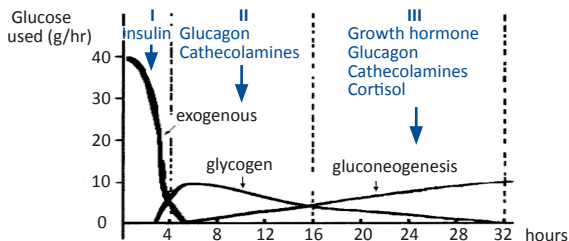


APPROACH TO RECURRENT HYPOGLYCAEMIA

Introduction

Definition of hypoglycemia: blood glucose <2.6 mmol/L for all ages

Figure 1. Glucose homeostasis time course



Origin of blood glucose	diet	glycogen gluconeogenesis	hepatic glycogen gluconeogenesis
Tissues using glucose	all	all except liver, muscle	brain, blood cells, renal medulla
Major fuel of brain	glucose	glucose	glucose

Clinical approach

- rule out: liver failure, septicemia, severe systemic illness, small for gestational age, maternal diabetes and drugs
- determine the fasting tolerance: when does hypoglycemia occur in relation to last meal?
- is it *ketotic* or *hypoketotic* hypoglycemia?
- any hepatomegaly?
- any clues and clinical signs to suggest an endocrine cause?
 - small genitalia, hyperpigmentation, short stature.
 - abnormal neonatal hypothyroidism screening result
 - glucose requirement > 10 mg/kg/min indicates hyperinsulinism unless there is marked loss in urine

Laboratory tests during symptomatic hypoglycemia

Adequate laboratory tests will help identify the cause, or else the diagnosis may be missed. Ensure samples are taken *before* correcting the hypoglycemia.

Table 2. List of investigations

Essential Tests	Other Tests
<ul style="list-style-type: none"> • ketones (serum or urine) • acylcarnitine (dried blood spots on Guthrie card) • blood lactate • venous blood gas • blood ammonia • urine organic acids • free fatty acids (if available) • serum insulin • serum cortisol • serum growth hormone 	<ul style="list-style-type: none"> • serum cholesterol/triglyceride • serum uric acid • liver function test • creatine kinase • urine reducing sugar • urine tetraglucoside • plasma amino acids • consider toxicology tests C-peptide • fasting tolerance test/glucagon test (only by metabolic clinician/ endocrinologist) • other special tests e.g. fatty oxidation study in cultured fibroblasts

Table 3. Determining the cause of hypoglycemia

Ketone level	Timing of hypoglycemia	Other clues	Diagnosis
hypoketotic	no specific timing	↑insulin ¹ when glucose <2.6mmol/L, ↑ ammonia in HIHA	Hyperinsulinism
ketotic	no specific timing	↓GH, ↓ cortisol, ↓ TSH, midline defect, micropenis	Hypopituitarism
hypoketotic	infant: < 3 hr	permanent hepatomegaly, ↑↑ lactate, ↑ uric acid, ↑ TG, ↑ cholesterol, ↑ ALT, ↑ AST	GSD type I
ketotic	3-8 hr	hepatomegaly, ↑lactate, ↑uric acid, ↑ TG, ↑ cholesterol, ↑ ALT, ↑ AST, ↑ CK (some GSD III), ↑ urine tetraglucoside (hypoglycaemia usually mild compared to GSD I)	GSD III/VI/IX
ketotic	>8 hr	hepatomegaly in acute phase, ↑ lactate, ↑ urine glycerol/2-ketoglutaric	Gluconeogenesis defects
hypoketotic	infant: >8 hr older children: >16 hr	hepatomegaly during acute phase, absent ketones, mild ↑ NH ₃ , mild ↑ lactate, mild ↑ AST/ALT, abnormal acyl-carnitine profile, ↓ free fatty acid, urine organic acid - dicarboxyluria	Fatty acid oxidation disorders
ketotic	1-2 hr	jaundice, liver dysfunction, GI symptoms, positive urine reducing sugar, galactosaemia: ↑Gal-1-P uridyltransferase (GALT), ↓Gal-1-P	Sugar intolerance (galactosaemia, fructosaemia)
ketotic	3-8 hr	no hepatomegaly; fasting: ↓glucose, ↓lactate, ↓alanine, ↑ketone postprandial: hyperglycemia, glucosuria, ↓ ketone, ↑ lactate; mild ↑ ALT/AST; liver biopsy: absent glycogen	GSD 0
ketotic	during acute crisis	metabolic acidosis, ↑ acetate, abnormal acylcarnitine and urine organic acids. Ketolytic defect: urine ketone persistently positive even when patient well	Organic acidaemias/ ketolytic defects

Abbreviations: HIHA, Hyperinsulinism-hyperammonaemia syndrome; GSD, Glycogen storage disease
GH, growth hormone; TSH, thyroid stimulating hormone; TG, triglyceride; CK, creatine kinase; NH₃, ammonia
Footnote: 1. normal range for insulin level: 2-5mU/L.

Differential diagnosis of congenital hyperinsulinism

- **transient hyperinsulinism in the neonate**
diabetic fetopathy, asphyxia, sepsis, rhesus incompatibility, etc.
- **overgrowth syndromes with diazoxide sensitive hypoglycemia**
Beckwith-Wiedemann syndrome (macrosomia, macroglossia, omphalocele, lateral ear lobe crease), Simpson-Golabi-Behmel syndrome, Sotos syndrome, Perlman syndrome.
- **hyperinsulinism-hyperammonaemia (HIHA) syndrome**
mild to moderate hyperammonaemia 100-200µmol/L (unaffected by feeding or fasting), usually hyperammonaemia is asymptomatic, may be prominent early but may disappear later in childhood, often leucine-sensitive, respond well to medical therapy with diazoxide.

- *monogenic forms of hyperinsulinism*
mutations in sulfonylurea receptor gene (SUR1, autosomal recessive), inward-rectifying potassium channel gene (Kir 6.2, autosomal recessive), glucokinase (autosomal dominant). Hypoglycemia is more severe and refractory to medical treatment with diazoxide and octreotide, and affected infants may require near-total pancreatectomy to control the hypoglycaemia.
- *mitochondrial short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency*
- *congenital disorders of glycosylation (CDGs)*
- *Leprechaunism and Rabson-Mendenhall's syndrome*
autosomal recessive, mutations in insulin receptor gene; clinical features: severe IUGR, lipotrophy, facial dysmorphism, paradoxical fasting hypoglycemia and postprandial hyperglycemia during infancy

Treatment

- ensure good IV line
- IV Glucose 7 - 10 mg/kg/min or glucose 10% 110 - 150 ml/kg/day
- aim to keep blood sugar > 5.5 mmol/L
- hourly blood sugar until the level is normalized
- if bolus glucose needed, do not give > 200 mg/kg or glucose 10% 2 ml/kg
- await results of special investigations mentioned above
- consult metabolic clinician or endocrinologist if necessary

Note:

- hypoglycemia due to metabolic disorders is easily corrected with IV glucose but may recur if the underlying metabolic defect is not treated.
- in contrast, hypoglycemia due to endocrine disorders especially hyperinsulinism is persistent and difficult to control requiring agents such as
 - IV glucagon (1 mg/day or 5 - 10 mcg/kg/hour, continuously over 2 - 3 days),
 - diazoxide (15mg/kg/day in 3 doses, takes up to 5 days to work, may cause cardiac failure which may require hydrochlorothiazide 2mg/kg/day in 2 doses)
 - IV somatostatin (1 - 5 mcg/kg/hour IV),
 - octreotide (3 to 20 mcg/kg/day in 3 to 4 doses) for long term treatment,
 - oral nifedipine (0.5 - 2 mg/kg/day) may be justified in selective cases.
- glycogen storage diseases/Gluconeogenesis disorders
 - frequent meals
 - nocturnal continuous feeding during infancy till preschool
 - uncooked cornstarch in older children
 - prevent prolonged fasting and catabolic states