Early Human Development (2005) **81**, 61—72

ELSEVIER

Early Human Development

www.elsevier.com/locate/earlhumdev

Contemporary strategies in the diagnosis and management of neonatal hyperinsulinaemic hypoglycaemia

Keith J. Lindley[a,*], Mark J. Dunne[b]

[a]*London Centre for Pancreatic Disease in Childhood, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK*
[b]*Faculty of Life Sciences, University of Manchester, Manchester, UK*

KEYWORDS
Hyperinsulinism;
Hypoglycaemia;
β-cell;
ABCC8;
KCNJ11;
GLUD1;
GCK;
HADHSC

Abstract Congenital hyperinsulinism (CHI) is a genetically and phenotypically diverse syndrome. Key management issues involve early diagnosis by ensuring that appropriate samples are taken at the point of hypoglycaemia, prevention of recurrent hypoglycaemia, and detailed charcterisation of the clinical, biochemical, and genetic features of each case. Infants with persistent diazoxide resistant CHI require evaluation at specialist referral centres equipped to differentiate those with focal (fo-HI) and diffuse (di-HI) pancreatic disease. Fo-HI is treated with selective pancreatic resection but di-HI is treated by surgery only if intensive medical management regimes are not efficacious.

1. Introduction

Hyperinsulinism (HI) is the most common cause of persistent or recurrent hypoglycaemia in infancy and childhood, although HI is itself comparatively rare in most populations (1/30,000—1/50,000 live births) [1]. In isolated European communities, including Eastern Finland, the incidence is much higher and may affect as many as 1/2500 live births in the Arabian peninsular [2,3]. Over the last 8 years, it has become clear that the characteristic failure of regulation of insulin release in HI has many different causes resulting in diverse clinical presentations and clinical phenotypes [4]. However, the importance of early diagnosis and appropriate management cannot be overemphasised because neuroglycopenia in association with HI is a preventable cause of neurological handicap which might affect up to 20% of infants who have suffered from congenital hyperinsulinaemic hypoglycaemia (CHI) [5,6]. Clinical management strategies for HI

* Corresponding author. Tel.: +44 20 7905 2111; fax: +44 20 7404 6181.
E-mail address: K.Lindley@ich.ucl.ac.uk (K.J. Lindley).

0378-3782/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2004.10.007

have changed in tandem with our increasing insight into its pathogenesis; the place of surgery has evolved in parallel [7,8]. This article discusses key contemporary issues in the management CHI.

2. Neonatal hypoglycaemia

The risk of hypoglycaemia in neonates is high. Up to 10% of normal-term neonates cannot maintain plasma glucose concentrations above 1.7 mmol/l if their first feed is delayed for as little as 6 h [9]. This may be a result of developmental immaturity of metabolic machinery involved in gluconeogenesis and ketogenesis within the liver that protect against hypoglycaemia during fasting [10]. Moreover, hepatic glycogenolysis is often compromised by peripartum stress. After 12 h of life, the risk of hypoglycaemia in healthy full-term neonates falls in the absence of birth asphyxia or low birth weight. Persistent or recurrent hypoglycaemia after this time is most commonly due to hyperinsulinism. The precise definition of neonatal hypoglycaemia is not without controversy; a full discussion of which is beyond the scope of this article [11]. There is, however, consensus that a blood sugar $\leq$ 2.5 mmol/l in a symptomatic infant constitutes an indication for clinical intervention. This is particularly important in hyperinsulinism in which hypoketosis deprives the brain of alternative energy sources. It is important that blood is drawn at this point of hypoglycaemia for measurement of intermediary metabolites and counter-regulatory hormones and that the next sample of urine passed is also collected for metabolic analysis (Table 1). Symptomatic hypoglycaemia of this kind should be treated with intravenous (i.v.) administration of 2 ml/kg of 10% dextrose over a few minutes followed by an infusion of approximately 5 ml/kg/h of 10% dextrose in the first instance (equating to ~8 mg/kg/min of glucose) and the response monitored by rechecking blood glucose within 15 min and adjusting the i.v. fluids accordingly. Diagnostic criteria for the diagnosis of hyperinsulism comprise the findings of hypoketotic hyperinsulinaemic hypoglycaemia and a raised glucose requirement to maintain normoglycaemia (Table 2). Not all forms of hyperinsulinaemic hypoglycaemia, for example, some of the postprandial forms, demonstrate a raised glucose requirement at steady state. The differential diagnosis of hypoglycaemia during the neonatal period will include a variety of other metabolic and endocrine disorders, all of which should be considered [12]. Many of these will be detected by the above approach or will be apparent following careful clinical examination and are not considered further here.

Table 1 Intermediary metabolites and hormones to be measured at the point of hypoglycaemia

Blood	Urine
Glucose	Ketones
Lactate/pyruvate	Reducing sugars
Ketone bodies	Organic acids
Free fatty acids	
Amino acids	
Ammonia	
Acyl-carnitine profile (Blood spot)	
Insulin/C peptide	
Cortisol/Growth hormone	
Other investigations:	
IGF-1	
Transferrin isoelectric focussing	

Presence of any measurable insulin in the face of hypoglycaemia is inappropriate; insulin concentrations should always be related to concurrent glucose concentrations. Insulin release is pulsatile. In cases in which hyperinsulinaemia is not florid, C peptide might prove a useful measurement, as this is a good measure of overall insulin production.

Measurement of ammonia at the time of hypoglycaemia is mandatory.

Table 2 Conventional diagnostic criteria for hyperinsulinism

Laboratory blood glucose $\leq$ 2.5 mmol/l
Detectable insulin at the point of hypoglycaemia with raised C peptide
Inappropriately low blood free fatty acids and ketones at the point of hypoglycaemia
Glucose requirement > 6—8 mg/kg/min to maintain blood glucose between 2.6 and 3.0 mmol/l
Glycaemic response after the administration of glucagon when hypoglycaemic
Absence of ketonuria

3. Neonatal hyperinsulinaemic hypoglycaemia

Most infants with hyperinsulinism present within the early neonatal period although infantile and childhood onset forms are also recognised [13,14]. Transient hyperinsulinism is seen in association with maternal diabetes, birth asphyxia, polycythaemia, and rhesus incompatibility. Other syndromic associations which might be evident at birth include Beckwith syndrome (see later), Sotos' syndrome, Perlman's syndrome, and the clinical phenotype characteristic of phosphomannose isomerase deficiency (carbohydrate-deficient glycoprotein syndrome type 1b) [15—17].