Congenital hyperinsulinism (CHI) comprises a group of disorders characterized by excessive insulin secretion from pancreatic β-cells, resulting in severe hypoglycemia. In neonates and infants, CHI is considered the most frequent cause of persistent hypoglycemia. Prompt diagnosis and treatment are crucial as a delay may cause severe brain damage and long-term neurodevelopmental disability. Therapeutic strategies for CHI can be medical, surgical, or combined.

**Keywords**

Congenital hyperinsulinism • Transient hyperinsulinism • Persistent hyperinsulinism • Hypoglycemia • Pancreatectomy

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**Introduction**

Congenital hyperinsulinism (CHI) represents a group of disorders characterized by excessive insulin secretion from pancreatic β-cells, which results in severe hypoglycemia. In the past, the same condition was named in several ways: nesidioblastosis, islet cell adenomatosis, beta cell dysregulation syndrome or dysmaturation syndrome, or persistent hyperinsulinemic hypoglycemia of infancy (PHHI).

**Epidemiology, and Types**

CHI is considered the most frequent cause of persistent hypoglycemia in neonates and infants. The estimated incidence is 1 in 50,000 live births, but it can be as frequent as 1 in 500 in countries with a high rate of consanguinity, such as Saudi Arabia.

CHI can present in different ways. The main distinction to make is whether it is a transient or a persistent phenomenon. *Transient hyperinsulinism* is caused mainly by nongenetic factors, such
as perinatal stress or small size for gestational age. However, some neonates, usually macrosomic, have transient CHI due to mono-allelic inactivating mutation of hepatocyte nuclear factor 4α (HNF4A) (Kapoor et al. 2008). Later in life, some of these patients may develop maturity-onset diabetes of the young type 1 (MODY1) and therefore should be followed up after resolution of CHI.

Conversely, most cases of persistent hyperinsulinism have recognized genetic etiologies (Yorifuji 2014; Rozenkova et al. 2015). The genetic forms are caused by recessive or dominant mutations of regulatory genes for glucose metabolism and insulin secretion. The main genes involved are ABCC8 and KCNJ11 genes, which encode for subunits (SUR1 and KIR6.2) of the ATP-sensitive K+ (KATP) channel (Nessa et al. 2016; Stanley 2016). Recessive inactivating mutations in ABCC8 or KCNJ11 cause continuous β-cell membrane depolarization and subsequent calcium influx, which result in unregulated insulin secretion. Dominant inactivating mutations in the same genes cause a milder form of CHI. Other genes implicated in rarer forms of CHI are those that regulate insulin secretion from the pancreatic β-cells, such as GLUD1 (encoding the enzyme glutamate dehydrogenase), GCK (encoding the enzyme glucokinase), HADH (encoding the L-3-hydroxyacyl-coenzyme A dehydrogenase), UCP2 (encoding the uncoupling protein2), and SLC16A1 (encoding the monocarboxylate transporter 1) (Nessa et al. 2016; Stanley 2016).

**Histology**

CHI can be classified into three histological variants: diffuse, focal, and atypical.

**Focal forms**, which are typically sporadic in inheritance, are restricted to a small area of the pancreas (2.5–7.5 mm), where β-cells have a large cytoplasm and abnormal nuclei of irregular shape. Within the focal lesion several abnormal lobules are interspersed with acinar foci, and a second endocrine-cell population can be detected. These features are representative of an abnormal developmental process rather than a tumorigenic process. Around the main focal lesion there could be satellite areas of abnormal pancreatic tissue. Therefore, clear resection margins are crucial to avoid recurrence.

**Diffuse forms**, which are typically inherited in an autosomal recessive or dominant manner, involve every β-cells throughout the whole pancreas with variable involvement of the islets. The islet pattern is preserved but contains active β-cells with abundant cytoplasm and abnormal nuclei.

**Atypical forms** are not well defined. The pancreas presents a diffuse CHI pattern in one large area, but the rest of the organ is histologically normal. Some forms are due to chromosomal mosaics, but their genetic basis has not been fully elucidated.

**Diagnosis**

The inappropriate insulin secretion that is seen in CHI results in increased glucose consumption, inhibition of glycogenolysis and gluconeogenesis, and ultimately hypoglycemia (Ferrara et al. 2016). This puts the brain at severe risk of injury, due to the suppression of ketone body production, i.e., its alternative energy substrate, secondary to insulin-induced inhibition of lipolysis and free fatty acid production. Expedite diagnosis is crucial to avoid complication.

The diagnostic criteria for CHI include the following:

- Fasting and/or postprandial hypoglycemia (<2.5–3 mmol/L).
- Inappropriate plasma insulin and C-peptide levels concomitant to hypoglycemia.
- Increased blood glucose levels (>1.7 mmol/L or 30 mg/dL) within 30–40 min following glucagon administration. This is important for the differential diagnosis with glycogen storage disease.
- Inappropriately low plasma and urine ketone bodies and low plasma free fatty acids for fasting hypoglycemia.
Infants with CHI have a fasting tolerance of less than 1 h, so that they require continuous intravenous glucose infusion at more than 8 mg/kg/min to maintain normal glycemic levels (normal: 4–6 mg/kg/min).

**Treatment**

It is crucial to make a prompt diagnosis and institute immediate treatment since delay in managing CHI can cause severe brain damage and long-term neurodevelopmental disability (Lord et al. 2015). It is essential to insert a central venous catheter to monitor blood glucose levels and to provide a reliable route for intravenous glucose administration. The goal of therapy is to achieve normal blood glucose levels, considered as >63 mg/dl or >3.5 mmol/L and to inhibit inappropriate insulin secretion.

Therapeutic strategies can be medical, surgical, or combined (Arnoux et al. 2011).

**Medical Treatment**

In the emergency setting, e.g., in case of seizures, the infant should receive an intravenous bolus of 2 ml/kg of 10% glucose, followed by a glucose infusion at >6–8 mg/kg/min. In absence of intravenous access, intramuscular glucagon may also be administered, in order to stimulate glycogenolysis and glucose release from the liver. Patients will also be started on continuous or frequent feeding regime.

Drug treatment includes diazoxide with chlorothiazide, nifedipine, octreotide, and new medicines such as long-acting octreotide.

*Diazoxide* is an inhibitor of insulin secretion, and it is used in all types of CHI. Diazoxide binds to the SUR1 subunit of KATP channel, which activates intact KATP channels and reduces insulin secretion. However, patients with diffuse CHI secondary to ABCC8 or KCNJ11 mutation and those with focal lesions are unresponsive to diazoxide, as they have no intact KATP channels. Diazoxide can cause fluid retention, which can be so severe to result in congestive heart failure especially in neonates. For this reason, chlorothiazide, a thiazide diuretic, is used in combination also thanks to its synergistic effect on insulin secretion suppression.

*Nifedipine* is a calcium channel blocker, which inhibits insulin secretion by inactivation of voltage-gated calcium channels.

*Octreotide* is a long-acting analogue of somatostatin, which naturally inhibits the insulin release from the pancreatic β-cells. Octreotide activates the somatostatin receptor 5 (SSTR5), thus inhibiting calcium mobilization and acetylcholine activity, and decreases insulin gene promoter activity, which reduces insulin biosynthesis and insulin secretion.

**Surgical Treatment**

Indication for surgery is the failure to respond to intensive medical treatment. Surgical procedures and approaches vary according to whether the patient has focal or diffuse CHI (Pierro and Nah 2011).

**Diffuse CHI**

When the whole pancreatic tissue is affected, the gold standard operation is to resect the majority of it (95%), carrying out a “near-total” pancreatectomy in order to prevent recurrent hyperinsulinemia. In near-total pancreatectomy, the tail, body, uncinate process, and part of pancreatic head are resected, leaving a rim of pancreatic tissue surrounding the common bile duct and along the duodenum. In refractory cases, a 98% pancreatectomy is performed, and only small islands of tissue are left along the pancreatico-duodenal arcade bordering the duodenum. A “near-total” pancreatectomy can be performed with an open or laparoscopic approach.

**Open Near-Total Pancreatectomy**

The abdomen is accessed via a transverse supraumbilical incision. The lesser sac is entered through the gastrocolic omentum; kocherization of the duodenum allows full exposure of the pancreas. The tail of the pancreas is sent for intraoperative frozen section histology, and the
diagnosis of diffuse CHI is confirmed before proceeding with pancreatectomy. A stay suture is placed in the tail of the pancreas to allow traction of the pancreas facilitating its dissection because direct handling of the pancreas results in fracture of this friable organ. The tail of the pancreas is carefully dissected away from the hilum of the spleen, and the short pancreatic vessels are coagulated. Dissection of the pancreas is carried out in a medial direction toward the head of the pancreas.

Pancreatic vessels passing from the splenic vessels into the pancreas are coagulated and divided using bipolar diathermy. Meticulous care is taken with the splenic artery and vein, which are closely related to the pancreas, as the spleen should be preserved. Once dissection has arrived at the superior mesenteric vessels, the uncinate process is mobilized. A sling may be placed around the superior mesenteric vessels, retracting them away from the uncinate process. As the head of pancreas is approached, attention is directed to identifying the course of the common bile duct. A sling is placed around the bile duct superior to the first part of the duodenum. A blunt forceps is then passed from within the C-loop of the duodenum behind the first part of the duodenum to grasp the sling, bringing it out superior to the head of pancreas. This becomes the guide to the position of the common bile duct during subsequent dissection of the pancreas. The head of the pancreas is mobilized, and the superior and inferior pancreaticoduodenal vessels are divided. The pancreatic duct is ligated with nonabsorbable sutures and divided. A rim of pancreatic tissue surrounding the common bile duct and along the duodenum is left remaining after near-total pancreatectomy (Fig. 1). The abdomen is closed in layers using absorbable sutures. Postoperatively, the patient has both nasogastric tube and bladder catheter. Enteral feeds are restarted after the gastrointestinal function has returned.

**Laparoscopic Near-Total Pancreatectomy**

An umbilical 10-mm Hasson port is inserted by an open technique, and a 5-mm 30° camera is introduced. Three additional ports are placed: a 5-mm port in the left lower quadrant, a Nathanson retractor at the epigastrium, and a further working port (3 or 5 mm) in the right flank. The gastrocolic omentum is divided, and the lesser sac is entered. The Nathanson retractor is used to retract the stomach. The head of the patient is elevated. A stay suture is inserted into the tail of the pancreas, which is used to retract the pancreas superiorly. Dissection of the pancreas proceeds toward the head. The short pancreatic vessels passing from the splenic vessels into the pancreas are divided using a 3-mm hook diathermy at very high coagulation settings. These vessels are the most common source of intraoperative hemorrhage, which may be controlled by applying gentle pressure using an atraumatic bowel grasper. The pancreatic tail is transected using the Harmonic scalpel (Ethicon Endo-Surgery). The pancreatic tail is removed via the umbilical 10 mm port and sent for frozen section analysis to confirm the diagnosis of diffuse CHI. No further resection takes place until this confirmation has been obtained. Subsequent dissection is facilitated by the insertion of a stay suture at the cut surface of the remaining

![Fig. 1 Near-total pancreatectomy. The grey area indicates the resected pancreas, leaving behind an amount of pancreatic tissue around the common bile duct and along the medial border of the duodenum](image-url)
pancreas, which is resected in segments of approximately 2 cm. As dissection nears the head of the pancreas, stay sutures are placed in the uncinate process and the head of pancreas, which are retracted superiorly. A near-total pancreatectomy is achieved by leaving an adequate amount of pancreatic tissue along the medial border of the duodenum where the common bile duct is expected (Fig. 1). Port sites are closed using absorbable sutures. No drains are used.

**Focal CHI**

In patients with focal CHI, a localized resection of the focal lesion is curative. The diagnosis of focal CHI and its localization is made using fluorine-18-L-3,4-dihydroxyphenylalanine positron emission tomography (18F-DOPA-PET) scan (Shah et al. 2014; Zani et al. 2011). This imaging technique allows an accurate differentiation between focal and diffuse forms and, in case of focal CHI, helps the localization of the lesions that are usually deep in the parenchyma and hardly visible macroscopically. Although the accuracy of localization in 18F-DOPA-PET-CT scan is approximately in 70% of cases, this imaging technique is beneficial for the preoperative surgical planning: in focal lesions of the head or neck of the pancreas, open resection of the lesion with a small rim of surrounding normal pancreatic tissue is carried out, and pancreaticojejunostomy is performed to allow drainage of the distal pancreas. In distal focal lesions, a distal pancreatectomy may be done laparoscopically.

**Surgery for Focal CHI**

The abdomen is accessed laparoscopically as described above.

The pancreas is inspected for a nodular area, which indicates the site of the focal lesion. In focal CHI, the lesion is often deep within the parenchyma of the pancreas and may not be visually evident. An intraoperative biopsy is performed for frozen section histologic examination. Histology may reveal the following: (1) the presence of the focal lesion completely resected (normal pancreas at the resection margin), (2) focal lesion not completely resected, and (3) the presence of normal pancreas excluding the presence of diffuse CHI and indicating that the focal lesion has not yet been excised.

**Focal Lesion in Head or Neck of Pancreas**

When the focal lesion is deep in the head or neck of the pancreas, the procedure may be converted to open, and dissection of the head of the pancreas is commenced (Fig. 2a). Superficial lesions may be enucleated laparoscopically.

A sling may be passed behind the neck of the pancreas to facilitate traction of the pancreas away from the pancreatic bed. Short pancreatic vessels are meticulously ligated using bipolar diathermy and divided. The head of the pancreas is dissected in the direction of the duodenum, carefully avoiding the common bile duct. A pancreaticojejunostomy is then constructed to allow drainage of the distal pancreas.

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**Fig. 2** Focal CHI.
(a) Lesion in the head or neck of pancreas (zone A: white area). Surgery: open excision of focal lesion and pancreaticojejunostomy. (b) Lesion in the body or tail of pancreas (zone B: grey area). Surgery: laparoscopic or open distal pancreatectomy
Focal Lesion in Body or Tail of Pancreas

In more distal lesions, the entire procedure may be completed either laparoscopically or open (Fig. 2b). Once histologic confirmation of focal disease is obtained, the pancreas is dissected as described previously. Dissection is performed until the resected specimen includes the lesion. The pancreas is transected with the Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH). An adequate resection margin is confirmed by further frozen section analysis. There is no need for drains.

Postoperative Management

Enteral feeds are recommenced as early as the first postoperative day and gradually advanced, reducing the intravenous infusion of dextrose. It is not unusual to observe a period of gastroparesis, particularly after excision of the head of the pancreas for focal lesions or near-total pancreatectomy for diffuse CHI. This may last 2–3 days. The management of postoperative hypoglycemia may require medical treatment. However, this is usually transient. Further resection of the pancreas is needed when bolus enteral feeding and cessation of continuous intravenous glucose are not achieved.

Conclusion and Future Directions

Congenital hyperinsulinism represents a group of disorders with heterogeneous incidence. Early diagnosis and treatment are fundamental as delay can cause brain damage and impair long-term neurodevelopment. As low or undetectable insulin levels do not exclude the diagnosis of hyperinsulinism, biomarkers such as C-peptide and insulin-like growth factor binding protein-1 may help to confirm the diagnosis (Ferrara et al. 2016).

Besides surgical treatment, interdisciplinary management of CHI together with pediatricians and dieticians is advisable to assure careful glucose/insulin balance and optimal long-term drug treatment. The treating pediatric surgeon should be aware that patients who underwent near-total pancreatectomy have a high risk of developing diabetes (Lord et al. 2015).

Cross-References

▶ Clinical Genetics
▶ Nutrition
▶ Pancreatic Disorders

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