East Kent Hospitals University NHS Foundation Trust

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GUIDELINE

BIOCHEMICAL INVESTIGATION OF PAEDIATRIC HYPOGLYCAEMIA (EXCLUDING NEONATES)

Version:	2.0
Ratified by:	Child Health Clinical Governance
Date ratified:	25 May 2021
Name of originator/author:	Dr Sally Stock
Director responsible for implementation:	Dr Edmund Lamb
Date issued:	25 May 2021
Review date:	25 May 2023
Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care.

Version Control

Version	Date	Author	Status	Comment
1.0	Jan 2019	Miss R Jones Dr S Stock	Active	
2.0	April 2021	Dr S Stock	For approval	Title of document amended to make it clear this document is for paediatrics only. Separate hypoglycaemia guideline for neonates. Removal of signs and symptoms of hypoglycaemia Reformatted into current template

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Dr Peter Christian, Consultant Paediatrician	29 April 2021
Dr Vimal Vasu, Consultant Neonatologist	21 April 2021

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Acute Paediatric Documentation Approval Group	19 May 2021
Clinical Biochemistry Senior Staff meeting	20 May 2021
Child Health Clinical Governance Meeting	25 May 2021

Contents

1. Introduction, Background and Purpose

This document provides guidance for the biochemical investigation of hypoglycaemia in paediatrics (excluding inpatients on neonatal units).

Please see document entitled 'Neonatal guideline on glucose screening and hypoglycaemia' for guidance regarding management of newborn babies who have low blood sugar (hypoglycaemia) or are at risk of developing low blood sugar in the post-natal ward or neonatal unit. The reason for this is that cut off values for definition of hypoglycaemia in neonates and paediatrics are different.

If a baby is admitted to paediatric services after discharge from hospital within 28 days of life (neonatal period), please discuss investigations with paediatric consultant, as neonatal guideline (described above) may apply.

2. Definitions

Clinical hypoglycaemia is defined as a plasma glucose concentration low enough to cause symptoms and/or signs of impaired brain function [2].

A plasma glucose concentration of <3.3 mmol/L (measured by laboratory assay) has been recommended by the **Paediatric Endocrine Society** as a threshold for the investigation of infants and young children who are unable to reliably communicate symptoms [3].

For children who are unable to communicate their symptoms, the Paediatric Endocrine Society [3] recommends evaluation and management only of those in whom Whipple's triad has been documented. Whipple's is defined as:

I. Symptoms and/or signs consistent with hypoglycaemia
II. A documented plasma glucose concentration <3.3 mmol/L
III. Symptom relief with treatment of hypoglycaemia

It may also be appropriate to investigate asymptomatic children with a glucose concentration of <2.6 mmol/L [8].

3. Scope

This policy outlines the laboratory investigations required to investigate the cause of hypoglycaemia in paediatrics. It may be used for patients both within the Trust and in primary care and the community.

Please see document entitled 'Neonatal guideline on glucose screening and hypoglycaemia' for guidance regarding management of newborn babies who have low blood sugar (hypoglycaemia) or are at risk of developing low blood sugar in the post-natal ward or neonatal unit. The reason for this is that cut off values for definition of hypoglycaemia in neonates and paediatrics are different.

4. Guidance

- Please include all relevant clinical details with requests.
- Hypoglycaemia must be confirmed on a blood sample (plasma - fluoride oxalate) sent to the laboratory for analysis.

A Causes of hypoglycaemia

Neonatal complications	Prematurity Small for gestational age Birth asphyxia Poor feeding	
Endocrine	Pituitary	- Hypopituitarism - Isolated GH deficiency - Isolated ACTH deficiency
	Adrenal	- Adrenal insufficiency - Congenital adrenal hyperplasia
	Pancreas	- Congenital hyperinsulinism (CHI) (suspected when intravenous glucose infusion rate is greater than 8 mg/kg/min) - Secondary hyperinsulinism (Infants of diabetic mothers; acquired neonatal disorders) - Beckwith-Wiedemann syndrome
Inherited metabolic disorders	Glycogen storage disorders (GSD's) (characterised by hypoglycaemia +/-	- Impaired glycogen synthesis - GSD 0 (fasting ketotic hypoglycaemia) - Impaired glycogenolysis - GSD I, III, VI, IX

	hepatomegaly, +/- muscle weakness, aches and pains)	
	Fatty acid oxidation disorders	- Medium chain acyl CoA dehydrogenase deficiency (MCADD) - Carnitine palmitoyltransferase 2 (CPT2) deficiency - Respiratory chain disorder e.g. Multiple acyl CoA dehydrogenase deficiency (MADD)
	Organic acidurias	- Methylmalonic aciduria (MMA) - Proprionic aciduria
	Amino acid disorders	- Maple Syrup Urine Disease (MSUD) - Tyrosinaemia -
	Carbohydrate disorders	- Galactosaemia - Hereditary fructose Intolerance - Fructose-1,6 bisphosphatase deficiency - Congenital disorder of glycosylation type 1B
Drug-related	Insulin	- Exogenous analogues - Secretagogs e.g. sulphonylureas
	Beta blockers Salicylates Alcohol	- Maternal use
Acquired	Liver disease Infections - Gastroenteritis - Sepsis - Malaria	

Adapted from [6]

It is important to remember that hypoglycaemia is common secondary to septicaemia, severe systemic illness, intrauterine growth retardation and maternal diabetes.

B Investigation of hypoglycaemia

Taking a good clinical history may help in directing investigations. Age and presentation are important clinical clues. Important things to note include:

- Timing of hypoglycaemia in relation to feeds
- Any history of drug or alcohol intake including steroids
- Glucose requirements (>8 mg/kg/min is suggestive of hyperinsulinism) [4]

- The presence of any physical signs, including, hepatomegaly, macrosomia, micropenis, hyperpigmentation, short stature and decreased subcutaneous fat

C Laboratory investigations

Point of care testing devices are at their least accurate at low concentrations. It is important to confirm any suspected hypoglycaemia by the analysis of a fluoride oxalate sample measured in a clinical laboratory. Appropriate samples should, if possible, be collected before administration of glucose to allow identification of the underlying cause. However, treatment should **NOT** be delayed by waiting for the laboratory glucose result or if samples are difficult to obtain [7].

Samples should be taken from a warm well-perfused heel by heel-prick, or from a free-flowing venous arterial sample. Abnormal lipid or protein content in samples may reduce the accuracy of all glucose results. Do not aspirate the sample from a catheter that has had a dextrose infusion running through it [5].

First line routine investigations

Test	Sample	Possible causes
Blood gases	Capillary gas tube	Metabolic acidosis in severe ketosis, lactic acidosis or organic acidaemia
LFTs	SST	Liver failure Inherited metabolic defects
Urea and electrolytes	SST	Low sodium and raised potassium in adrenal insufficiency

Hypoglycaemia screen

This screen includes the necessary tests to investigate severe and/or persistent hypoglycaemia in, infants and children. **SAMPLES FOR ALL TESTS SHOULD IDEALLY BE TAKEN AT THE TIME OF THE HYPOGLYAEMIC EPISODE**, which has been confirmed by laboratory analysis of a fluoride oxalate (grey top) sample. Samples for β-hydroxybutyrate and free fatty acids **MUST** be taken at time of hypoglycaemia. The most important samples to obtain are **glucose and insulin followed by those for cortisol and lactate** [8]. Results can be available in a significantly shorter timeframe in urgent situations. This should be discussed with the Duty Biochemist (x723 6287).

Test	Sample type	Additional information
Blood		
Glucose (laboratory) Lactate (can be measured on blood gas analyser)	Plasma (fluoride oxalate) (>0.5 mL)	
Cortisol Insulin	Serum (>1 mL)	Deliver to the lab as soon as possible (maximum of 4 hours)
Free fatty acids β-hydroxybutyrate		Urine or blood ketones can be measured by a point of care device as an alternative to measurement of 3- βOH
Acylcarnitine	Blood spots on a Guthrie card	
Plasma amino acids	Plasma (lithium heparin) (>0.5 mL)	
Ammonia	Plasma (EDTA) (>0.5 mL)	
Urine		
Urine organic acids	Random urine sample in plain container (5-10 mL)	

The following tests may be requested in special circumstances, which largely depend on the clinical signs/symptoms of the patient and results of other biochemical and radiological investigations. Please discuss with the Duty Biochemist prior to requesting any of the following.

Blood/plasma:

- C-peptide
- Glucagon
- Growth hormone, IGF1, IGF2, IGFBP1 & IGFBP3
- Plasma metanephrines

D Interpretation of test results

The results of these investigations should be evaluated in the context of the clinical symptoms. Further specialist investigations may be indicated, but these tests are usually undertaken by specialist metabolic or endocrine laboratories. The Duty Biochemist (x723 6287) is available to discuss any abnormal results and offer advice on further investigations, including details of specimen requirements for specialist metabolic laboratories.

5. Duties

All staff involved in the investigation of hypoglycaemia, whether clinical or laboratory must adhere to this policy.

6. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff and Dr Peter Christian (Paediatric Consultant, clinical lead for diabetes). Communication is held on the pathology shared-drive.

7. Review and Revision Arrangements

Two years from implementation date, by author.

8. Training

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology and/or Paediatric MicroGuide.

9. Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

10. Monitoring

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry, in collaboration with the relevant clinical teams.

11. References and Associated Documents

[1] Heap S, Gray J, Ewer A. Neonatology and laboratory medicine. ACB Venture Publications

[2] Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2009 Mar 1;94(3):709-28.

[3] Thornton, PS, Stanley, CA, De Leon, DD, Harris, D, Haymond, MW, Hussain, K, Levitsky, LL, Murad, MH, Rozance, PJ, Simmons, RA and Sperling, MA, 2015. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. The Journal of Pediatrics, 167(2), pp.238-245.

[4] Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine—Framework for Practice). Archives of Disease in Childhood-Education and Practice. 2018 Jun 14:edpract-2017.

[5] April 2017. Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant Framework for Practice. British Association of Perinatal Medicine.

[6] Ghosh A, Banerjee I, Morris AA. Recognition, assessment and management of hypoglycaemia in childhood. Archives of Disease in Childhood. 2016 Jun 1;101(6):575-80.

[7] National Metabolic Biochemistry Network Guidelines for the investigation of hypoglycaemia in infants and children: http://www.metbio.net/docs/MetBio-Guideline-GARU968012-23-01-2012.pdf

[8] BIMDG Recurrent hypoglycaemia guidelines: http://www.bimdg.org.uk/store/guidelines/Hypoglycaemia_2016_189288_09092016.pdf