localisation and limited surgical removal of the focal lesion has transformed the outcome for these patients (Otonkoski et al, 2006). The pancreatic remnant left behind after a near total pancreatectomy can sometimes still produce too much insulin, hence hypoglycaemia occasionally still occurs. In such cases, a re-trial of medical treatment is often effective. In rare cases, infants may develop diabetes mellitus immediately following a near total pancreatectomy.

**Case study**

For the purpose of this article, a case study of an infant will be used to illustrate the patient journey from presentation to cure using the algorithm in Figure 4. The infant’s name has been altered in line with The Code: Standard of conduct, performance and ethics for nurses and midwives (Nursing and Midwifery Council, 2008). It is important to remember that infants with congenital hyperinsulinism are unique; however, many similarities occur along the patient journey. For the purpose of this article the focus is on the blood glucose control, and other aspects of pancreatic surgery will not be discussed.

**Presentation and transfer**

Sam was born at 36 weeks gestation by caesarean section due to decreased foetal activity. His birth weight was 2.73 kg. He was immediately taken to the special care baby unit (SCBU) due to temperature instability and poor feeding; however, he was later thought to be well, gaining weight and discharged home. At the age of 7 weeks, he was found to be sleepy and lethargic with short periods of rigidity and abnormal eye movements were noted. A blood glucose level was taken by the nurses in accident and emergency, which showed hypoglycaemia and a true laboratory glucose confirmed hypoglycaemia as 0.7 mmol/litre.

On seeking advice from a tertiary centre, Sam was transferred, requiring a glucose infusion of 20 mg/kg/minute. The transport policy was followed, which highlights the need for two secure intravenous lines, blood glucose monitoring throughout the journey and the availability of glucogel, intravenous glucose and intramuscular glucagon. A Hickman line was immediately inserted under a general anaesthetic in order to safely administer the high concentration of intravenous glucose Sam required. The controlled hypoglycaemia screen was performed by specialist nurses 24 hours post the anaesthetic to allow for a safe period of time to elapse, ensuring the stress response to the surgery did not interfere with the interpretation of the results of the hypoglycaemia screen.

**Diagnosis**

**Results of the hypoglycaemia screen:**
- True plasma glucose concentration – 2.6 mmol/litre
- Serum insulin level – 20.4 mU/L (should be undetectable at time of hypoglycaemia)
- Low levels of serum non-esterified fatty acid level
- Low levels of serum beta-hydroxybutyrate level (ketone bodies).

Sam’s maximum glucose requirement was 20 mg/kg/minute on intravenous total parenteral nutrition, fortified continuous nasogastric feeds and small oral feeds of only 10 ml every 6 hours (these were given to maintain Sam’s ability to suck and swallow). Large bolus oral feeds were avoided as this can stimulate increased insulin production, causing the risk of further hypoglycaemic episodes.

**Response to medical management**

Sam was initially commenced on diazoxide and chlorothiazide plus his fluid requirement was reduced to 120 ml/kg/day to avoid fluid retention. Despite gradually increasing to the maximum recommended dose, only a partial response was seen. Octreotide and glucagon continuous subcutaneous infusions were used, again resulting in only a partial response.
Nurses and midwives play a pivotal role and are advised to have a low threshold for checking blood glucose levels in any infant who is symptomatic. If the infant has persistent hypoglycaemia then the diagnosis of congenital hyperinsulinism should be considered.


Further investigations
Genetic results showed that Sam’s congenital hyperinsulinism was likely to be due to a focal lesion hence an 18F-dopa PET scan was performed. The PET scan gives an image of the activity of the pancreas plus the anatomical structure (Figure 5).

Surgical treatment
Sam had a focal lesion in the head of the pancreas, which was surgically excised. Laparoscopic surgery was attempted, but eventually he underwent an open procedure. Sam recovered well postoperatively. The diagnosis of focal lesion was confirmed by histology showing adenomatous pancreatic hyperplasia.

Outcome
Sam recovered well postoperatively, with the blood glucose levels returning to within normal ranges. He was taken off intravenous glucose and was sent home feeding four hourly. His parents were instructed to only monitor his blood glucose levels returning to within normal ranges. He was taken off intravenous glucose and was sent home feeding four hourly.

Hyperinsulinaemic hypoglycaemia is an important cause of hypoglycaemia in childhood and early recognition with prompt, appropriate management is essential to avoid the neurological consequences associated with this condition (Kapoor et al, 2009b).

It is hoped that this article has demonstrated the need to recognize those infants who have hyperinsulinaemic hypoglycaemia and the urgent need to treat them appropriately. Congenital hyperinsulinism can be complicated and difficult to manage; however, with continued research and knowledge a cure can now be offered to those infants with focal lesions. All other infants with congenital hyperinsulinism can reach their full potential in life, if hypoglycaemic episodes are avoided.

With increased knowledge and research, the outcomes for all these infants are continuously improving. Nurses and midwives, at the bedside, play a pivotal role in early identification of infants with congenital hyperinsulinism, hence preventing the potential neurological damage which can, if left untreated, result. It is advisable for nurses and midwives to have a low threshold for checking blood glucose levels in any infant who is symptomatic. If the infant has persistent hypoglycaemia then the diagnosis of congenital hyperinsulinism should be considered.

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