National Metabolic Biochemistry Network
Guidelines for the investigation of hypoglycaemia in infants and children

Aim

To provide guidance on the biochemical investigation of hypoglycaemia in infants and children in the non-specialist setting, particularly in relation to the investigation of inherited defects of intermediary metabolism.

Introduction

Hypoglycaemia is usually defined as a blood glucose of less than 2.6 mmol/L. POCT (point of care testing) devices are at their least accurate in the low part of their range and it is important to confirm any suspected hypoglycaemia by a accurate laboratory based measurement of glucose. Treatment should not be delayed by waiting for the laboratory glucose but, if possible, appropriate samples should be collected before giving glucose to allow identification of the underlying cause.

When to suspect hypoglycaemia?

There is usually compelling clinical evidence of symptomatic hypoglycaemia. The early features are associated with the adrenergic response. Neuroglycopaenic symptoms follow and become more predominant as the hypoglycaemia persists.

Adrenergic symptoms include pallor, anxiety, sweating, tachypnoea tremor, weakness, nausea and vomiting.

Neuroglycopenic symptoms include jitteriness, hunger, abdominal pain, apnoea, headache, confusion, feeding problems, visual disturbances and convulsions and coma.

The predominance and severity of symptoms depend on the age of the patient and the rapidity of onset and duration of the hypoglycaemia.

The investigation and treatment of symptomatic hypoglycaemia is a clinical emergency as delayed treatment leads to a risk of permanent brain damage.

Table 1 Causes of hypoglycaemia

Causes of hypoglycaemia may be split into several main groups:

Endocrine
Hyperinsulinism Adrenal insufficiency Hypopituitarism Growth Hormone Deficiency Hypothyroidism
Metabolic
Disorders of Fatty Acid Oxidation and Carnitine Transport Disorders of Carbohydrate Metabolism Disorders of Organic Acid Metabolism Disorders of Gluconeogenesis
Other Causes
Neonatal complications: prematurity, birth asphyxia, congenital heart defects, infants of diabetic mother – secondary hyperinsulinism Drug Related: insulin, alcohol, aspirin, chemotherapy Liver and multi-organ failure Sepsis, Gastroenteritis, tumors
Idopathic ketotic hypoglycaemia
The most common cause for hypoglycaemia in young children after the neonatal period is idiopathic ketotic hypoglycaemia. This is usually precipitated by an relatively mild illness, or it can present drowsiness after an overnight fast

Taking a good clinical history may help in directing the investigations. Age and presentation often give important clinical clues. Any history of drug or alcohol, including inhaled steroids needs to be noted. The main points to note include the time since the last meal and whether there is hepatomegaly, liver dysfunction, short stature, hyperpigmentation or small genitalia. High glucose requirements (>10 mg/kg/min) indicate hyperinsulinism (Table 1 – causes of hypoglycaemia).

Neonatal hypoglycaemia

Biochemical hypoglycaemia is common in the neonatal period (<72 hours after birth) prior to establishing feeds. In these infants the full biochemical screen is not usually required unless the hypoglycaemia does not respond to a feed or the blood glucose remains persistently or recurrently low. It is important to remember that in the neonate hypoglycaemia is commonly secondary to septicaemia, severe systemic illness, intrauterine growth retardation or maternal diabetes.

Investigations of hypoglycaemia

1. Before giving glucose draw blood for following analytes:

Analyte	**Minimum volume and common preservative** **check with local laboratory for sample types and minimum volumes*
Glucose 3 OH butyrate Free Fatty Acids Lactate	2ml Fluoride Oxalate*
Insulin Cortisol Growth Hormone Amino Acids	3ml Lithium Heparin*
Acyl carnitines	1ml Lithium Heparin plasma (preferred) or 2-3 blood spots collected on a Guthrie Card*

Save any residual plasma from these samples as this may be used for further tests if indicated

*check with local laboratory for sample types and minimum volumes

DO NOT DELAY CORRECTING HYPOGLYCAEMIA IF THE BLOOD IS DIFFICULT TO OBTAIN.

2. First line investigations (samples can be taken after glucose has been given)

Blood gases
Liver function tests
Urea and creatinine
Electrolytes
Ammonia

Save any residual plasma for further tests

3. Collect first passed urine sample for -

Ketones - usually measured by dipstick on a POCT device
Reducing substances or sugar chromatography
Organic acids
Toxicology screen (only required if there is a clinical suspicion of factitious or accidental illness).

Interpretation of tests

The results of these investigations should be evaluated in the context of the clinical symptoms and a differential diagnosis established. See table two for some examples of interpretation.

Further specialist investigations may be indicated for example specific molecular and/or enzyme analysis. These tests are usually undertaken by specialist molecular and metabolic laboratories. For details of specimen requirements by specialist metabolic laboratories see www.metbio.net metabolic assay directory.

Prolonged fast tests

Occasionally it may be necessary to provoke hypoglycaemia by undertaking a prolonged fasting test. This is potentially a very dangerous procedure and should only be carried out under close medical supervision and after discussion with a metabolic specialist. It is essential that a metabolic screen (urine organic acids and plasma/blood spot amino acids and acylcarnitines) has been carried out prior to any fast.

Table two

Examples of interpretation of the biochemical results (please note this is not an exhaustive list of interpretation but an aid to basic biochemistry/metabolic tests in investigating hypoglycaemia).

General biochemistry	General biochemistry is unlikely to give a definitive cause for the hypoglycaemia but some clues into a metabolic cause can be derived from them, some examples include: • Low sodium with raised potassium will be seen in many endocrine disorders associated with low glucocorticoids. • Abnormal liver function tests are seen in liver failure and in numerous inherited metabolic defects (e.g. the glycogen storage diseases). • A raised lactate may indicate a glycogen storage disease or defect of energy metabolism. However a raised lactate may be secondary to sepsis or HIE in the unwell neonate • An unexplained acidosis with an increased anion gap may indicate a defect of organic acid metabolism, particularly if the lactate and/or ketone concentration is insufficient to explain the finding. • Many organic acidaemias are associated with hyperammonaemia.
Intermediary metabolites: Free fatty acids 3-hydroxybutyrate Glucose Lactate	Sample must be taken at time of hypoglycaemia to allow accurate interpretation. 1. Low FFA and 3-hydroxybutyrate concentrations at time of hypoglycaemia suggest hyperinsulinism. Note that in neonates panhypopituitarism also presents as a poor lipolytic and ketogenic response at the time of hypoglycaemia. 2. FFA/3-hydroxybutyrate ratio ≤ 1 provided that the ketones are >1.0 suggests an appropriate lipolytic and ketogenic response to hypoglycaemia 3. FFA/3-hydroxybutyrate ratio >2 suggests a FA oxidation defect Note that neonates may have a poor metabolic response to stress/hypoglycaemia and patients on chemotherapy/TPN or with liver disease may produce an unusual pattern of intermediary metabolites in response to hypoglycaemia. Certain GSD's may also have an abnormal FFA/3-hydroxybutrate pattern. See appendix one for further interpretation.

Endocrine tests Insulin,cortisol and growth hormone	Detectable insulin in a hypoglycaemic sample indicates hyperinsulinism. Low cortisol indicates either hypoadrenalism or hypopituitarism – further tests, such as dynamic function tests, are indicated. Low growth hormone may indicate hypopituitarism or isolated growth hormone deficiency
Amino acids	Raised ketogenic (branched chain) and low gluconeogenic amino acids are seen as part of a normal response in ketotic hypoglycaemia. Generalised low plasma amino acids are noted in anabolic patients or patients on low protein intake/ low body reserves.
Acylcarnitines	Specific acylcarnitine species are invariably raised in fatty acid oxidation defects/organicacidaemias. Certain ratios will aid the diagnostic process e.g. C8/C10 ratio >2 suggests MCADD. Note that ketotic patients will often show a generalised non-specific mild to moderate rise in medium to long chain acylcarnitines.
/Organic acids	Ketone bodies and dicarboxylic acids are seen as part of the normal response to fasting hypoglycaemia. Specific organic acids will usually be present in a crisis sample from patients with fatty acid oxidation disorders or organic acidaemias. High lactate levels are seen in patients with GSD type I and defects of gluconeogenesis as well as the congenital lactic acidaemias and organic acidaemias (when they are accompanied by more specific findings). Glycerol is often present in the “acute” urine of patients with fructose bisphosphatase deficiency (as well as in glycerol kinase deficiency).
Urine chemistry	Urinary ketones are often absent or inappropriately low in fatty acid oxidation defects Urinary reducing substances will be positive in disorders of sugar metabolism (e.g. Galactosaemia). This is particularly important if the urine is negative for glucose (test by specific glucose dipsticks).

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Suggested review date:	2019
Disclaimer	These are laboratory guidelines reflecting current best practice in specialist metabolic laboratories in the UK. They are not evidence based but reflect expert opinion. The network cannot accept any responsibility for the use of these guidelines.

Appendix one. Algorithm for the interpretation of intermediary metabolites.