Hyperinsulinemic Hypoglycemia

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KEYWORDS

• Hyperinsulinism • Hypoglycemia
• 18F-L-dihydroxyphenylalanine positron emission tomographic scan • Diazoxide
• Octreotide • Mammalian target of rapamycin (mTOR) inhibitor • Pancreatectomy

KEY POINTS

- Hyperinsulinemic hypoglycemia (HH) is characterized by the inappropriate secretion of insulin from pancreatic β-cells and is a major cause of hypoglycemic brain injury.
- It is recommended that blood glucose concentrations be maintained greater than 3.5 mmol/L in patients with HH because of the lack of alternative substrates for the brain to use.
- Genetic testing for mutations in the genes *ABCC8/KCNJ11* for congenital HH helps in determining if the child has focal or diffuse disease.
- The 18F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA)-PET/computed tomographic (CT) scan is now the gold standard for the accurate preoperative localization of the focal lesion.
- Novel therapeutic drugs such as mammalian target of rapamycin (mTOR) inhibitors (like sirolimus) and glucagon-like peptide-1 (GLP-1) receptor antagonist offer new medical treatment options for severe diffuse disease, decreasing the requirement for a near-total pancreatectomy.

INTRODUCTION

In HH there is dysregulation of insulin secretion so that insulin continues to be secreted despite blood glucose levels being in the hypoglycemic range. Typically HH occurs in the neonatal period, but it can also occur in the infancy and childhood periods. In the neonatal and infancy periods, it is a major cause of persistent and recurrent hypoglycemia associated with hypoglycemic brain injury.[1]

The biochemical basis of HH involves not only the dysregulation of insulin secretion but also defects in glucose counterregulatory hormones.[2,3] The unregulated insulin secretion drives glucose into the insulin-sensitive tissues especially skeletal muscle,

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adipose tissue, and liver causing profound hypoglycemia. This situation is compounded by the fact that insulin simultaneously inhibits glycogenolysis (glycogen breakdown), gluconeogenesis (glucose production from noncarbohydrate sources), lipolysis, and ketogenesis. The normal physiologic glucagon and cortisol counterregulatory hormonal response to hypoglycemia are blunted in the neonatal period, further exacerbating the hypoglycemia.[2,3] This biochemical milieu is a recipe for depriving the brain of its most important fuel, namely, glucose. This brain glucopenia is accompanied by the lack of alternative substrates such as ketone bodies and lactate. Under these conditions, the risk of brain damage is the highest.

HH can be either congenital or secondary to certain risk factors (such as intrauterine growth retardation [IUGR]). Congenital HH is caused by defects in key genes involved in regulating insulin secretion from pancreatic β-cells. The major causes of congenital HH involve defects in the genes *ABCC8* and *KCNJ11* (encoding the 2 proteins SUR1 and KIR6.2 of the pancreatic β-cell ATP-sensitive K^+ channel [K_{ATP} channel], respectively)[4,5] or abnormalities in the enzymes glucokinase (GCK), glutamate dehydrogenase (GDH), and short-chain acyl-coenzyme A (CoA) dehydrogenase.[6–8] Loss-of-function mutations in the genes *ABCC8* and *KCNJ11* cause the most severe forms of HH, which are usually medically unresponsive.

Histologically, HH can be classified into 2 broad categories: diffuse (affecting the whole pancreas) and focal (localized to a single region of the pancreas) disease. Recent developments in using 18F-DOPA-PET scanning help to differentiate focal from diffuse disease and accurately localize the focal lesion preoperatively. With the advent of 18F-DOPA-PET scan and laparoscopic surgery, the clinical approach has changed dramatically. This review provides an overview of HH by outlining the physiologic mechanisms of insulin secretion, discussing the genetic mechanisms of congenital HH, reviewing the histologic basis of HH, and finally, reviewing the latest advances in management.

DEFINITION OF HYPOGLYCEMIA

The definition of hypoglycemia remains one of the most contentious and confusing areas (especially in the newborn) in glucose physiology.[9] This confusion stems from the fact that there is poor correlation between plasma glucose concentrations, the onset of clinical symptoms, and the long-term neurologic sequelae. It is difficult to define a blood glucose level that requires intervention because there is uncertainty over the level and duration of hypoglycemia that can cause neurologic damage.

Several different approaches have been used to define hypoglycemia (based on clinical manifestations; epidemiology; acute changes in metabolic, endocrine responses; neurologic function; and long-term neurologic outcome), but none of these approaches are satisfactory.[10] The approach based on neurophysiological responses to falling blood glucose concentrations has led to the proposal that hypoglycemia should be defined as a blood glucose concentration less than 2.6 mmol/L as measured with a laboratory research method.[11] However, around 20% of entirely normal full-term infants have blood glucose concentrations less than this in the first 48 hours after delivery. These infants demonstrate concurrent hyperketonemia, and the assumption (which still needs to be proved) is that these babies will not demonstrate neural dysfunction at this time because of the protective effect of the alternative fuels available.

Recently, it has been recommended that operational thresholds be used when assessing an interventional response in a patient with hypoglycaemia.[9] An operational threshold is defined as the concentration of plasma or whole blood glucose at which