Congenital Hyperinsulinism (CHI)

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Contents

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Abstract

The aim of this chapter is to highlight a rare endocrine condition (Congenital Hyperinsulinism, CHI), which can cause low blood glucose levels leading to permanent brain injury. Many Paediatric Nurses are unfamiliar with this condition. CHI is caused by

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unregulated insulin secretion from the pancreas and typically presents in the newborn period, but it can also present later in life. It is imperative for Paediatric Nurses to be knowledgeable on the subject of CHI as they are usually the first to identify the infant's low blood glucose levels, often accompanied by non-specific symptoms such as floppiness, jitteriness, fitting, lethargy, or poor feeding. It is always important to consider CHI if an infant or child presents with unexplained recurrent and persistent hypoglycaemia.

The chapter will focus on understanding how to interpret blood glucose levels, explain the biochemical basis of CHI, provide some background to the genetic causes of CHI, discuss the signs and symptoms of hypoglycaemia and finally, offer guidance for the diagnosis and management of patients with CHI. A case study will be used to illustrate the importance of early identification and prompt treatment.

Keywords
Congenital hyperinsulinism · Brain injury · Insulin · Glucose

Abbreviations

18F-DOPA	Fluorine-18-L-dihydroxyphenylalanine
A&E	Accident and Emergency
ABCC8	ATP Binding Cassette Subfamily C Member 8
ADP	Adenosine diphosphate
ATP	Mitochondrial adenosine triphosphate
b-HOB	Beta-hydroxybutyrate
CHI	Congenital hyperinsulinism
CNS	Clinical Nurse Specialist
CRP	C-reactive protein
EEG	Electroencephalogram
GA	General anaesthetic
GCK	Glu-cokinase
GH	Growth hormone
GLUD1	Glutamate dehydrogenase
G.P	General Practitioner
HADH	Hydroxyacyl-coenzyme A dehydrogenase
HNF1A	Hepatocyte nuclear factor 1A
HNF4A	Hepatocyte nuclear factor 4A
KATP	Mitochondrial adenosine triphosphate-sensitive potassium
KCNJ11	Potassium Voltage-Gated Channel Subfamily J Member 11
Kgs	Kilograms
Kir6.2	Inward rectifying potassium channel
mg/kg/day	Milligram per kilogram per day
mg/kg/min	Milligram per kilogram per minute
mL/kg	Millilitre per kilogram
mLs/kg/day	Millilitres per kilogram per day
mm	Millimetre
mmols/L	Millimoles per Litre
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
mU/L	Milliunits per Litre
NEFA	Non-esterified fatty acids
NHS	National Health Service
nmol/L	Nanomole per litre
PES	Pediatric Endocrine Society
PET	Positron emission tomography
pmol/L	Picomoles per litre
SLC16A1	Solute Carrier Family 16 Member 1
SLE	Systemic lupus erythematosus
SUR 1	Sulfonylurea receptor
µg/L	Micrograms per litre
µmol/L	Micromole per litre

Key Terms

- **Hypoglycaemia screen:** Diagnostic investigation to examine endocrine and metabolic causes of hypoglycaemia.
- **Transient hyperinsulinism:** Usually occurs for a short period post birth. Can occur with or with out associated risk factors.
- **Persistent congenital hyperinsulinism:** Ongoing hypoglycaemia often needing ongo-

ing medical or surgical treatment and can be subdivided into focal or diffuse disease.

- **Focal disease:** A specific area of the pancreas is affected. Focal lesions are usually small, measuring 2–10 mm across.
- **Diffuse disease:** Affects the entire pancreas. It can be inherited in a recessive or dominant manner or can occur sporadically.

Key Points

- If the infant has persistent hypoglycaemia, then the diagnosis of congenital hyperinsulinism (CHI) should be considered.
- Nurses at the bedside should have a low threshold for checking blood glucose level in any infants who are symptomatic of hypoglycaemia.
- Early referral to a specialist CHI centre is important to establish best medical treatment and outcomes.
- A full multidisciplinary team should be in place in order to fully support and guide the family in the treatment needed.

8.1 Introduction

Congenital hyperinsulinism (CHI) is a serious disorder, which, whilst rare, can have lifelong consequences, with severe psychomotor retardation and epilepsy being more common in patients who present in the neonatal period (Menni et al. 2001). The incidence of sporadic forms of CHI is about 1 in 40,000–50,000 with familial forms more common in communities with high consanguinity (Glaser et al. 2000).

CHI is characterized by the presence of insulin in the blood at an inappropriately high level for the concentration of blood glucose (Aynsley-Green et al. 2000). Insulin is a hormone produced by the beta-cells of the pancreas; its purpose is to lower blood glucose levels, facilitating the transport of glucose into the body's cells (Fain 2009). In CHI, the inappropriately high insulin switches off all alternative fuels for the brain to use (free fatty acids and ketone bodies), hence the risk of brain injury and even death.

There has been much debate over the definition of hypoglycaemia, especially in the neonatal population. This uncertainty has caused confusion in the past as to when to diagnose CHI and how to treat hypoglycaemia. The Pediatric Endocrine Society (PES) considered this gap in evidence-based knowledge and in 2015 convened an expert panel of Paediatric Endocrinologists and Neonatologists. Articles on transitional neonatal hypoglycaemia made recommendations for the diagnosis and management of persistent hypoglycaemia. Stanley et al. (2015) suggests that during the first 24–48 h of life, the normal neonates' blood glucose level is typically lower due to the transitional phase from intrauterine to extra uterine life. This initial period of hypoglycaemia is called transitional neonatal hypoglycaemia and should be managed according to the clinical symptoms and findings at the time. The PES recommends that the focus for the first 24–48 h of life should be on stabilization of glucose levels; however, after this initial transitional period, the physiological and biochemical mechanisms regulate the blood glucose level above 3.5 mmols/L. (Guemes et al. 2016; Thornton et al. 2015) highlights the importance of distinguishing between the normal neonates who may have transitional hypoglycaemia and the infants who have identifiable risk factors for CHI, including those normal neonates whose hypoglycaemia persists beyond 3 days. These neonates need prompt diagnosis and effective treatment to avoid the known serious consequences of hypoglycaemia including seizures and brain injury.

Nurses and midwives by the bedside have the potential to identify these infants with hypoglycaemia and to prevent possible brain injury. If there is any concern that an infant is displaying symptoms such as poor feeding, lethargy, and jitteriness, then a simple blood glucose measurement is essential to identify if the infant is

Box 8.1 Normal blood glucose values

Acceptable blood glucose range in a tertiary specialist centre (in the UK)
3.5 mmol/L—10.0 mmol/L or 63 mg/dL—180 mg/dL
(To convert mmol/L to mg/dL multiple by 18)

hypoglycaemic. Normal blood glucose values as in Box 8.1.

8.2 Clinical Presentation of CHI

Patients presenting with CHI can have persistent or recurrent hypoglycaemia despite frequent/continuous feeds or intravenous glucose (Kapoor et al. 2009a). Many neonates with CHI typically present at birth though older infants and children can show signs of hypoglycaemia when fasting. As already stated, hypoglycaemic symptoms are often non-specific, but infants are typically lethargic and hypotonic with seizures (Guemes et al. 2016). Parents often describe their infants as "not feeding well, sleepy and jittery". For the nurse by the bedside, a simple blood glucose reading at this time is a powerful tool. Unfortunately, this has been known to be overlooked. Clinical examination may also detect macrosomia, cardiomyopathy, and hepatomegaly, but the absence of these does not exclude CHI.

On taking a clinical history, there are key questions to ask when faced with an infant with CHI, which include the following:

- A thorough neonatal and birth history (looking for risk factors such as prematurity, small size for gestational age, and perinatal stress).
- Length of time for which the infant can fast (is this appropriate for age and weight?).
- Family history of diabetes mellitus (gestational or in any family member).
- Relationship between hypoglycaemic episodes to the timings of feeds or certain foods (e.g. protein or large intakes of glucose).
- In older patients, a potential relationship between hypoglycaemia and exercise. It is important to ask about this.
- Establishing if the infant/child has had any abdominal surgery, e.g. Nissens fundoplication. Again, this may be significant to the diagnosis and the treatment (Bufler et al. 2001).
- Establishing, where appropriate, if hypoglycaemia is only triggered when the infant/child is unwell with an intercurrent illness, as this could be caused by other mechanisms other than CHI**.**

8.3 Biochemical Basis of CHI

The body maintains blood glucose concentrations within a narrow range, typically 3.5–5.5 mmol/L (Kaufman 2000). In normal physiology, the pancreatic beta-cells are sensitive to the plasma glucose concentration and secrete appropriate amounts of insulin (Hussain 2005). When describing insulin secretion from the pancreatic beta-cell, it is the ATP-sensitive potassium channels (KATP channels) that are thought to play a pivotal role in glucose-stimulated insulin secretion. Figure 8.1 provides an outline of the function of the beta-cell KATP channel.

This channel consists of two proteins, SUR1 and KIR6.2 (encoded by genes *ABCC8* and *KCNJ11*), which are responsible for maintaining the electrical potential of the beta-cell membrane (Inagaki et al. 1995). The KATP channel in the beta-cell is thought to be an "on–off" switch for triggering insulin secretion (Dunne and Petersen 1991). The release of insulin is a result of glucose being metabolized in the beta-cell, and this causes an increase in the intracellular ratio of nucleotides such as ATP/ADP which closes the KATP channel. When the KATP channel is closed, the cell membrane depolarizes, which causes calcium influx via voltage-gated calcium channels, and this is thought to be the stimulus for the release of insulin (insulin exocytosis) into the bloodstream.

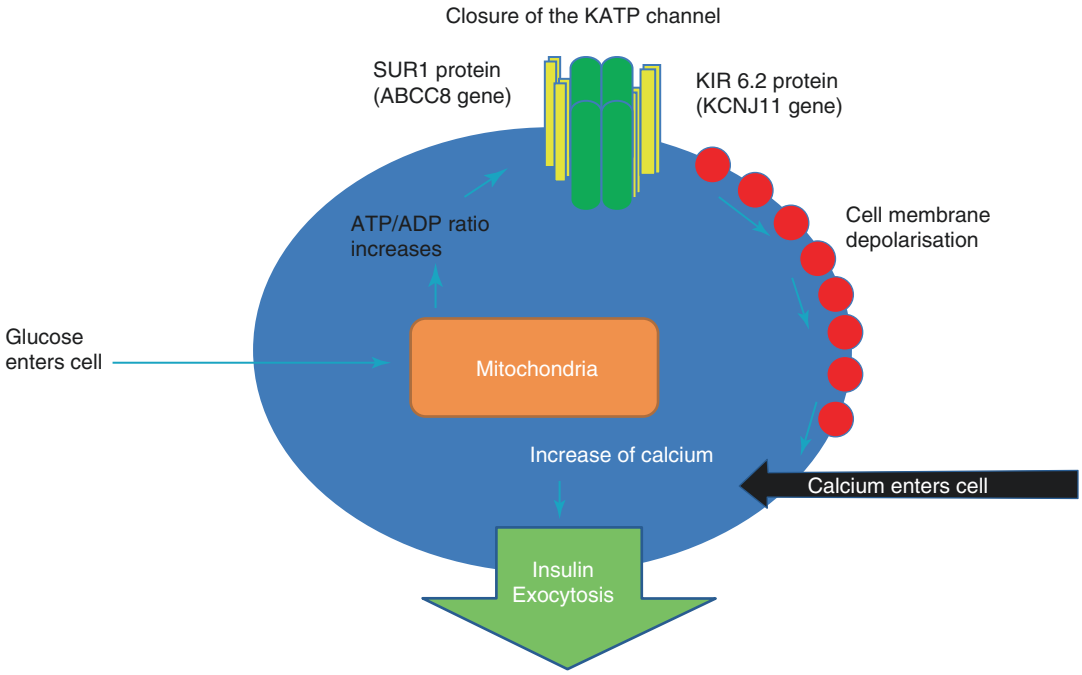

Fig. 8.1 Illustrates the mechanism of insulin secretion when glucose enters the pancreatic beta cell

In CHI, the beta-cells constantly release inappropriate amounts of insulin which is not regulated by the blood glucose level (Aynsley-Green et al. 2000). One of the major causes of this continuous inappropriate insulin production is the "on–off" KATP channel being faulty and permanently in the closed position, resulting in insulin exocytosis. This inappropriate insulin secretion has several effects: it causes glucose to be taken up by insulin-sensitive tissues (such as skeletal muscle, adipose tissue, and the liver); it reduces glucose production in the liver (via glycolysis and gluconeogenesis); and it suppresses fatty acid release and ketone body synthesis (inhibition of lipolysis and ketogenesis) (Kapoor et al. 2009b). This explains the biochemical basis of CHI being hyperinsulinaemic hypoglycaemia, with inappropriately low fatty acids and ketone body formation, hence the increased risk of brain injury (Kapoor et al. 2009b). Simply, this means that the brain is deprived of glucose plus fatty acids and ketone bodies and thus there is a risk of brain injury with this condition.

8.4 Diagnosis of CHI

Persistent hypoglycaemia and an intravenous glucose infusion rate >8 mg/kg/min (normal is 4–6 mg/kg/min) are virtually diagnostic of CHI (Kapoor et al. 2009a). However to confirm the diagnosis, critical blood samples are needed during a controlled hypoglycaemia screen (See Table 8.1) (Steinkrauss et al. 2005). A central venous access device is often the only way to safely administer high concentrations of glucose and to obtain these crucial blood samples. During this hypoglycaemia screen, there are some key factors the nurse must consider.

During the hypoglycaemia screen, the counter-regulatory hormonal response to hypoglycaemia is examined. Glucagon, growth hormone, and cortisol are all endocrine hormones that act against insulin. These hormones all act at various points of glucose metabolism to increase plasma glucose concentration; however, insulin is a glucose lowering hormone. In conclusion, if the hypoglycaemia screen shows that all other causes of hypoglycaemia are ruled out and that the

Table 8.1 Hypoglycaemia Screen

Local practice at a UK tertiary specialist centre when performing a hypoglycaemia screen
1. If the infant has had a general anaesthetic (GA) for a central venous line insertion, then it is important to wait 24 h after the GA to ensure the stress hormones are not raised, thus altering the hypoglycaemia screen results. (This is a practice based on experience in a NHS tertiary hospital.)
2. When weaning the intravenous glucose infusion rate, it is essential to do this slowly to ensure accuracy of the results.
3. All diagnostic bloods (see an example hypoglycaemia screen results) and urine should be taken when the patient is hypoglycaemic <3.0 mmols/L.
4. The laboratory glucose must be a capillary sample. At no time should a true glucose sample be taken from the intravenous line, through which glucose has been administered, as contamination can occur. From clinical experience, capillary samples are always advocated for laboratory glucose samples.
5. Based on clinical practice at an NHS tertiary hospital, the hypoglycaemia screen blood samples are taken when the blood glucose level is <3.0 mmols/L, ensuring the patient is hypoglycaemic for the shortest amount of time possible. Often this means that two nurses are required (one taking the blood samples from the central venous line and the other obtaining the capillary laboratory glucose).
6. Once all the samples are obtained, the hypoglycaemia is corrected by administering. 1 mL/kg 10% glucose bolus and intravenous fluids are recommenced. The blood glucose level is immediately rechecked and checked again after 10 min to ensure the patient is no longer hypoglycaemic.

insulin level is inappropriately raised for the blood glucose level, with corresponding low ketone bodies and fatty acids, then CHI is diagnosed (Aynsley-Green et al. 2000).

8.5 An Example of a Hypoglycaemia Screen

***Plasma glucose 2.0 mmol/L (normal range = 3.5–5.5 mmols/L).**

***Insulin 7.5 mU/L (Abnormally raised during hypoglycaemia).**

Serum cortisol 450 nmol/L.

Serum glucagon 12 (normal = <50 pmol/L).

Serum GH 1.6 μg/L (normal = 0.9–14.1 μg/L).

Serum ammonia 36 mmol/L (normal = <40 μmol/L).

Plasma lactate 1.3 mmol/L (normal = 0.7–2.1 mmol/L).

***Serum NEFA 0.07 mmol/L (Fatty acids—suppressed).**

***Serum b-HOB <0.05 mmol/L (Ketone bodies—suppressed).**

Acyl-carnitine profile reported as normal.

Urine organic acids: no abnormality.

***Glucose requirement of 20 mg/kg/min. (Normal = 4–6 mg/kg/min to maintain blood glucose levels above 3.5 mmols/L).**

***Indicates results are abnormal.**

8.6 Causes of CHI

KAPT channel defects (encoded by genes *ABCC8* and *KCNJ11)* account for the majority of causes of CHI though abnormalities in other genes account for the dysregulation of insulin secretion of approximately 10% of patients with CHI (Nessa et al. 2015). CHI is known to be caused by mutations in certain identified genes (See Table 8.2); however, there is ongoing research to explore other genetic causes.

8.7 Transient CHI

CHI can be subdivided and is distinguished by the length of treatment required and the infant's response to medical management. If CHI is evident for only a short duration and is simply treated with a small dose of diazoxide, then transient CHI is the diagnosis and is usually associated with intrauterine growth retardation, the infants of diabetic mothers, or infants with perinatal asphyxia (Mehta and Hussain 2003). Transient hyperinsulinism can, however, occur in infants with no predisposing factors. Also, some syndromes are also associated with CHI such as Beckwith-Wiedemann syndrome (Munns and Batch 2001).

Table 8.2 Genetics of CHI

Gene	Inheritance
ABCC8/KCNJ11 (Nestorowicz et al. 1996)	*Autosomal recessive* – Diffuse disease, mostly diazoxide unresponsive and often diagnosed within a few days of life *Autosomal dominant* – Often diazoxide unresponsive diffuse disease – Later presentation can be diazoxide responsive plus have family history of type 2 diabetes
GLUD1 (Stanley et al. 1998)	*Autosomal dominant* – Protein (leucine)-sensitive hypoglycaemia which is diazoxide responsive – Asymptomatic hyperammonemia
HADH (Clayton et al. 2001)	*Autosomal recessive* – Diazoxide responsive – In some patients can have abnormal levels of acylcarnitine metabolites present in plasma and urine
GCK (Davis et al. 1999)	*Autosomal dominant* – Can present at any age and variable response to diazoxide
SLC16A1 (Otonkoski et al. 2003)	*Autosomal dominant* – Exercise-induced hyperinsulinaemic hypoglycaemia
HNF4A (Pearson et al. 2007)	*Autosomal dominant* – Patients may go on to develop MODY 1
HNF1A (Stanescu et al. 2012)	*Autosomal dominant* – Diazoxide responsive – May go on to develop MODY 3

8.8 Persistent CHI

Persistent CHI is characterized by ongoing hypoglycaemia, often needing complex medical or surgical treatment**.** Histological examination of pancreatic tissue from patients who have undergone a pancreatectomy shows that there are two major histological forms of CHI, diffuse, and focal (Rahier et al. 2002). Focal lesions are characterized by beta-cell hyperplasia in a small lesion surrounded by normal pancreatic tissue (See Fig. 8.2).

These small lesions often measure only 2–10 mm and are invisible to the naked eye, though they produce excessive insulin, causing severe hypoglycaemia. Approximately 40–50% of infants with persistent CHI will have the focal form; however, this focal CHI is considered to be sporadic with very low chances of it occurring again in the same family (Ismail et al. 2011). Genetic blood results from the infant and both parents are used to lead the clinician in identifying those patients who need an 18F-DOPA-PET (positron emission tomography) scan to determine if the patient has a focal lesion, and if so, its position in the pancreas (See Fig. 8.3).

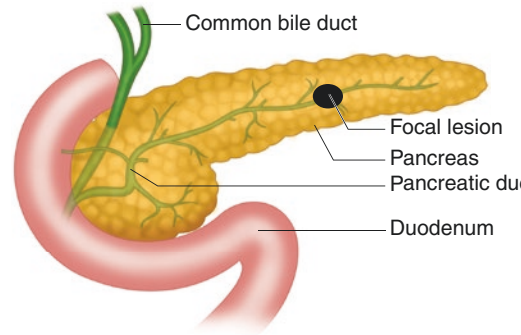

Fig. 8.2 Focal Disease

Diffuse CHI (See Fig. 8.4) affects the whole of the pancreas and is characterized by beta-cell hypertrophy and hyperplasia of the whole pancreas. Diffuse disease can be familial or sporadic and can result from recessively inherited or dominantly acting mutations (de Lonlay et al. 1997).

If located and completely surgically removed, the focal CHI can be completely cured (Barthlen et al. 2011). However with diffuse CHI, the aim

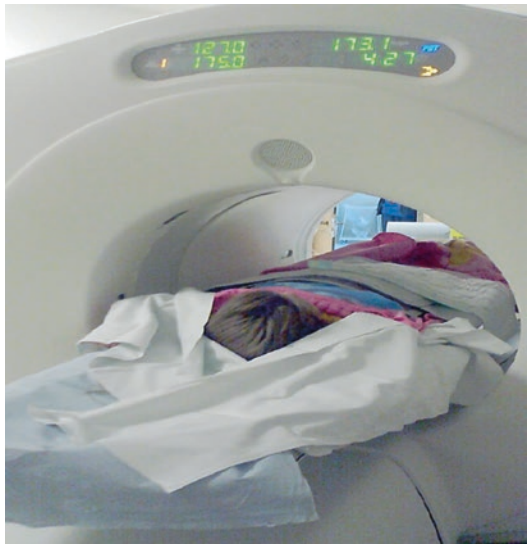

Fig. 8.3 PET scan to localize possible focal lesion

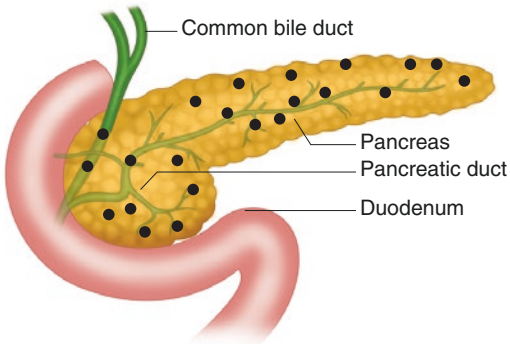

Fig. 8.4 Diffuse disease

of treatment is to medically manage the condition, avoiding surgery if possible, as this could cause the patient to develop diabetes and pancreatic enzyme deficiency in the future. If the patient is unresponsive to all medical therapy, then surgical removal of almost the entire pancreas is occasionally the only option.

8.9 Management of a Patient with CHI

In the acute management phase, high concentrations of intravenous glucose (such as 20% and 30%) are often needed to stabilize the blood glucose levels above 3.5 mmols/L. An intravenous or subcutaneous glucagon infusion is also administered as it releases glycogen stores from the liver (gluconeogenesis and glycogenolysis) (Nessa et al. 2015). A subcutaneous infusion of octreotide (a somatostatin analogue) also inhibits insulin secretion by decreasing insulin gene promoter activity and reducing insulin biosynthesis from pancreatic beta-cells. The aim of this acute treatment is to maintain a safe blood glucose level whilst allowing the infant to establish an oral feeding regimen.

8.10 Medical Therapy

Once the diagnosis of CHI has been established, medical management is trialled. The first-line medication is diazoxide, which needs an intact KATP channel in order for the channels to open and insulin secretion can be inhibited (Aynsley-Green et al. 2000). Diazoxide can cause fluid retention (especially in newborns) and so it must be used with caution, especially in patients who are receiving large volumes of intravenous fluids or oral feeds. There are also a small number of reports that diazoxide can potentially cause pulmonary hypertension and possible cardiopulmonary toxicity (Nebesio et al. 2007). It is recommended that if pulmonary hypertension is identified, then diazoxide should be stopped.

Other medical treatments include subcutaneous octreotide injections four times a day, for patients who show little or no response to oral diazoxide. Long-acting somatostatin analogues such as Lanreotide administered every 28 days are now being used, (see Table 8.3) reducing the intensity of injection therapy of octreotide from four daily subcutaneous injections to one deep subcutaneous injection four weekly.

Lastly, Sirolimus, an immunosuppressant (mTOR inhibitor), has been successfully used in a small number of patients with diffuse CHI who were unresponsive to all previous medical treatments. It is suggested that sirolimus action may affect the number of insulin receptors although the mechanism in treatment of CHI has not been fully delineated (Senniappan et al. 2014). It has been recommended

Table 8.3 Lanreotide

Lanreotide is available in a pre-filled syringe containing 60 mg Lanreotide under the brand name Somatuline® Autogel. It is a white to pale yellow semi-solid gel—a similar texture to petroleum jelly. The starting dose of Lanreotide is often 30 mg but is adjusted according to the child's response to the medicine. The injection is given every 28 days—the aim is that the daily doses of octreotide or diazoxide can be gradually cut down and then stopped.
Before starting Lanreotide injections, a child will need a series of blood tests plus an ultrasound of their liver and gall bladder. During treatment, they will then need to have blood tests along with an ultrasound scan of their gall bladder every 6 months.
Lanreotide is injected into the deep layer of subcutaneous fat under the skin, usually in the upper and outer part of the buttock as there is usually a substantial amount of subcutaneous fat in this area. This also reduces the risk of hitting the sciatic nerve with the injection. One important way to reduce the pain and irritation of injections is to rotate the administration site. Changing injection area also reduces the risk of lipohypertrophy (fatty lump) developing. Whilst this is not dangerous, it will affect how the medicine is absorbed.
It is important that a child is prepared for the injection and distraction therapy can be used whilst the injection is being administered.
Parents and/or Community Children Nurses are trained by the Clinical Nurse Specialists to administer the injection at home, once treatment has been established.

that sirolimus should only be used with caution in CHI specialized centres as adverse events have been reported (Szymanowski et al. 2016). If, after all medical treatment has been trialled, the patient remains unresponsive to medical and dietary interventions, then surgery may be deemed necessary.

8.11 Case Study to Illustrate an Infant's Presentation, Diagnosis, and Treatment for CHI

CT was born at 36 + 4 weeks gestation via a normal vaginal delivery. His birth weight was 2.73 kgs (50th centile). His mother had been treated for the first 12 weeks of pregnancy with oral steroids due to systemic lupus erythematosus (SLE). All her pregnancy scans had been reported as normal and the labour was induced due to her history of SLE. CT's parents were non-consanguineous and were of Filipino origin; he was their first child. At birth, CT was reported to be well and had normal neonatal baby checks. He was discharged after 24 h of birth, but presented in Accident and Emergency (A&E) on day 3 of life with a history of not waking and poor feeding. His mother had been trying to breast feed him but this was not well established and CT received formula top ups from day 2 of life.

On presentation, CT had reportedly had jerky movements over the previous 12–24 h as described by his parents. Seizure activity was witnessed in A&E, which included lip smacking and jerking of all limbs with evident desaturations. A blood glucose level at the time of presentation was 0.4 mmols/L and it was estimated that CT had lost 20% of his body weight since birth. His routine bloods and a blood gas sample were taken and reported as unremarkable. An initial 2 mL/kg bolus of 10% glucose was administered intravenously to correct his hypoglycaemia, which led to a clinical improvement. However, six further seizures were observed and two loading doses of phenobarbitone, one loading dose of phenytoin, and two doses of clonazepam were required to control his seizures. CT was also initially treated for sepsis but his antibiotics were ceased when his CRP was reported as normal as well as microbiologist advice. He was commenced on intravenous fluids containing glucose, though it was noted that whenever his intravenous fluids were interrupted, he would then become hypoglycaemic.

At this time, a referral was made to a tertiary specialist centre and treatment was advised. The initial hypoglycaemia screen showed evidence of CHI as the true glucose was 0.4 mmols/L with corresponding inappropriately raised insulin reported as 86 pmol/L. The protective fuels of fatty acids and ketones were both very low at the time of hypoglycaemia; hence, the diagnosis of CHI was made. All other metabolites were reported as normal. The local hospital reported that CT had abnormal tone but that he had a good suck and was alert on handling. An EEG was reported as normal though an MRI scan showed evidence of cortical necrosis and was sadly grossly abnormal.

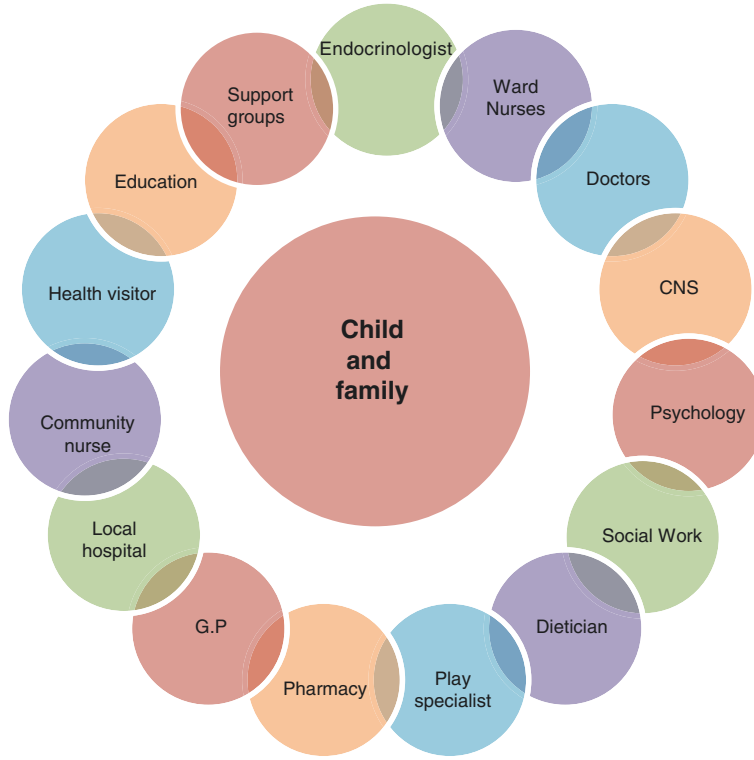

Fig. 8.5 The multidisciplinary team

CT's treatment was to fluid-restrict him to 120 mL/kg/day using a combination of high concentration glucose intravenously via central venous access device and small oral feeds of Aptamil®. On this regime, his blood glucose levels were maintained between 3.6 and 4.8 mmols/L, and his glucose requirement was calculated to be slightly raised at 10 mg/kg/min. On reducing his fluid requirement, this allowed for the safe introduction of diazoxide 5 mg/kg/day with chlorothiazide 7.5 mg/kg/day. Over the next 10 days, CT's intravenous fluids were safely titrated with his oral feeds so that he was eventually on four hourly feeds with no hypoglycaemia, as he was considered to be fully responsive to diazoxide to control his CHI. He was discharged home once his parents were competent in measuring his blood glucose levels pre-feed and in administration of his medications.

After 8 weeks, he was reviewed in the tertiary specialist centre where his dose of diazoxide was calculated to be 2.3 mg/kg/day due to his good weight gain, and there were no hypoglycaemic episodes reported by his parents. It was therefore decided to admit CT for two nights to reassess his CHI. This was done by safely stopping his medications 3 days prior to admission, then completing a 24 h glucose profile and a 6 h fast off diazoxide and chlorothiazide. The results showed that CT no longer had any hypoglycaemic episodes on his normal feeding regimen and when fasted for 6 h, his blood glucose level no longer dropped and his insulin level remained appropriately low. This means that his CHI had been transient in nature and had successfully resolved after only a short time of treatment with diazoxide. Despite the resolution of the CHI, CT's neurological developmental needed long-term follow-up. A multidisciplinary team approach is essential when caring for children with CHI (See Fig. 8.5).

This case study highlights the importance of early identification and prompt management of CHI, as untreated severe hypoglycaemia can result in severe brain injury and subsequent neurodevelopment handicap. Box 8.2 demonstrates the management pathway from diagnosis to treatment of CHI.

Box 8.2 Management pathway

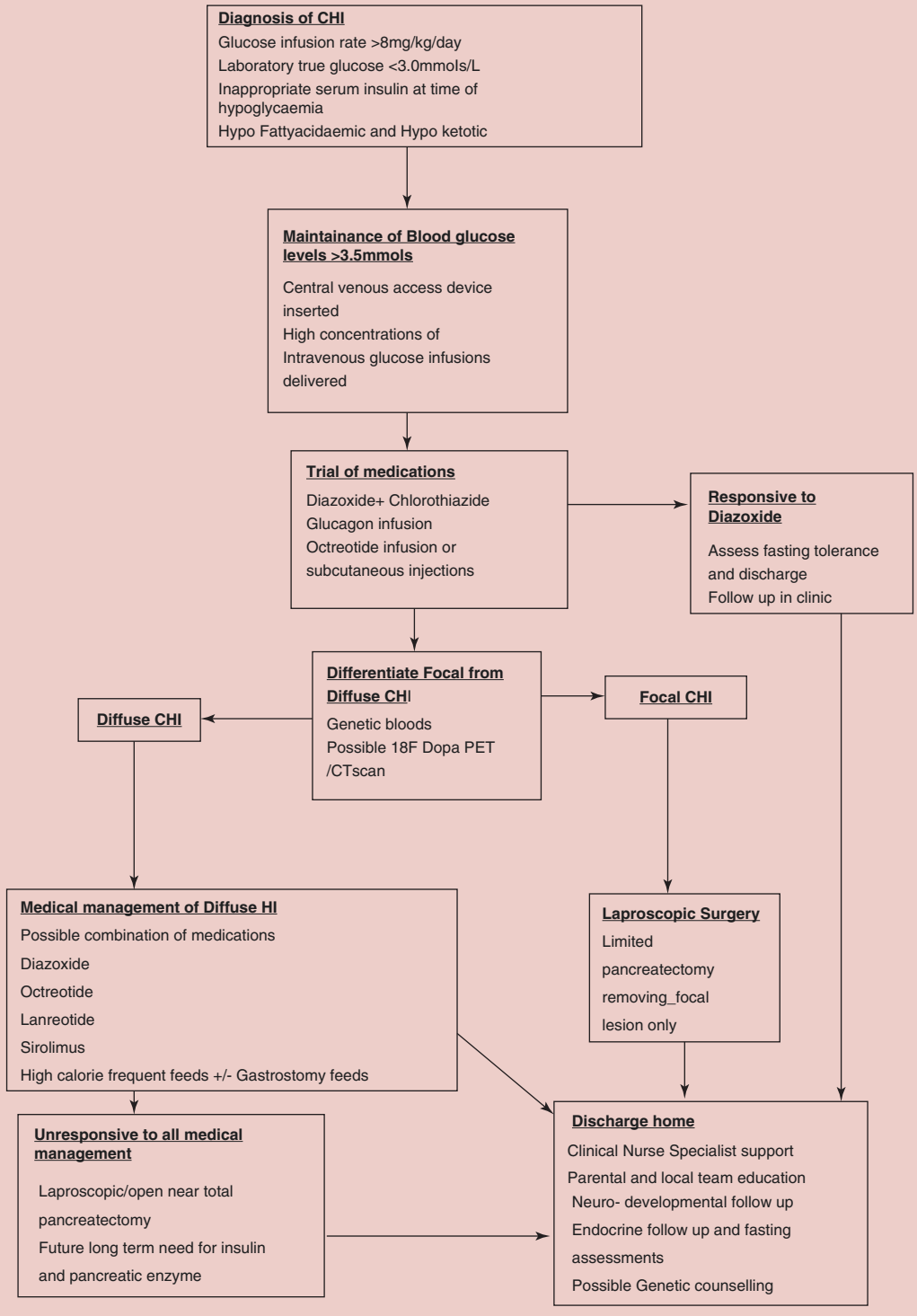

Table 8.4 Example: hypoglycaemia plan for parents

1.	If their blood glucose level is 3.5 mmols or less, re-check after 10 min on an alternative site.
2.	If their blood glucose level is still below 3.5 mmols, give one-third of a Glucogel® tube and a small feed.
3.	Re-check their blood glucose level 10 min later to ensure their blood glucose level has risen.
4.	If they have had a hypo before a feed, give the full feed.
5.	If they continue to be hypoglycaemic and do not respond to Glucogel®, please repeat step 2 and call an ambulance to take them to the nearest hospital for management. This may include insertion of an intravenous cannula and intravenous 10% glucose to stabilize their blood glucose levels especially if they are unwell and unable to tolerate feeds.
6.	If they present to hospital with a hypoglycaemic episode, they should always be admitted to have their blood glucose levels monitored and corrected with intravenous glucose.

Term infants with no risk factors are often difficult to identify due to non-specific symptoms. Parental education to recognize early symptoms of hypoglycaemia would be recommended, and education plans are drawn up and agreed with families (see Table 8.4) and prompt medical advice should be swiftly sought. Blood glucose levels measurements should be of utmost priority for babies presenting to midwives or A&E nurses with non-specific symptoms such as poor feeding and lethargy.

8.12 Neurological Outcomes

In neonates, the treatment of CHI must be diligently and intensively performed to prevent irreversible brain damage (Hussain et al. 2007). Avatapalle et al. (2013) stated that one-third of patients with CHI developed some form of developmental delay. The degree of brain injury can be variable, with some infants developing seizures and global developmental delay, although some may have very subtle problems with memory, which often manifests itself when the children are of school age. Further studies into the long-term neurological consequence of CHI are needed. The importance of the nursing role in identifying these patients with CHI—leading to a swift diagnosis and implementation of a safe management plan—cannot be over emphasized. Ultimately, by preventing hypoglycaemia, possible brain injury is also prevented.

8.13 Advances in Treatments for CHI

Research into the causes and treatment of CHI has recently exploded with advances in molecular genetics and medical therapies, including the recent use of Lanreotide and Sirolimus as treatments. The 18F-DOPA-PET imaging technique has revolutionized the diagnostic approach and accuracy of localizing focal CHI, with research continuing to make great advances in this area. The surgical approach to CHI has now advanced to being predominately laparoscopic. With this continuing research and advancement of knowledge, the aim is always to achieve more favourable outcomes for patients with this condition. The far-reaching objective is always to prevent brain injury for this patient group.

8.14 Conclusions

The purpose of this chapter was to briefly illustrate to Paediatric Nurses the importance of monitoring and managing blood glucose levels. Although CHI is a complex endocrine disorder, the outcome for this patient group is continuously improving with evidence-based knowledge and research. The key message is: early detection and treatment is crucial. Nurses at the bedside play a pivotal role in early identification of infants with CHI, and it is vital for them 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 CHI should be considered (Kapoor et al. 2009b).

8.15 Questions to Consider

1. If the bedside blood glucose monitor indicated hypoglycaemia and the hyposcreen results suggested a diagnosis of CHI but the laboratory

glucose was elevated (7.8 mmols), what could this imply?

- Answer—The laboratory glucose is possibly inaccurate as it may have been taken from the intravenous line and contaminated with glucose.
- *Take home message—always take laboratory glucose from a capillary sample, preventing any risk of contamination*.

2. A student nurse has forgotten to inform you that her patient's intravenous glucose infusion is running out and needs changing. What would your actions be?

- Answer—(1) To check blood glucose level, work out how much time you have left before the infusion runs out. (2) Ensure you have an intravenous correction bolus of 1 mL/kg 10% glucose prescribed along with a new bag of fluids. (3) Urgently discuss with medical team appropriate intravenous fluids for the short term as this is an emergency. (4) Do not leave the patient without intravenous glucose and monitor blood glucose levels very closely to prevent hypoglycaemia.

3. What would you do if your central venous access device was to become dislodged and your intravenous glucose infusion was unable to be delivered?
    - Check blood glucose levels every 5–10 min.
    - Give glucogel in the oral mucosa and assess response.
    - Examine the patient and line. If the infant has a central venous device, try to bleed back on this line using Aseptic Non-Touch Technique and flush to check if the line is patent. If the intravenous line is patent, a 1 mL/kg bolus of 10% glucose should be administered. (An emergency prescription of 1 mL/kg 10% glucose should always be written for an infant at risk of hypoglycaemia). A rise in blood glucose level should be seen within 10 min. Always follow the hypo plan in the patient's notes.
    - If intravenous access is lost, please have two attempts of peripheral cannulation only. If successful, give 1 mL/kg bolus of 10% glucose to correct hypoglycaemia. Then administer infusion of 10% glucose maintenance fluids to prevent rebound hypoglycaemia. (Only 10% glucose can be administered safely via a peripheral cannula. For higher concentrations, central access is required).
    - In the event cannulation is not promptly obtained, then prescribe and give IM glucagon 1 mg stat dose. This will raise the blood glucose level within 10 min releasing the infants own glycogen stores. However, intravenous access must now be obtained as the infant will become hypoglycaemic once the stores of glycogen are utilized. An anaesthetist should be called to aid in cannulation or for reinsertion of a central line as this is now a clinical emergency.

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