UK Metabolic Biochemistry Network Recommendations for Investigation of Metabolic Causes of Cardiomyopathy

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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

Cardiomyopathy is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality [1].

Inborn metabolic diseases (IMD) account for 15 – 20% of all cases of paediatric cardiomyopathy. The following findings should raise the suspicion of an IMD in a patient with cardiomyopathy:

- Family history of cardiomyopathy, sudden or unexplained death;
- Parental consanguinity;
- Multisystemic involvement with unusual or unexplained extracardiac disease including, but not limited to, developmental delay or regression, hypotonia, coarse facial features, macroglossia, feeding difficulties, failure to thrive, recurrent respiratory infections or rhabdomyolysis.
- Episodic metabolic decompensation with signs including, but not limited to, hypoglycaemia, vomiting or lethargy [2,3].

This guideline provides an overview of IMDs reported to cause cardiomyopathy, the affected genes and relevant laboratory investigations (table 1). A suggested panel of laboratory tests useful in the diagnosis of IMD in a patient with cardiomyopathy is provided (table 2). These investigations should normally be performed in conjunction with analysis of relevant gene panels. It is important to liaise with the local laboratory to determine the availability of tests, sample requirements and to discuss priority sample analysis where a treatable IMD is suspected. Information about laboratories providing analysis of specialist metabolic investigation and sample requirements is available on the MetBioNet website:
https://metbio.net/resources/assay-directory/

Mitochondrial disease is an important metabolic cause of cardiomyopathy in children and adults. Detailed investigation of mitochondrial disorders is not included in this guideline, but further information is available on the NHS Rare Mitochondrial Disorders Service website:
Home - Rare Mitochondrial Disorders Service (mitochondrialdisease.nhs.uk)

Patients with severe cardiomyopathy may require extra-corporeal membrane oxygenation (ECMO). The challenges of IMD investigation in a patient on ECMO are discussed.

Table 1. Inherited metabolic disorders which may be associated with cardiomyopathy, the causative gene(s), supporting clinical signs and metabolic investigations which may be helpful in making the diagnosis. Abbreviations: ACY, acylcarnitines; AA, amino acids; BS, bloodspot; L, leukocytes; OA, organic acids; P, plasma; S, serum; U, urine. *Plasma acylcarnitines is recommended in the investigation of disorders of long-chain fatty acid oxidation [4].

Disorder	Gene	Supporting clinical signs	Metabolic Investigations
Fatty acid oxidation and carnitine disorders			
Carnitine transporter deficiency (primary carnitine deficiency)	*SLC22A5*	Arrhythmia, heart failure, muscle weakness, hypotonia, fatigue, hypoketotic hypoglycaemia, may be symptomatic	Free and total carnitine (P) ACY (BS, P) Fractional excretion of carnitine (P & U)
Carnitine-acylcarnitine translocase deficiency (CACTD)	*SLC25A20*	Arrhythmia, liver disease, hyperammonaemia, hypoketotic hypoglycaemia	ACY (P)*
Carnitine palmitoyltransferase II deficiency (CPT2D)	*CPT2*	Arrhythmia, liver disease, muscle weakness, rhabdomyolysis, hyperammonaemia, hypoketotic hypoglycaemia	ACY (P)*
Very long chain acyl-CoA dehydrogenase deficiency (VLCADD)	*ACADVL*	Severe form: infant cardiomyopathy, hypoketotic hypoglycaemia Attenuated form: muscle weakness, rhabdomyolysis. May be asymptomatic	ACY (BS, P) OA (U)
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) / Mitochondrial Trifunctional Protein deficiency	*HADHA* *HADHB*	Lactic acidaemia, hypotonia, hypoketotic hypoglycaemia, liver dysfunction, rhabdomyolysis, retinopathy, neurology.	ACY (BS, P) OA (U)
Multiple acyl-CoA dehydrogenase deficiency (MADD) (glutaric aciduria type II)	*ETFA* *ETFB* *ETFDH*	Severe form: neonatal acidosis, hypotonia, hypoglycaemia, hyperammonaemia, hepatomegaly, facial dysmorphism. Attenuated form: episodic hypoglycaemia, liver dysfunction, progressive encephalopathy epilepsy, myopathy.	ACY (BS, P) OA (U)
Mitochondrial disorders			
Complexes I - V deficiencies	Various	Heterogeneous disorders, any organ may be affected; lactic acidosis	AA (P, U) ACY (BS, P) Lactate (CSF, P) OA (U)
Barth syndrome	*TAZ*	Neutropenia, muscle weakness, growth retardation	OA (U) Cardiolipin (BS)

Disorder	Gene	Supporting clinical signs	Metabolic Investigations
Lysosomal storage disorders			
Glycogen storage disease type II (Pompe disease)	*GAA*	Hypotonia, progressive respiratory failure, failure to thrive, muscle weakness	α-glucosidase (BS, L)
MPS type I (Hurler)	*IDUA*	Recurrent upper respiratory tract infections, slow growth, dysmorphism, progressive hepatosplenomegaly, impaired growth	GAG (U) α-L-iduronidase (L)
Fabry disease	*GLA* (X-linked)	Limb pain, recurrent fever, hypohidrosis, angiokeratomas, angiectasis Cardiomyopathy may develop in adulthood and/or renal failure, stroke, hearing loss	α-galactosidase A (BS, L) (males) Lyso globotriaosylceramide (P ,U) and α-galactosidase A (BS, L) (females) [5]
Glycogen storage disorders			
Glycogen storage disease type IIIa (glycogen debrancher enzyme deficiency)	*AGL*	Poor growth, delayed motor milestones, ketotic hypoglycaemia, hyperlipidaemia, raised transaminases, progressive myopathy, hepatomegaly.	AA (P) Glycogen debrancher enzyme (L, liver biopsy)
Glycogen storage disease type IV (glycogen brancher enzyme deficiency); neuromuscular form	*GBE1*	Hypotonia, myopathy, exercise intolerance	Glycogen brancher enzyme (L, liver biopsy, muscle biopsy) Histology (liver biopsy, muscle biopsy)
Muscle glycogen synthesis deficiencies	*GYS1* *GYG1* *PRKAG2*	Muscle weakness	Histology (muscle biopsy)
Amino and organic acid disorders			
Propionic aciduria (propionyl-CoA carboxylase deficiency)	*PCCA* *PCCB*	Dehydration, hepatomegaly, lethargy, high anion gap metabolic acidosis, hyperammonaemia	AA (P) ACY (BS, P) OA (U)
Methylmalonic aciduria (methylmalonyl-CoA mutase deficiency)	*MMUT*	Dehydration, hepatomegaly, lethargy, high anion gap metabolic acidosis, hyperammonaemia	AA (P) ACY (BS, P) OA (U) Methylmalonic acid (P, U)
Malonic aciduria (cytosolic malonyl-CoA decarboxylase deficiency)	*MLYCD*	Developmental delay, epilepsy, recurrent vomiting	ACY (BS, P) OA (U)
Tyrosinemia type 1 (fumarylaceoacetase deficiency)	*FAH*	Liver failure, vomiting, bleeding, renal tubulopathy	AA (P, U) OA (U) Succinylacetone (BS, P, U)

Disorder	Gene	Supporting clinical signs	Metabolic Investigations
2-methyl-3-hydroxybutyric aciduria (HSD10 disease)	*HSD17B10*	Progressing neurodegeneration, epilepsy, blindness,	ACY (BS, P) OA (U)
D-2-hydroxyglutaric aciduria type 2	*IDH2*	Intractable epileptic encephalopathy, severe developmental delay, hypotonia	OA (U) 2-hydroxyglutarate enantiomer analysis
Other metabolic disorders			
Congenital Disorders of Glycosylation (CDG)	Various	Any organ can be affected	Transferrin isoelectric focussing (S)
Hemochromatosis	*HFE* (type 1, classical) *HJV, HAMP* (type 2, juvenile) *TFR2* (type 3, severe) *SLC40A1* (type 4)	Iron overload, liver disease, diabetes, hypogonadism, may present in neonatal period	Ferritin (S) Transferrin saturation (S)

Table 2. A suggested protocol for collection of samples for the investigation of a metabolic cause of cardiomyopathy

Investigation	Sample type*	Notes
Routine laboratory tests		
Blood gases	Arterial blood	
Lactate	Fluoride plasma	
Creatinine, urea, electrolytes, including chloride, bicarbonate and calculation of anion gap	Plasma or serum	
Liver function test	Plasma or serum	
Calcium, magnesium, phosphate	Plasma or serum	
Thyroid function test	Plasma or serum	
Uric acid	Plasma or serum	Raised in some glycogen storage disorders
Cholesterol, triglyceride	Plasma or serum	
FBC and film	EDTA-blood	
Metabolic investigations		
Amino acids	Plasma, urine	Plasma recommended for investigation of amino acid disorder; urine useful in assessment of renal tubular function [6]
Acylcarnitine profile	Blood spots and/or plasma	Include measurement of free carnitine. Plasma acylcarnitines is more sensitive in the detection of disorders of long chain fatty acid oxidation [5]. Analysis of both bloodspot and plasma acylcarnitines may be helpful.
Tubular reabsorption of carnitine	Plasma and urine	Calculated from urine and plasma carnitine results
Organic acids	Urine	Qualitative analysis is sufficient for diagnosis of the majority of organic acid disorders. Quantitation of specific organic acids may be useful e.g. methylmalonic acid.
Intermediary metabolites (glucose, lactate, free fatty acids, 3-OH butyrate)	Plasma	For majority of disorders most informative when the patient is hypoglycaemic
Glycosaminoglycans (mucopolysaccharide screen)	Urine	Quantitation and 2D electrophoresis
Lysosomal enzymes: α-glucosidase, α-L-iduronidase and α-galactosidase A	Whole blood	
Lyso globotriaosylceramide	Plasma or urine	Useful in investigation of Fabry disease in females [5]
CSF lactate	CSF	If mitochondrial disorder suspected
Cardiolipin	Blood spots	For investigation of Barth syndrome in males
Transferrin isoelectric focussing	Plasma/serum	Unsuitable in patients less than 3 weeks of age or following recent blood transfusion.
Ferritin, transferrin saturation	Plasma/serum	For investigation of haemochromatosis
Succinylacetone	Blood spots, plasma or urine	May be useful where there is a high index of suspicion for tyrosinaemia type 1.

The effect of ECMO support on metabolic investigations for cardiomyopathy

ECMO is a form of cardiopulmonary life-support where blood is circulated outside the body, oxygenated, then reinfused into the circulation. A portion of the patient's blood volume is replaced with transfused blood. It is used to treat patients with severe cardiac and/or pulmonary dysfunction, often maintaining life while diagnosing or treating the underlying disease. [7]

The effect of ECMO on metabolic investigations is unclear, but there is a risk of false negative results due to dilution of samples with transfused blood. Interpretation of results may be complicated by secondary effects of ECMO including acute inflammatory response, liver failure and bowel ischemia.

Ideally, samples for metabolic investigations should be taken before ECMO is started, but this is rarely practical. To avoid the effects of ECMO on pathognomonic metabolites, samples for investigation of a metabolic cause of cardiomyopathy should be taken at least 72 hours after cessation of ECMO. This is based on guidance from the UK newborn screening programme for IMD screening in patients who have received blood transfusions. [8]

In practice, metabolic investigations may be required urgently in a patient who is severely unwell and may not survive post-ECMO support or in whom a treatable disorder is suspected. Samples should be accepted and analysed with a disclaimer on the report stating that a metabolic disorder cannot be excluded. This balances the risk of missing an acute presentation, while not producing misleading or unreliable results. Where possible, a repeat sample should then be collected when the patient is 72-hours post-ECMO.

References

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Definitions

ECMO	Extra-corporeal membrane oxygenation
MetBioNet	Metabolic Biochemistry Network

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