Seminars in Fetal & Neonatal Medicine (2005) **10**, 369—376

ELSEVIER

Seminars in FETAL & NEONATAL MEDICINE

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Congenital hyperinsulinism

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KEYWORDS
Congenital hyperinsulinism;
Hypoglycaemia;
Insulin;
Glucose;
Potassium channels;
SUR1;
KIR6.2

Summary Congenital hyperinsulinism is a cause of persistent hypoglycaemia in the neonatal period. It is a heterogeneous disease with respect to clinical presentation, molecular biology, genetic aetiology and response to medical therapy. The clinical heterogeneity may range from severe life-threatening disease to very mild clinical symptoms. Recent advances have begun to clarify the molecular pathophysiology of this disease, but despite these advances treatment options remain difficult and there are many long-term complications. So far mutations in five different genes have been identified in patients with congenital hyperinsulinism. Most cases are caused by mutations in genes coding for either of the two subunits of the β-cell K_{ATP} channel (*ABCC8* and *KCNJ11*). Two histological subtypes of the disease — diffuse and focal — have been described. The preoperative histological differentiation of these two subtypes is now mandatory as surgical management will be radically different. The ability to distinguish diffuse from focal lesions has profound implications for therapeutic approaches, prognosis and genetic counselling.

Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent and recurrent hypoglycaemia in the neonatal period. For decades, the disease was thought to be due to 'nesidioblastosis'. This term, which was first used by Laidlaw, describes the persistence of a diffuse and disseminated proliferation of islet cells budding off from the pancreatic ductal tissue.[1] However, it is now quite clear that nesidioblastosis is a common feature of the pancreas in normoglycaemic neonates.[2] Neonatal onset CHI is a major risk factor for development of severe mental retardation and epilepsy.[3]

Biochemically, CHI is characterized by inappropriate and unregulated insulin secretion from pancreatic β-cells. The biochemical profile at the time of hypoglycaemia reflects the metabolic actions of insulin. The dysregulated and uncontrolled release

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1744-165X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.siny.2005.03.001

of insulin from the β-cells reflects the final manifestation of a number of different processes that alter intracellular biochemical pathways of the β-cell, thereby generating abnormal signals for the secretion of insulin.[4] These abnormalities perturb the normal physiological mechanisms which normally ensure that the amount of insulin secreted is directly related to the ambient blood glucose concentration. CHI is characterized by the presence of insulin and c-peptide concentrations that are inappropriately high for the level of blood glucose. A 'normal' insulin level for normoglycaemia is usually inappropriate in the presence of hypoglycaemia, especially taken in the context of high glucose requirement to maintain normoglycaemia.[5] There appears to be very little correlation between circulating levels of insulin at presentation and the severity of hypoglycaemia.[5]

Recent advances have begun to unravel the pathophysiology of this intriguing disease as well as providing an understanding of the normal physiological and biochemical mechanisms regulating insulin secretion from pancreatic β-cells. It is now clear that CHI is a heterogeneous disorder with respect to clinical presentation, histology, molecular biology and genetics.[6] The histological differentiation of focal and diffuse forms of CHI has radically changed the surgical approach to this disease, and the focal form of the disease can now be cured by partial pancreatectomy.[7,8] So far, mutations in five different genes have been described which lead to dysregulated insulin secretion from β-cells.[9–13] Despite these advances the genetic defect is still unknown in about 50% of cases.

Clinical presentation and diagnosis

Typically, CHI presents in the neonatal period, usually within the first few days of birth, although it can present later in infancy and childhood.[14] Neonates will present with specific symptoms (such as fits) or non-specific symptoms (lethargy, irritability, poor feeding) of hypoglycaemia. Macrosomia may be a feature in some patients, but not all neonates with CHI are macrosomic. The hypoglycaemia in CHI is persistent and recurrent, and in most cases normoglycaemia can only be maintained by giving large volumes of intravenous glucose. CHI can occur in preterm babies, in which case it appears to be more severe and aggressive.[15] Hypertrophic cardiomyopathy is a common clinical finding in patients with CHI, but the underlying mechanism for this is unclear.

Hyperinsulinism can also be transient. The transient form is associated with infants born to mothers with diabetes mellitus (gestational and insulin-dependent), in infants with Beckwith–Weidemann syndrome, in intrauterine growth retardation babies, and in babies subjected to perinatal asphyxia.[16] Transient hyperinsulinism may also occur in babies where there is no predisposing factor.[17] The mechanisms causing transient hyperinsulinism in these conditions are not clear.

Hyperinsulinism may also be a manifestation of a rare syndrome such as Kabuki, Costello or Turner's syndrome (Hussain K, unpublished observations) or congenital disorders of glycosylation[18] and some undiagnosed syndromes.[19]

Foregut dysmotility and gastro-oesophageal reflux is common in CHI.[20] The pathophysiology of the gut dysmotility and the gastro-oesophageal reflux is unclear. Infants may show poor sucking and swallowing, retching, vomiting, and intestinal dilatation; feeding problems are compounded by the use of nasogastric or gastrostomy feeds, which delay the establishment of normal feeding patterns, taste, and 'orality'. In severe cases, the deprivation of oral stimulation may require months of rehabilitation with skilled speech and language therapists.

The biochemical hallmark of CHI is hyperinsulinaemic, hypoketotic, hypofattyacidaemic hypoglycaemia. These biochemical abnormalities reflect the metabolic actions of insulin. The unregulated insulin secretion causes increased glucose disposal in insulin-sensitive tissues such as the liver (hepatomegaly on clinical examination), adipose tissue and skeletal muscle, and simultaneously inhibits glucose production. There is also higher glucose demand in the absence of alternative fuels. This is reflected in the increased glucose clearance rate (above the normal of 5 mg/kg/min) required to maintain normoglycaemia. The serum cortisol counter-regulatory hormone levels are blunted in hyperinsulinaemic hypoglycaemia due to the lack of drive from the hypothalamic–pituitary axis, and replacement therapy with glucocorticoids does not seem to affect the severity of the disease.[21]

In most cases the diagnosis of CHI is relatively straightforward, but in difficult cases other supportive evidence is required: for example, decreased serum levels of insulin growth factor binding protein 1 (IGFBP-1) (as insulin suppresses the transcription of the IGFBP-1 gene),[22] a positive glycaemic response to intramuscular/intravenous glucagon at the time of hypoglycaemia (a clear increment in blood glucose concentration despite severe hypoglycaemia),[23] and a positive glycaemic