Chapter

26 Congenital Hyperinsulinism and Pancreatectomy

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An 18-day-old 4.3 kg female was admitted for evaluation of persistent hypoglycemia. The patient was born full term at 37 weeks 2/7 days. At one hour of life, the patient was listless and tremulous. Point of care glucose was noted to be <25 and the patient was treated and transferred to the NICU on a 20% dextrose infusion. Vital signs: Temp 37.2°C, RR 63, HR 138, BP 76/34.

What Is the Differential Diagnosis for Neonatal Hypoglycemia?

- Acquired hyperinsulinism from diabetic mother
- Beckwith–Wiedemann syndrome
- Congenital hyperinsulinism
- Fatty acid oxidation disorders
- Glycogen storage disease
- Growth hormone deficiency
- Hypopituitarism
- Inborn errors of metabolism
- Ketotic hypoglycemia
- Primary or central adrenal insufficiency
- Type 1 diabetes mellitus
- Exogenous insulin administration or other antidiabetic agents
- Administration of beta blockers

What Are the Clinical Characteristics of Neonatal Hypoglycemia?

Hypoglycemia in newborns or young infants may be characterized by lethargy, feeding difficulty, hypothermia, sweating, respiratory distress, cyanosis, or apnea. However, seizures are often the presenting symptom.

What Is Congenital Hyperinsulinism?

Congenital hyperinsulinism (HI) is the most common hypoglycemic disorder in infants. It is a heterogeneous disorder of the pancreas consisting of two main types of histologic abnormalities of pancreatic structure: focal adenomatous hyperplasia and diffuse abnormality of the islet cells.

HI results from inappropriately high insulin secretion by the pancreatic B-cells. A failure to reduce pancreatic insulin secretion in the presence of hypoglycemia (serum glucose <60 mg/dL) is caused by structural or functional molecular abnormalities in the insulin secretory mechanism or glucose-sensing mechanism.

Increased insulin levels cause hepatic and skeletal muscle glycogenesis. Glycogenesis decreases the amount of free glucose in the bloodstream causing a suppression of free fatty acids (FFA) formation resulting in hypoglycemia.

What Is the Genetic Component of HI?

The congenital pancreatic abnormalities associated with HI are caused by genetic mutations on various genes that regulate insulin secretion. Although approximately 50% of HI cases have no known genetic abnormality, 11 genes have been identified in relation to pancreatic beta cells involved in insulin secretion regulation. The most common cause of HI is inactivating mutations in ABCC8 or KCNJ11 genes of the Na^+/K^+ ATP channel.

What Are the Two Types of HI?

There are two forms of HI, diffuse and focal. In diffuse HI, beta cells throughout the pancreas are affected, with nucleomegaly seen through the pancreas. In focal HI, a distinct area of beta cell adenomatosis is seen. Focal HI involves the combination of

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paternally inherited ABCC8 or KCN11 mutations along with the somatic loss of the maternal tumor suppressor genes on chromosome 11p 15.

What Is the Incidence of HI?

The estimated incidence of HI is 1/50,000 live births. However, in countries with substantial consanguinity incidences may be as high as 1/25,000.

What Is the Age of Presentation?

HI can present between birth and 18 months of age, with most cases diagnosed shortly after birth. Although rare, adult-onset cases have been documented.

What Is the Presentation of HI?

Patients present with hypoglycemia ranging from asymptomatic hypoglycemia noted on routine blood glucose monitoring, to life-threatening hypoglycemic coma or status epilepticus. Many are diagnosed by routine blood work, while others are diagnosed later when they present with hypoglycemia symptoms. The risk of severe hypoglycemia causing seizures and permanent brain damage is high. Some infants may be large for gestational age.

How Is the Diagnosis of HI Made?

Diagnostic criteria for HI include blood glucose $<$40 mg/dL, +/− detectable insulin, decrease in beta-hydroxybutyrate, decrease in free fatty acids, decrease in IGF-BP1, and positive glucagon response.

How Is Congenital Hyperinsulinism Managed?

First-line treatment is diazoxide, a benzothiazine derivative, which activates the SUR 1 subunit of the K^+/ATP channel and opens the K/$^+$ATP channel leading to a decrease in insulin. Diazoxide dose range is 5–15 mg/kg/day given orally twice a day. Side effects include hypertrichosis and fluid retention. Many neonates require diuretic therapy along with diazoxide. Pulmonary hypertension may occur in patients without adequate diuretic therapy.

Diazoxide is given as a 5-day trial (Figure 26.1). If diazoxide is not successful in maintaining a blood glucose $>$70 mg/dL during a 12 hour fast, it may suggest that the patient has a defect on the K^+ ATP channel. A genetic workup should be initiated immediately.

If diazoxide is stopped, then IV dextrose with/without glucagon infusion is started to maintain blood glucose $>$70 mg/dL. Blood glucose, vital signs, and mental status should be assessed regularly.

A second-line agent for managing HI is the somatostatin analog octreotide, which acts on the somatostatin receptors by inhibiting the secretion of a variety of hormones including insulin. Insulin secretion is decreased through beta cell hyperpolarization and calcium channel inhibition.

Glucagon, a polypeptide hormone secreted by the alpha cells of the pancreatic islets, triggers glycogenolysis and gluconeogenesis to increase hepatic glucose output. HI patients generally have an inappropriate rise in blood glucose due to the mobilization of hepatic glycogen by glucagon. Glucagon can be used as a rescue medication for acute or severe hypoglycemia.

What If Medical Management Is Ineffective?

If the patient fails to respond to the maximum dose of diazoxide (15 mg/kg/day) after five days of treatment, a K^+ ATP channel defect is suspected as the cause of hyperinsulinism. These children are potential surgical candidates and require referral to a specialized HI center to undergo an 18–fluorol-3, 4-dihydroxphenylalanine positron emission tomography (18-F-Dopa PET) scan.

18 [F]–Dopa, an analog of L-Dopa, is a dopamine precursor and is used as a positron emitting compound. In the pancreas, normal islet cells take up a small amount of 18 F-DOPA and decarboxylate it to produce insulin. The uptake of the tracer in hyperfunctioning islets can be quite pronounced. 18 F-DOPA uptake in diffuse HI is uniform, whereas in focal HI the uptake is greater in a specific region compared to the surrounding tissue. 18 F-DOPA PET scans diagnose 75% of focal cases and are 100% accurate in identifying the location of the lesion (Figure 26.2).

What Is the Surgical Management for Congenital HI?

If medical management is ineffective a focal (partial) or diffuse (sub-total) pancreatectomy is indicated. The extent of the pancreatic resection depends on the

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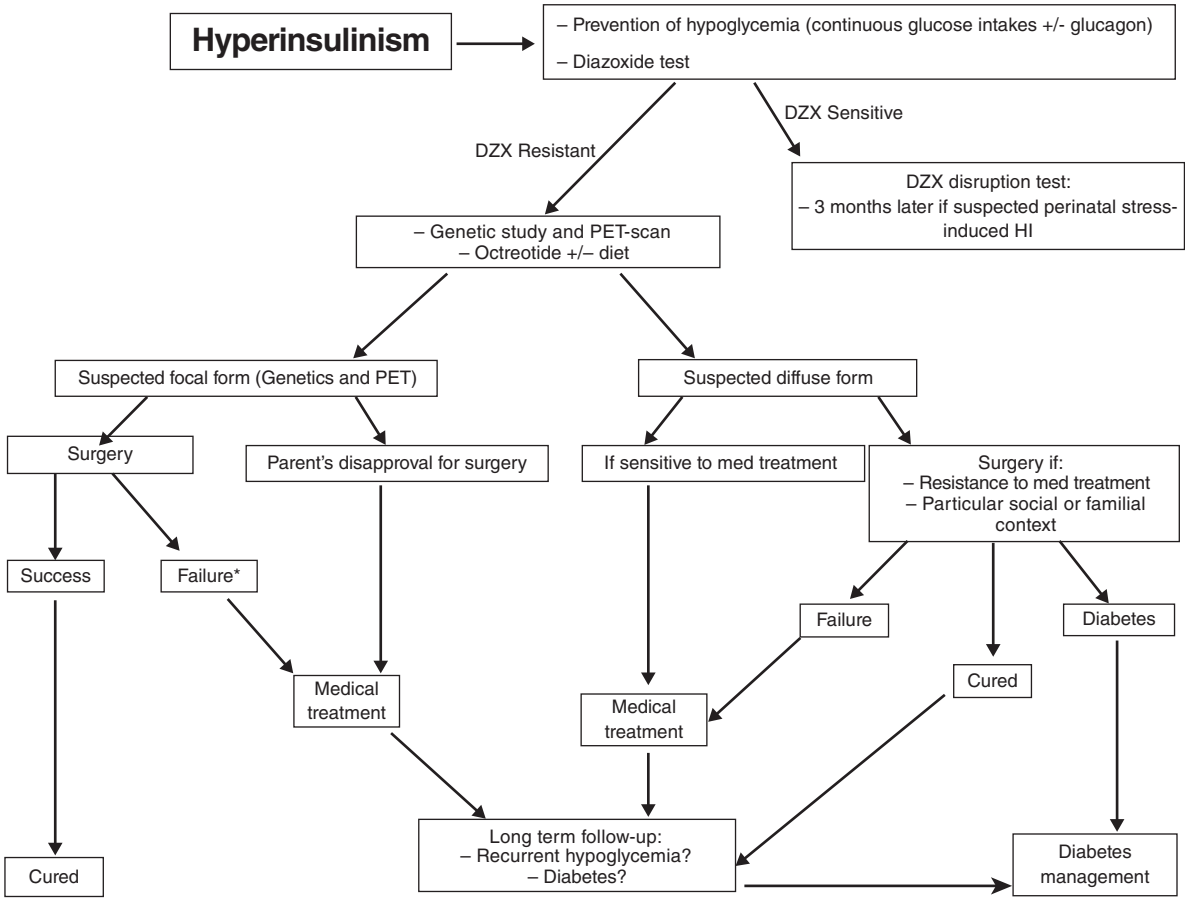

Figure 26.1 Diagnostic and management schematic for patients with suspected hyperinsulinism. DZX, diazoxide. Adapted from (open access copyright) Arnoux JB, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet Journal of Rare Diseases* 2011;6:63

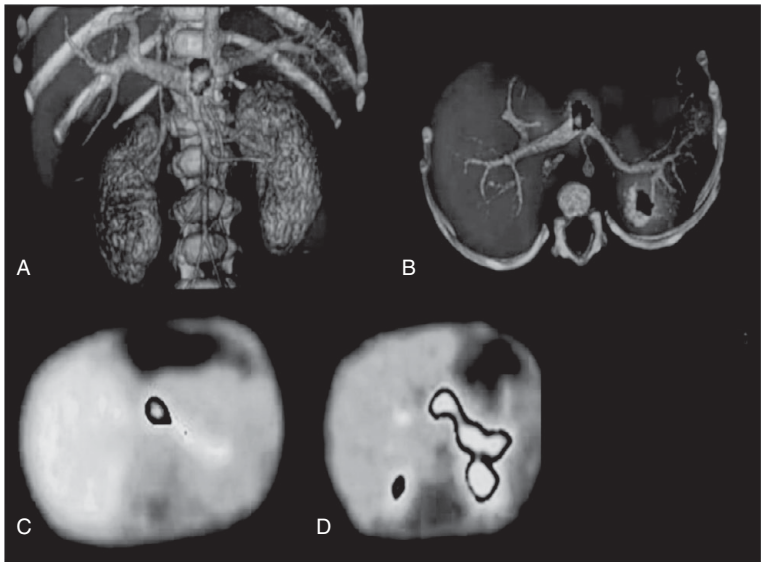

Figure 26.2 18 F-fluoro-L-DOPA PET-scan imaging in patients with HI. Focal form (A, B, C): PET-scan localizes accurately the focal lesion. A, B: 3D CT-scan reconstruction fused with PET imaging showing pancreatic uptake of the radiotracer to be almost exclusively located at the head of the pancreas. C: Transversal PET imaging in a suspected focal form. D: Transversal PET imaging in a suspected diffuse form showing uptake of the radiotracer appears in the whole pancreas. Adapted from (open access copyright) Arnoux JB, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet Journal of Rare Diseases* 2011;6:63

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Table 26.1 Postoperative management of glucose post pancreatectomy. GIR, glucose infusion rate; BG, blood glucose; TPN, total parenteral nutrition

POD 0	POD 1
IV D30W @ 2xGIR with 0.45NaCl titrated to 80–100 mL/kg/day	IV D30W infusion is increased to provide GIRx5, TPN is ordered to provide a GIR=8
Hourly BG measurement targeting 80–180 mg/dL	GIR remains at 8 until feeds started
BG >250 is tolerated for 6–8 h. postoperatively prior to starting insulin. For BG >250 within the 6–8 h. Post-op, urine should be checked for presence of ketones.	Sepsis evaluation considered for persistent hyper C or hypoglycemia following the immediately postoperative period
If BG >250 consistently, insulin infusion should be started at 0.005 Units/kg/h GIR is not reduced when starting insulin infusion	Consider residual lesions for patients with persistent hypoglycemia requiring GIR>8
	Monitor BG every 1–2 h
	Do not wean GIR if insulin infusion required

results of the PET scan. All open procedures are performed via a transverse supra-umbilical laparotomy.

A partial pancreatectomy is performed for those patients with a focal lesion, which may necessitate a longer OR time. If a focal lesion is not identified, intraoperative biopsies are taken and immediately analyzed by frozen section from the head, body, and tail of the pancreas. Patients with diffuse HI undergo near total pancreatectomy (removal of >95% of tissue). In these cases, a small portion of pancreatic tissue is left between the common bile duct and duodenum. In patients undergoing partial resection, a Roux-en Y pancreatojejunostomy may be necessary to ensure adequate pancreatic duct drainage, if the head of the pancreas is resected. These patients usually do not need to have a G-tube placed and are less likely to require insulin. For those patients who have a diffuse disease a near-total pancreatectomy is indicated. These patients require G-tube placement and will most likely require insulin.

What Are the Anesthetic Considerations for Congenital HI?

For patients undergoing a pancreatectomy, room set up should include all standard considerations for neonates.

Point of care glucometer must be readily available.

At minimum, a type and screen should be performed preoperatively, however, consideration should be given to have cross-matched blood available in the operating room.

Intra and postoperative pain control may be augmented with a caudally threaded epidural catheter which may be placed using the assistance of fluoroscopy and a radiopaque catheter.

Glucose homeostasis may be extremely challenging in these patients. The patient will present to the OR on concentrated IV dextrose solutions. The dextrose concentration should be maintained at the level at which the patient is best managed to avoid hypoglycemia (i.e., if using 20% dextrose, 20% should be maintained). General anesthesia will cause a hyperglycemic response. The blood glucose level may rise as the abnormal pancreatic tissue is excised and the surplus insulin secretin tissue is removed. Glucose monitoring should be performed approximately every 30 minutes during the procedure.

Prior to anesthetic induction, the glucose maintenance solution should be decreased to one-half to two-thirds of the original rate. Hypoglycemia and hyperglycemia should be corrected. At the end of the procedure, the target is 2xGIR as provided below:

$$\textbf{Glucose infusion rate}\ (\textbf{mg/kg/min}) = \frac{\%\textbf{Dextrose} \times IV\ \textbf{rate} \times 0.167}{\textbf{Weight in kg}}$$

Postoperative Care

A sample template for glucose management for the first 48 h postoperatively is seen in Table 26.1.

Adequate analgesia is vital, as poor pain management may result in hyperglycemia. Therefore, when an epidural is present, the pain management team is consulted to manage. Epidural infusion of chloroprocaine is used in patients less than 12 months old. If

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patients are older than 12 months, an epidural infusion of ropivacaine with/without adjuncts such as fentanyl or clonidine is given. Morphine and nalbuphine rescues of 0.05 mg/kg per dose can be given every 3–4 hours as needed for pain. However, if pain is not controlled with epidural and rescue medications, a continuous opioid infusion may be required to augment analgesia.

On Post Op Day #1

Ketorolac 0.5 mg/kg per dose every 6 hours maybe considered if creatinine and platelets are normal.

On Post Op Day #2

Consider removing the epidural. The epidural is usually maintained for 48–72 hours post-op.

Considerations for Care

Throughout the postoperative course, it is essential to monitor the blood glucose and maintain adequate hydration and nutrition by adjusting the IV fluid rate. All medications should be ordered in normal saline. Any persistent hyperglycemia or hypoglycemia will warrant a sepsis evaluation including blood and urine cultures.

A feeding regimen may commence once the bowel function has returned, usually five to seven days post-op. Infants with extensive duodenal manipulation or Roux-en-Y pancreaticojejunostomy may have duodenal edema necessitating longer NPO durations (one to two weeks).

Symptoms of bilious emesis and retractable pain could indicate bowel obstruction or intussusception. These patients commonly need antireflux medication and a small amount of emesis is expected when advancing feeds.

Outcomes

The outcomes are based on the presence of focal vs. diffuse disease. The cure rate without medication management for focal disease approaches 95%. For patients with diffuse disease, approximately 15% are controlled without medication, 50% require ongoing management with insulin, and 35% require ongoing management for control of hypoglycemia.

Suggested Reading

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