SPECIAL ARTICLE

Congenital Hyperinsulinism – Notes for the General Pediatrician

Maria Salomon Estebanez,[1] Chris Worth,[1] Indraneel Banerjee[1,2]

[1]*Department of Pediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, United Kingdom*
[2]*Manchester Academic Health Sciences Center (MAHSC), University of Manchester, Manchester, United Kingdom*

ABSTRACT

Congenital hyperinsulinism (CHI) is a rare condition but is a common cause of severe and persistent hypoglycemia in early life. Prompt recognition of CHI is critical to prevent the impact of neuroglycopenia and consequent lifelong neurodisability. It is important to be alert to the possibility of CHI in newborn babies with recurrent hypoglycemia associated with high glucose requirements. Pediatricians are advised to mitigate the risk of hypoglycemia by early treatment with high concentration dextrose and intravenous glucagon infusions. Specific medical therapies with diazoxide and/or somatostatin receptor analogues may be commenced after the finding of detectable insulin at hypoglycemia, a biochemical characteristic of CHI. Early exploration of genetic etiology is recommended, chiefly in the search for a focal form, amenable to limited pancreatic surgery. Genetic ascertainment is also useful to understand the basis of disease, variable responses to medical therapies and escalation of conservative treatment to subtotal pancreatectomy. CHI is a heterogeneous disorder with varying natural history. Many newborns and infants with CHI have severe and complex illness features; their long-term care is best achieved through review at specialist centers.

Keywords: *β-cells, Hypoglycemia, K-ATP channel, Neonate, Pancreas*

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Congenital Hyperinsulinism (CHI) is a relatively rare disease of hypoglycemia in childhood. Excess and dysregulated insulin production from the pancreas in CHI can cause profound hypoglycemia with resultant brain injury leading to adverse neurodevelopment [1,2]. While hypoglycemia is common in early life, not all etiologies have the same impact as CHI. It is therefore important to identify the possibility of CHI and provide prompt treatment to prevent long-term neurodisability.

Etiology

Insulin production is normally tightly regulated by the circulating glucose levels and mediated by an ATP-sensitive K^+ channel (K-ATP) on the cell membrane of the pancreatic β-cell [3]. In CHI, the glucose-mediated insulin regulation is lost, therefore, insulin production is dysregulated and uninhibited. Patients with mutations in the genes coding for the K-ATP channel (*ABCC8*/*KCNJ11*) release excessive insulin in circulation, regardless of their glycemic status. Several gene mutations have been identified, outside the K-ATP channel but within the insulin production pathway causing similar dysregulated excess insulin release [4,5].

Correspondence to: Professor Indraneel Banerjee, Department of Pediatric Endocrinology, Royal Manchester Children's Hospital, Oxford Road, Manchester, United Kingdom.
indi.banerjee@manchester.ac.uk
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Heterogeneity of CHI

While CHI is considered a genetic disease, genetic etiology is ascertained in only approximately 50% of patients. In the rest, the cause remains uncertain [4]. A significant group of patients develop hyperinsulinism from pregnancy-related stresses such as intra-uterine growth restriction and perinatal hypoxia [6]. Such patients do not have a genetic cause for hyperinsulinism; they are often termed "perinatal stress related hyperinsulinism" to differentiate from persistent and/or genetic forms of CHI. Such hyperinsulinism is often transient, resolving in a few days to a few weeks, although no less severe than genetic forms in its capacity to injure the developing brain. The diagnosis of perinatal stress related hyperinsulinism is made by association of pregnancy related risk factors. The phenotype of severe and persistent hypoglycemia, remains the same as with genetic CHI. Genetic testing is not required for perinatal stress related hyperinsulinism but is advisable for persistent forms of CHI and best undertaken at specialist laboratories with expertise in the interpretation of CHI gene variants.

Although perinatal stress may be transient, the depth and severity of hypoglycemia should not be

underestimated for detrimental effects on the brain. The impact of early life hypoglycemia is not different between transient and persistent forms of CHI, suggesting the need for prompt treatment irrespective of the underlying cause or duration of illness [7].

Hyperinsulinism leads not only to severe hypoglycemia but also reduced ketogenesis. In all forms of CHI, there is a reduction in ketones that serve as alternative brain fuel in the absence of glucose. Therefore, in CHI, there is loss of both primary and alternative neuronal fuels, leading to a high predilection for brain injury [3].

Getting it right

Regardless of the cause or genetic basis of CHI, it is critical to treat hypoglycemia promptly and effectively. A hypoglycemia screening test is advisable to establish the diagnosis of hyperinsulinism [1,2]. **Table I** gives a list of blood tests and associated specific containers for laboratory analysis. The diagnosis is established by the finding of detectable insulin levels at the time of hypoglycemia. The cut-off level of insulin depends on assay sensitivity and performance and is specific to the biochemistry laboratory. In all other forms of hypoglycemia, insulin levels are suppressed, differentiating from CHI. However, it can be difficult to demonstrate hyperinsulinism in some cases, even if CHI is strongly suspected. In such cases, the reader is guided to alternative testing strategies [2]. The blood glucose cut-off for hypoglycemia is contentious but an operational cut-off for investigation at 3.0 mmol/L (54 mg/dL) may be used [1,3], although a lower cut-off level of 2.8 mmol/L (50 mg/dL) has also been advocated [2]. In the first 72 hours of life, newborn babies have relatively low glucose levels as they pass through a phase of metabolic transition. Therefore, investigation may need later repetition if hypoglycemia screening is undertaken in the first two to three days.

A hypoglycemia screen guides the clinician to a probable diagnosis. In the context of severe and recurrent hypoglycemia, with increasing dextrose requirement, CHI is a likely diagnosis. The measurement of a glucose infusion requirement (GIR) is additionally helpful. While normal neonatal GIR is 4-6 mg/kg/min, CHI may be considered if GIR exceeds 8 mg/kg/min and the newborn baby becomes dependent on intravenous dextrose [3]. In addition to a high GIR, the finding of low or absent ketones in blood or urine may be helpful. However, bedside ketone measurement may not be readily available and frequent feeding may suppress ketogenesis, confusing the diagnosis. In contrast to low ketones supporting the diagnosis of hyperinsulinism, robust ketogenesis (exceeding 1.5 mmol/L) [1] is often suggestive of other causes of hypoglycemia.

Most infants require fluid volumes of 90-100 mL/kg/day on day 3-4 of life; a 10% dextrose infusion at 100 mL/kg/day gives a GIR of approximately 7 mg/kg/min. By contrast, a peripherally infused 12.5% dextrose solution suggests a GIR of 8.6 mg/kg/min. Increasing concentrations of dextrose, for example 20% dextrose through a central venous catheter at the same volume suggests a significantly high GIR of 14 mg/kg/min, implying severe CHI.

Although a high GIR suggests CHI, it remains important to document biochemical confirmation of hyperinsulinism. It is also important to exclude suspected neonatal sepsis as a cause of hypoglycemia. If in doubt, the

Table I Hypoglycemia Screening Tests Required to Diagnose Hyperinsulinism or Other Causes of Hypoglycemia

Parameter	*Sample Containers and Methods of Analysis*
Bedside glucose, ketones	Point of Care device
Glucose, Lactate	1 mL fluoride/oxalate
Insulin/C-peptide	1 mL heparinised, to biochemistry lab immediately
3-OH butyrate, Free fatty acids	1 mL heparinised, to biochemistry lab immediately on ice
Liver function test	1 mL heparinised
Acylcarnitines	Blood spot cards (or 1mL heparinised sample)
Ammonia	1mL EDTA (to biochemistry lab immediately, on ice)
Venous blood gas	Capillary tube
Growth hormone, cortisol	2 mL clotted to biochemistry lab
Organic acids, amino acids	5-10 mL in a sterile container; Collect aliquots of all urine passed from beginning of fast till 4 hours after end of fast

Sample containers and methods of analysis are likely to be assay dependent and vary between laboratories. Modestly raised serum ammonia may be associated with defects in glutamate dehydrogenase causing hyperinsulinism.

newborn infant may need to be treated with antibiotics until a blood culture result becomes available.

Once a hypoglycemia screen has been taken, the focus must be to correct hypoglycemia. In the acute phase, a 10% dextrose bolus of 2 mL/kg may be administered intravenously, whilst a maintenance 10% dextrose infusion is set up [1]. Ideally glucose levels should be maintained in the normal range (4-6 mmol/L, 70-108 mg/dL) but this may require significant treatment intensification. While glucose levels below 3.0 mmol/L (54 mg/dL) are likely to be significantly detrimental to the newborn brain, it would be helpful to keep glucose at a level nearer the normal range [3]; a recent consensus defined a safe cut-off at 3.5 mmol/L (63 mg/dL) [1]. It is advisable to keep most blood glucose measurements above this level to minimize the risk of neuroglycopenia. Ideally, glucose levels should be kept in the normal range, i.e. above 4 mmol/L (70 mg/dL) [2], but this may require significant treatment escalation, with consequent risk of treatment related side effects.

As hypoglycemia in CHI is erratic, unpredictable, and severe, frequent blood glucose monitoring, possibly 1-2 hourly, by point-of-care glucometer devices might be required during the acute inpatient phase. Alternatively high frequency subcutaneous continuous glucose monitoring (CGM) devices are increasingly used in neonatal units, but point accuracy is suboptimal [8]. Therefore, the use of CGM in neonatal units should be assisted by heel prick blood glucose testing, particularly when glucose levels are at or below 3.5 mmol/L (63 mg/dL).

Focus on treatment of hypoglycemia

To keep the focus on normalizing glucose levels, greater dextrose volumes or concentrations may be required. A central venous catheter, for example an umbilical venous line, may be required, failing which, a peripheral long line or a surgical central venous catheter may need to be planned. It is tempting to simply increase the volume of 10% dextrose administered by a peripheral line; however, this increases fluid volume and the propensity for right heart failure and pulmonary oedema. This is particularly important as diazoxide, the first line definitive treatment for CHI, may cause fluid overload and increase the risk of pulmonary hypertension [9].

Intravenous glucagon administered by continuous infusion is helpful to reduce dextrose dependence and the risk of volume overload prior to treatment with diazoxide [10]. Glucagon is a counter-regulatory hormone that stimulates hepatic production of glucose from glycogen and has a paracrine effect on pancreatic β-cells. Glucagon can be mixed in 0.9% saline or 5% dextrose and administered slowly using small volumes (10-20 mL in 24 hours). It is not advisable to mix glucagon in higher concentrations of dextrose as this encourages drug fibrillation and precipitation within intravenous tubing.

Glucagon can be started at a dose of 5 mcg/kg/hour, escalating incrementally to 20 mcg/kg/hour to achieve normal glucose levels [1]. Some centers dilute 1.0 mg glucagon in the same volume and run over 24 hours [11]. For a 4.0 kg infant, this gives a glucagon rate of 10 mcg/kg/hour. Fixed dose glucagon administration has the advantage of simplicity and minimizing medication errors.

Glucagon is well tolerated and reduces side effects from excessive fluid intake. As the standard formulation of glucagon fibrillates readily, infusion sets need to be changed every 24 hours. Long-term intravenous glucagon is not sustainable but soluble analogues in clinical trial could be given by continuous subcutaneous infusions at home, in the near future [12]. In the neonatal unit, side effects from glucagon are minimal; however, high doses of glucagon over prolonged periods may cause necrolytic migratory erythema (NME) of the skin, for which treatment must be stopped [3].

Medical therapies

Once a biochemical diagnosis of CHI is achieved, diazoxide may be started as oral therapy. Diazoxide maintains the K-ATP channel in the open state, which ensures β-cell stability and reduction in insulin secretion (in contrast to the closed state which causes membrane instability) [13]. The action of diazoxide is dependent on the integrity of the K-ATP channel; in gene mutations affecting the channel, diazoxide is rarely effective.

The starting dose of diazoxide is generally 3-5 mg/kg/day in three divided doses, with lower doses being used for small preterm infants and those born small for gestational age. The effect of diazoxide is usually apparent 24-48 hours after commencing treatment. Diazoxide is generally effective for mutations outside the K-ATP channel and in those without a known genetic cause. However, diazoxide has several side effects, for which vigilance is required. Diazoxide has vascular effects and increases the risk of fluid accumulation (which can be reduced by the concomitant use of chlorothiazide in a dose of 7-15 mg/kg/day in two divided doses). Some CHI patients may have existing cardiac defects [14] and may be predisposed to pulmonary hypertension [9]; therefore, baseline echocardiography prior to diazoxide treatment is recommended.

Diazoxide is usually prescribed as a liquid formulation for newborn infants. Several formulations, including those prepared as "specials" are available, but for assurance of quality control, the use of diazoxide preparations recognized by the US Food and Drugs Administration

(FDA) is advisable. In the Indian context, liquid preparations are not available and therefore tablets and capsules have to be used as alternatives.

Most CHI patients who respond to diazoxide do so at low doses. Dose may be escalated in aliquots of 2.5 mg/kg/day every 2 days if dose response is inadequate. If dose requirement is greater than 10 mg/kg/day, it is likely that the patient is diazoxide unresponsive. Nonetheless, dose could be further escalated to 15 mg/kg/day with a review of the fasting interval before concluding diazoxide unresponsiveness [3].

Once glucose levels stabilize in diazoxide-responsive patients, intravenous dextrose and glucagon may be reduced. The choice to reduce either agent depends on individual circumstances and clinician choice. The goal is to transition the newborn infant to milk feeds and diazoxide (and chlorothiazide) with a plan for discharge from the hospital. Prior to this, a safety fast is advised. The duration of the fast depends on local protocols. Generally, newborn infants feed 3-4 hourly through the day, so a fasting period of 6-8 hours, to demonstrate stability without hypoglycemia, is desirable. This fast provides reassurance that missing an overnight feed is well tolerated, whilst on diazoxide. Some centers advocate a longer fast to test true diazoxide responsiveness and robust ketogenesis. However, if infants are responsive to modest doses of diazoxide, a longer fast is not required.

It is expected that parents will continue home glucose monitoring to ensure glucose stability after discharge. Therefore, parents need to be trained in glucose monitoring using a glucometer. If infants require nasogastric tube feeding, they should be taught to insert and check a tube. Follow-up for those on diazoxide treatment depends on local arrangements for monitoring and review. Ideally, this can be undertaken in two weeks by virtual or in-person appointments to ensure no recurrence of hypoglycemia, absence of hyperglycemia and no undue side effects from diazoxide, including facial swelling and/or abnormal breathing.

Newborn infants with transient CHI, such as those with perinatal stress, often demonstrate rising glucose levels as hyperinsulinism resolves. In such cases, a stepped reduction of diazoxide (and chlorothiazide) is necessary. Diazoxide may be progressively reduced and stopped whilst continuing home monitoring. For CHI resolving 4-8 weeks after discharge, a further fast is not required, unless there is doubt about resolution. For patients on prolonged diazoxide (> 1 year) but resolving over time, an age-appropriate fast (**Table II**) [15] to demonstrate stable glucose levels and a ketone rise to > 1.5 mmol/L is recommended [1]. For patients with resolution of CHI between 8 and 52 weeks, clinicians may choose to undertake a fast, considering individual circumstances.

Long-term use of diazoxide is often associated with excess body hair [3,16]. This side effect is less pronounced with lower doses. Once diazoxide is stopped, body hair reduces after several weeks. While excess body hair may not be significant in small children, it can be perceived as a problem for older children. Prolonged diazoxide use is also associated with coarsening of facial features and widening of the nasal bridge, such that children on diazoxide resemble one another facially. The cause for bone changes is likely to be vascular in origin. Diazoxide can be associated with other side effects, such as neutropenia and thrombocytopenia, more likely in the early neonatal phase. Necrotizing enterocolitis has also been attributed to diazoxide in the newborn period. Therefore, a range of blood tests (blood counts, renal function, liver function) are required both at diagnosis and in follow up (**Table III**) [1]. Diazoxide may increase serum uric acid levels without symptoms; therefore, measurement of urate is additionally reassuring for monitoring.

If a patient has mutations in the K-ATP channel, it is unlikely that diazoxide will be effective. If a patient is diazoxide unresponsive (persistent hypoglycemia and short fasting tolerance), second line treatment with a somatostatin analogue (SSA) is required. Octreotide is a short acting SSA, with action on cAMP mediated reduction in insulin secretion in the pancreatic β-cell [17]. Octreotide is a non-specific analogue and has action across other organs, including the splanchnic vascular bed. Thus, while octreotide reduces insulin induced hypoglycemia, it may cause unacceptable side effects such as hepatitis, necrotizing enterocolitis, gall stones and feeding problems. It is best that octreotide treatment is undertaken in specialized centers, starting at a low dose (5 mcg/kg/day) in 4-6 divided doses (subcutaneous or intravenous injections) and escalating to a maximum of 30 mcg/kg/day

Table II Age-appropriate Fast Duration

Age	*< 6 months*	*6-8 months*	*8-12 months*	*1-2 years*	*2-7 years*	*> 7 years*
Duration	8 hours	12 hours	16 hours	18 hours	20 hours	24 hours

Fast duration can vary according to local guidelines and preferences. An example used by the Pediatric Endocrinology and Metabolic Teams in Manchester is provided.

Table III Commonly Used Medications Used in the Conservative Treatment of Congenital Hyperinsulinism (CHI)

Drug	*Dose*	*Monitoring*	*Side effects*
Diazoxide	Initial 3-5 mg/kg/day in 3 divided doses, increased to 15 mg/kg/day	Pre-treatment: Echocardiography and fluid restriction (150 ml/kg/day) 4-6 monthly: Serum electrolytes, blood count, uric acid	Fluid retention, pulmonary hypertension, necrotising enterocolitis (NEC), neutropenia, thrombo-cytopenia, hypertrichosis
Chlorothiazide	Initial 7 mg/kg/day in 2 divided doses	Serum electrolytes	Hyponatremia, hypokalemia
Glucagon	5-20 mcg/kg/hr(start at 5.0 mcg/kg/hr)	Glucose monitoring; infusion set to be changed at least every 24 hours	Intravenous line occlusion, necrolytic migratory erythema
Octreotide	5-30 mcg/kg/day, usually given 6 hourly by subcutaneous injection	Liver ultrasound, liver function test, thyroid function test	NEC, biliary sludge, growth faltering, gastrointestinal dysmotility, cholelithiasis, pituitary hormone suppression

if treatment is ineffective (**Table III**). The initial glucose response with octreotide may be generous but transient, necessitating dose escalation after 24-48 hours.

Long-acting SSA such as somatuline autogel and octreotide long-acting release preparations are available and may be used by specialists [18]. However, the treatment benefit over octreotide (as subcutaneous bolus injections/continuous subcutaneous infusions) has not been clarified and treatment remains off-label. Some centers choose therapies such as long-acting SSA or more experimental therapies such as sirolimus, but they are best undertaken by specialists with experience in CHI who are fully cognizant of the range of side effects [19].

While standard glucagon formulations are designed for intramuscular bolus injections and not suitable for use as subcutaneous continuous infusions, novel soluble glucagon analogues like dasiglucagon have been tested in clinical trials with good evidence of benefit [12]. It is expected that dasiglucagon as licensed medication will change treatment paradigms replacing octreotide as second line therapy.

Surgical treatment

Most children with CHI have diffuse hyperfunctioning islets throughout the pancreas. Diffuse CHI is typically associated with autosomal dominant or recessive (compound heterozygous/homozygous) mutations in *ABCC8*/*KCNJ11*. Here, first line treatment is medical, but subtotal pancreatectomy (leaving approximately 5% residual pancreas) may be required to reduce hypoglycemia. Despite this extensive resection, 30-50% of patients continue to have persistent hypoglycemia even after surgery [20]. Most patients become hyperglycemic over time and insulin-dependent during their teenage years [21]. Subtotal pancreatectomy is also associated with exocrine pancreatic insufficiency, the onset of which is variable. Treatment is with pancreatic enzyme supplements several times a day.

In contrast to diffuse CHI, surgical treatment to remove a focal lesion is first line treatment for focal CHI, where a solitary part of the pancreas is affected, the rest being normal [22]. Focal lesions arise typically with a combination of a paternally inherited *ABCC8*/*KCNJ11* mutation with corresponding suppression of maternal alleles and are detected by 18 fluoro-dopa PET CT/MR scanning, best undertaken at specialist centers with expertise in CHI [1,3].

Other forms of hyperinsulinism

Although CHI is most commonly a disease in newborn infants, in about 10% of individuals, hypoglycemia can be of late onset, after 12 months of life, including those with monogenic causes [23]. It is possible these children have missed hypoglycemia with suboptimal intellectual developmental abilities [24]. It is important to recognize the possibility of late-onset CHI, for example with mutations in glucokinase (*GCK*). On rare occasions, older children presenting with hypoglycemia may have insulinomas.

The treatment of late-onset CHI is like that of early-onset hypoglycemia. Treatment response with diazoxide may be less marked than in those with early onset, for instance in those with GCK-CHI. It is important to investigate for insulinoma if genetic CHI has been excluded, to plan for surgery.

CHI can also occur with syndromes, for example the Beckwith Wiedemann syndrome (BWS). In most cases, hypoglycemia manifests in the newborn period and is responsive to diazoxide. However, some patients with paternal uniparental disomy BWS may be unresponsive to standard medical therapy and may require pancreatectomy [25].

Rarely, CHI may be misdiagnosed by biochemical testing in fabricated illness prompted by exogenous insulin administration [26]. Such cases are suspected by the finding of a high insulin alongside a suppressed serum C-peptide level.

Managing complex care

It is important to recognize the variability and complexity in patient phenotype, response to treatment and significant burden of care on families [27]. It is expected that initial diagnosis and management of CHI will be undertaken by general pediatricians and neonatologists; however, it would be good practice to involve specialist centers if requiring treatment escalation, e.g., higher doses of diazoxide, need for high concentration dextrose or unusual side effects. Some patients with resolving CHI do not usually require long-term follow-up arrangements, but most with genetic etiology require careful monitoring, review of medications and their side effects. Specialist CHI centers should be identified for long-term care, particularly for pancreatic imaging and surgery, in networked arrangements with peripheral hospitals, providing safe, accessible and effective care [1].

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