UK Metabolic Biochemistry Network Recommendations for the Investigation of Hypoglycaemia in Infants and Children

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

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Introduction

Hypoglycaemia is usually defined as a blood glucose concentration of less than 2.6 mmol/L. 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 an accurate laboratory-based measurement of glucose. Treatment should not be delayed by waiting for confirmation of hypoglycaemia with a laboratory glucose result. But for the investigation of the underlying cause, it is crucial to obtain appropriate samples before treatment is given. This guideline provides guidance on the biochemical investigation of hypoglycaemia in infants and children 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. Neuroglycopenic symptoms follow and become more predominant as the hypoglycaemia persists (table 1). The predominance and severity of symptoms depend upon the age of the patient and the rapidity of onset and duration of the hypoglycaemia.

Table 1: Adrenergic and neuroglycopenic symptoms of hypoglycaemia

Adrenergic symptoms	Pallor, anxiety, sweating, tachypnoea, tremor, weakness, nausea and vomiting.
Neuroglycopenic symptoms	Jitteriness, hunger, abdominal pain, apnoea, headache, confusion, feeding problems, visual disturbances, convulsions and coma.

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

Causes of hypoglycaemia

The causes of hypoglycaemia may be split into several main groups (table 2) [1, 2]. Taking a good clinical history can help in directing the investigations. It is useful to document the following:

a. Neonatal history (diabetic mother, small for dates etc.)
b. Diet and last time of feed
c. Feeding history and symptoms of early morning hypoglycaemia
d. Possibility of intoxications (e.g. alcohol, drugs)
e. Recent / current illness
f. Past history of unexplained seizures
g. Family history of unexplained deaths
h. Parental consanguinity
i. Hepatomegaly
j. Glucose requirement (>10 mg/kg/min usually indicates hyperinsulinism)

Table 2: Causes of hypoglycaemia

Category	Examples
Metabolic	Disorders of Fatty Acid Oxidation and Carnitine Transport Disorders of Carbohydrate Metabolism Disorders of Organic Acid Metabolism Disorders of Gluconeogenesis Disorders of ketogenesis and ketolysis Mitochondrial respiratory chain defects
Endocrine	Hyperinsulinism Adrenal Insufficiency Hypopituitarism Growth Hormone Deficiency Hypothyroidism
Other Causes	Neonatal complications: prematurity, birth asphyxia, congenital heart defects, infants of diabetic mother (secondary hyperinsulinism) Drug Related: e.g. insulin, sulfonylureas, β-blockers, alcohol, aspirin, chemotherapy Liver and multi-organ failure Sepsis, Gastroenteritis, tumors
Idiopathic ketotic hypoglycaemia (IKH)	The most common cause for hypoglycaemia in young children after the neonatal period is idiopathic ketotic hypoglycaemia. This is usually precipitated by a relatively mild illness, or prolonged fasting.

Investigations of hypoglycaemia

Section A: For paediatric patients >48 hours old

Blood glucose < 2.6 mmol/L in non-diabetic paediatric patient > 48 hours old:

1. ABC
2. Obtain blood samples including bedside glucose and ketones
3. Correct hypoglycaemia
4. Obtain next void urine

Table 3 details the full biochemical screen for hypoglycaemia. These blood samples should ideally be collected prior to giving glucose, however **do not delay correcting the hypoglycaemia if the blood is difficult to obtain.** Analytes in italics may not be required (depending upon the results of initial investigations) but it is important to collect these samples during the hypoglycaemic episode in case they are necessary.

Table 3: Biochemical screen for hypoglycaemia

Analyte	Common tube type stated*
Glucose **Lactate** **3 OH butyrate** **Free Fatty Acids**	Fluoride Oxalate plasma
Insulin **Cortisol** **Growth Hormone** **U&E** **LFT** **Bicarbonate** **Chloride** **Anion Gap** **CRP** **Triglycerides**	Lithium Heparin plasma or serum
Acyl carnitines	Lithium Heparin plasma or 2-3 blood spots collected on a Guthrie Card
Ammonia **C-peptide**	K-EDTA
Store sample	Save any residual lithium heparin and EDTA plasma from these samples as this may be used for further tests if indicated. Store at -20 °C
Organic acids **	Urine

*Common sample tube is listed. Please confirm tube type and minimum volumes with local laboratory before sending.

**Urine for organic acids does NOT need to be collected prior to correcting blood glucose. Do not delay giving treatment to collect a urine sample. Collect the first void urine after hypoglycaemia.

NOTE: If sample volume is limited, prioritise glucose, basic biochemistry and insulin. Then review results to guide further tests order. If there is no fluoride oxalate sample, glucose should be measured using a lithium heparin sample, taking into account any pre-analytical delays before the glucose was measured.

It may not be necessary to analyse all samples for specialist investigations, but it is important to collect them during hypoglycaemia in case they are required. This will depend upon the results of the general biochemistry investigations, including insulin, and should be discussed with your local biochemist. Further guidance for when these specialist investigations are useful is given in table 4.

Table 4: Examples of criteria for specialist investigations

Specialist Investigation	Notes
C-peptide	If insulin is appropriately suppressed during hypoglycaemia, C-peptide does not routinely need to be measured. It can be useful if the insulin level is borderline or there is concern regarding exogenous insulin administration. The limitations of the insulin assay in use should be carefully considered when confirming or excluding hyperinsulinism as a cause. (see table 7) The sample should be stored in case of discrepancies or other requirements for further investigation.
3-OH Butyrate **Free fatty acids**	Limited use if patient is not biochemically hypoglycaemic Should be analysed if insulin is appropriately suppressed during hypoglycaemia
Acyl carnitines	If patient is < 24 hours old, an underlying metabolic disorder may not be detected and repeat analysis advised. Should be analysed if insulin is appropriately suppressed during hypoglycaemia

All remaining plasma and urine should be kept and stored frozen (-20 °C) to be used if and when required.

SECTION B: Neonatal hypoglycaemia (infant <48 hours of age)

Current evidence suggests that lower levels of blood glucose can be tolerated in newborn infants (< 48 hours of age) compared with normal levels for children and adults in an otherwise well neonate. Biochemical hypoglycaemia is common in the neonatal period prior to establishing feeds. In these infants the full biochemical screen (table 3 above) is not usually required unless the hypoglycaemia does not respond to a feed or the blood glucose remains persistently or recurrently low, or the infant is symptomatic (table 5).

Table 5: Signs of hypoglycaemia in the newborn

Signs of Hypoglycaemia in the Newborn
• Lethargy • Abnormal feeding behaviour, especially after a period of feeding well • High pitched cry / irritability • Altered level of consciousness • Hypotonia • Seizures • Hypothermia (<36.5 ^{0}C) • Cyanosis • Apnoea

The British Association for Perinatal Medicine (BAPM) 2017 guideline [3] outlines alternative criteria for hypoglycaemia in neonates and it is recommended a hypoglycaemia screen is performed in any of these scenarios (table 6). It is important to remember that in the neonate hypoglycaemia is commonly secondary to hyperinsulinism, septicaemia, severe systemic illness, intrauterine growth restriction or maternal diabetes.

Table 6: Hypoglycaemia in the newborn, BAPM 2017 [3]

Neonatal Hypoglycaemia (BAPM 2017)
1. Blood glucose < 1 mmol/L at any time 2. Neonate with abnormal clinical signs and a single blood glucose < 2.5 mmol/L 3. Neonate at risk*, but well, with 2 consecutive glucose measurements 1 – 1.9 mmol/ ***Risk factors include:** • Preterm >/= 34 – 36+6 weeks gestation • Term infants with IUGR (birthweight <2nd centile) • Infants of diabetic mothers • Infants of mothers taking beta blockers in third trimester and/or at the time of delivery • Cord pH < 7.1 and/or base deficit >/= -12 mmol/L

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 7 for some examples of interpretation. Please note, this is not an exhaustive list. Consideration of the clinical history prior and at the time of the hypoglycaemia episode is important as is any pre-analytical issues which may affect interpretation of the results. It is important that the times samples were taken is recorded so that results can be accurately compared with the concomitant blood or plasma glucose.

Table 7: Examples of interpretation of biochemical results

Investigation	Interpretation
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 these common tests, 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 could be secondary to poor perfusion, infection/ sepsis or HIE in the unwell neonate. However, may indicate a glycogen storage disease or defect of energy metabolism. • An unexplained acidosis with an increased anion gap may indicate a defect of organic acid metabolism, particularly if the lactate and/or ketoacid concentration is insufficient to explain the finding. • Many organic acidaemias are associated with hyperammonaemia. • Normal CRP in a patient in whom infection or sepsis is suspected strongly indicates another underlying disorder e.g. IMD Increased triglycerides with no lipaemia is suggestive of glycerol, either dietary or due to a disorder of glycerol metabolism.
Intermediary metabolites: **Free fatty acids 3-hydroxybutyrate**	Sample must be taken at time of hypoglycaemia to allow accurate interpretation. 1. Free fatty acids/3-hydroxybutyrate ratio <1 provided that the ketones are >1 mmol/L suggests an appropriate lipolytic and ketogenic response to hypoglycaemia 2. Low free fatty acids and 3-hydroxybutyrate concentrations at the time of hypoglycaemia suggest hyperinsulinism. Note that in neonates pan-hypopituitarism also presents as a poor lipolytic and ketogenic response at the time of hypoglycaemia. 3. Free fatty acids/3-hydroxybutyrate ratio >2 suggests a fatty acid oxidation defect

	Note that neonates may have a poor metabolic response to stress/hypoglycaemia and patients on chemotherapy or parental nutrition, or with liver disease may produce an unusual pattern of intermediary metabolites in response to hypoglycaemia. Certain glycogen storage disorders may also have an abnormal free fatty acid/3-hydroxybutrate pattern. See appendix one for further interpretation.
Endocrine tests: **Insulin (and C-peptide), cortisol and growth hormone**	Detectable insulin in a hypoglycaemic sample indicates hyperinsulinism; note individual labs will have their own defined cut-offs and reporting units. C-peptide should be added to confirm endogenous hyperinsulinism. Understanding the limitations of the insulin assay in use is important. Not all insulin assays detect insulin analogues (i.e. exogenous insulin) so if it is important to exclude surreptitious insulin administration, a broad-specificity assay should be used. All results should be interpreted in the context of the clinical history and plasma glucose from a sample taken at the same time as insulin is measured and evidence of any lipolytic or ketogenic response. Low cortisol indicates either hypoadrenalism or hypopituitarism – further tests, such as dynamic function tests, are indicated. Note, however, that in neonates the adrenal response to hypoglycaemia may be blunted. Low growth hormone may indicate hypopituitarism or isolated growth hormone deficiency.
Acylcarnitines	Specific acylcarnitine species are invariably raised in fatty acid oxidation defects/organic acidaemias. 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. This is a normal response to hypoglycaemia.
Organic acids	Ketone bodies and dicarboxylic acids are seen as part of the normal response to fasting and/or hypoglycaemia. Specific organic acids will usually be present in a crisis sample from patients with fatty acid oxidation disorders or organic acidaemias. The laboratory will provide a full interpretation of any organic acids present in the profile. Note, samples collected post-treatment, or when the patient is well, may not always show abnormalities.

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. These usually do not need to be collected whilst the patient is hypoglycaemic and can be requested later after review by a specialist.

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 or endocrine specialist. Liaising with your local laboratory in advance to ensure samples are appropriately grouped and analysed is advantageous with these procedures.

References

[1] Recognition, assessment and management of hypoglycaemia in childhood
Ghosh A, Banerjee I, Morris AAM. *Archives of Disease in Childhood* 2016;**101:**575-580.

[2] Inborn Metabolic Diseases and Treatment. Saudubray, Baumgarther, Garcia-Cazorla, Walter; 7th Edition

[3] Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant. British Association of Perinatal Medicine, April 2017

Definitions

ABC Airways, breathing, circulation

BAPM British Association for Perinatal Medicine

CRP C-reactive protein

HIE Hypoxic ischemic encephalopathy

IKH Idiopathic ketotic hypoglycaemia

LFT Liver Function Tests

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