All Wales Clinical Biochemistry Audit Group

REVISED STANDARDS FOR THE BIOCHEMICAL INVESTIGATION OF INHERITED METABOLIC DISEASE IN CHILDREN

INTRODUCTION

The first set of standards were published in 2005 to provide guidance and recommendations for the biochemical investigation of inherited metabolic disease in children. This was following an audit of 13 laboratories in Wales performed in 2002, which showed variable practice and test availability.

A re-audit was performed in 2010. The aims were to audit against the previously published standards, to review current practice and to offer new recommendations based on national guidelines now available from the UK National Metabolic Biochemistry Network (MetBioNet). A questionnaire was sent out to 12 laboratories in Wales, and 11/12 responses were received. Results were presented (November 2010) and proposals for revised standards were discussed (November 2012) with the All Wales Audit Group.

STANDARDS

(1) Testing Requirements

When to test?
Acute setting – this is the best time to collect samples (for example, during episodes of hypoglycaemia, acidosis, rhabdomyolysis).
Non-acute setting (for example, investigation of developmental delay) – pre-prandial (fasting) samples are preferable, to exclude dietary effects and aid interpretation.

In all cases, it is useful to provide details of feeds/diet, medications (eg. anticonvulsants) if information is available.

How to test?
Ensure appropriate IQC and EQA in place for all assays.
Awareness of limitations of point of care testing (POCT) assays (see details below for ammonia and glucose testing).

(2) First Line Testing

It is recommended that the following tests are done:

- urea and electrolytes, LFTs
- blood gases, lactate, ammonia
- plasma glucose, urate, CK
- plasma amino acids
- urine organic acids
- bloodspot acylcarnitines

Notes:

(i) depending on the age and presentation of the patient, it may be appropriate to include other tests (for example, red cell galactose-1-phosphate uridyl

transferase / galactosaemia screen, total plasma homocysteine, urine glycosaminoglycans, CSF amino acids).

(ii) urine amino acid analysis should *only* be included if investigating for a renal tubular disorder of amino acid transport (such as cystinuria or Hartnups), or when no plasma sample is available for amino acid analysis.

(iii) for laboratories using ammonia meters (dry slide chemistry strips for whole blood ammonia measurements), ensure awareness that this method has a **limited working range up to 285 μmol/L**, therefore is **only suitable for initial screening** of hyperammonaemia. All abnormal results should be confirmed by a quantitative method.

(iv) awareness of possible interferences in POCT glucose analysis – notably, effect of haematocrit, bilirubin, galactose. Always confirm with laboratory glucose analysis, and investigate any discrepancies observed between results.

(v) increases in CK and hyper- or hypo- uricaemia may be helpful in the diagnosis of a number of inherited metabolic disorders (for example. glycogen storage disorders, mitochondrial disease, purine disorders, sulphite oxidase deficiency and molybdenum cofactor deficiency).

(3) Use of hypoglycaemia kits

These are recommended by MetBioNet (see Guidelines for the investigation of hypoglycaemia on www.metbio.net or http://www.metbio.net/docs/MetBio-Guideline-GARU968012-23-01-2012.pdf). A pre-packed "kit" (containing appropriate collection tubes with labelled request forms) can be supplied to paediatric and neonatal wards, to aid collection of correct samples at the time of hypoglycaemia.

An example kit:

Sample Type	**Tests**
Heparinised capillary tube	Blood gases, lactate
3x lithium heparin paed tubes	(i) cortisol, (ii) ammonia, amino acids, (iii) insulin, C-peptide
Fluoride oxalate tube	Glucose
EDTA tube	Non-esterified fatty acids, 3-hydroxybutyrate
Guthrie card	Bloodspot acylcarnitines
Universal container	Urine organic acids

(4) Further testing

This will depend on clinical symptoms or main presenting features, and the results of first line tests. For guidance on further testing, suggest refer to MetBioNet Best Practice Guidelines (www.metbio.net/metbioGuidelines.asp). Guidelines are available for Investigation of Seizures / Hypoglycaemia / Hyperammonaemia / Neonatal Jaundice / Rhabdomyolysis / Global Developmental Delay.

For further information, discussion with a metabolic specialist is advisable.

(5) Protocol for Sudden Infant Death (SID)

It is recommended that each laboratory should have a protocol in place for the collection and storage of ante- and peri-mortem samples. MetBioNet has published guidelines (http://www.metbio.net/docs/MetBio-Guideline-RASU337946-27-11-2010..pdf) with full details of storage requirements and necessary analyses.

Note: in cases where no samples have been collected, it may be possible to retrieve the newborn screening Guthrie card (contact Newborn Screening Laboratory, University Hospital of Wales) for analyses.

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VERSION: 2.

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APPENDIX 1 Calendar of audit process for standards for inborn metabolic error investigation

Nov. 2002	Findings of a survey of all 13 Welsh biochemistry laboratories that provide services for acute paediatric units, undertaken by Mrs A Wayte (Principal Biochemist, Bangor), presented at an All Wales Clinical Biochemistry Audit Group meeting in Llandudno.
May 2003	Initial draft standards prepared by Mrs A Wayte, considered at an All Wales Clinical Biochemistry Audit Group committee meeting and presented at an audit meeting held at Morriston Hospital, Swansea.
April 2005	Further draft of standards prepared and sent for consultation to clinical biochemists and paediatricians in Wales, to seek their views.
Nov 2005	Further draft prepared after comments from Paediatricians
Nov 2005	Final Standard. Version 1
2010	Re-audit against previously published standards performed in 2010.
Nov 2010	Results of questionnaire presented by Maryam Khan at an audit meeting in Swansea.
Nov 2012	New standards and recommendations for the biochemical investigation of metabolic disease presented by Maryam Khan at an audit meeting in Cwmbran.
May 2013	Final standards. Version 2.