MetBioNet Best Practice Guidelines

Investigation of an inherited metabolic cause of cardiomyopathy

Introduction

Inborn errors of metabolism (IEM) account for at least 5% of cases of cardiomyopathy. In some disorders, cardiomyopathy is the major cause of morbidity and mortality, in others it is an incidental finding. The diagnosis of an IEM as a cause of cardiomyopathy is important as there is often disorder-specific treatment and information is useful for genetic counselling.

This Guideline lists the most common metabolic causes of cardiomyopathy, the types of cardiomyopathy found in each disorder and biochemical tests which should be performed in order to make a diagnosis. However in some cases the cardiomyopathy may not be the major clinical feature and in others may appear later in the progression of the disease.

Cardiomyopathy caused by IEM can result in sudden death, and may be identified at post mortem. The investigation of these patients presents additional challenges and is outlined below.

There are many other genetic causes of cardiomyopathy besides IEM. One of the most common causes of hypertrophic cardiomyopathy is a defect in one of at least 15 genes that code for cardiac sarcomere proteins; these are predominantly inherited in an autosomal dominant fashion. Inherited defects leading to dilated cardiomyopathy often involve defects in cardiac cytoskeleton genes and these may be X-linked, autosomal dominant or autosomal recessive. Some genetic syndromes are also strongly associated with cardiomyopathy e.g. Noonan's Syndrome. Investigation of these disorders is not included in this Guideline.

Clinical presentation

Symptoms of cardiomyopathy are caused by biventricular failure and arrhythmias. They include dyspnoea, syncope, palpitations, peripheral oedema, chest pain and thromboembolic stroke. Additional non-cardiac clinical features, a positive family history and presentation in childhood or young adulthood all point towards an IEM as the underlying cause.

Echocardiography distinguishes between hypertrophic and dilated cardiomyopathy, which aids further investigations to determine the underlying cause. Storage disorders (e.g. glycogen storage disorders, lysosomal disorders) typically cause hypertrophic cardiomyopathy, whereas accumulation of toxic metabolites (e.g. in organic acidurias) are more often associated with dilated cardiomyopathy. Many patients have features of both.

Cardiac conduction defects which may cause arrhythmias are found in the respiratory chain disorders in particular the Kearns-Sayre Syndrome

It is important to note that atypical variants exist and an IEM cannot be excluded because of the absence of characteristic clinical features or a functional cardiac abnormality.

IEMs causing cardiomyopathy

A list of the major metabolic causes of cardiomyopathy and an overview of investigation of these disorders is shown in table 1.

Investigation of cardiomyopathy

Investigations which should be performed to investigate a metabolic cause of cardiomyopathy are listed in table 2. It is important to note that sample requirements may vary between laboratories, so please refer to your local laboratory for advice before taking samples for analysis.

Post mortem investigation of a metabolic cause of cardiomyopathy

Isolated cardiomyopathy as a primary cause of death, or in conjunction with other organ involvement is a relatively common finding for the paediatric histopathologist. Metabolic causes include fatty acid oxidation disorders, respiratory chain disorders, storage disorders and Barth syndrome.

It is essential that appropriate samples are taken as soon as possible after death. A summary of samples for specialist metabolic investigations and how they should be stored is given in table 3. These are in addition to samples taken for histological investigations. See the MetBioNet Guideline 'Metabolic Investigation of Sudden Unexplained Death in Childhood' for more information. http://www.metbio.net/docs/MetBio-Guideline-RASU337946-27-11-2010..pdf .

References

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Disclaimer

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Table 1: Metabolic causes of cardiomyopathy and investigations required for their diagnosis.

Disorder	Most prominent cardio-myopathy	Other cardio-myopathy	Supporting clinical signs	First line metabolic tests	Diagnostic test
Fatty acid oxidation and carnitine disorders					
Carnitine transporter deficiency (primary carnitine deficiency)	DCM	HCM, mixed	Arrhythmia, muscle weakness/hypotonia, liver disease, hypoketotic hypoglycaemia	Paired plasma + urine carnitine, ACY, OA	Fibroblast carnitine transport assay, *SLC22A5* gene
Carnitine acylcarnitines translocase deficiency CAT	Mixed	HCM, DCM	Arrhythmia, liver disease, hyperammonaemia, hypoketotic hypoglycaemia	ACY, OA, IM	Fibroblast fatty acid oxidation flux / in vitro probe assay, CAT assay, *SLC25A20* gene
Carnitine palmitoyltransferase II (CPT2) deficiency (neonatal & infantile forms)	HCM, mixed	DCM	Arrhythmia, liver disease, hyperammonaemia, hypoketotic hypoglycaemia	ACY, OA, IM	Fibroblast fatty acid oxidation flux / in vitro probe assay, CPT2 assay, *CPT2* gene
Very long chain acyl-CoA dehydrogenase deficiency (VLCADD) (severe form)	HCM	DCM, mixed	Liver disease, hepatomegaly, hypoketotic hypoglycaemia	ACY, OA, IM	Fibroblast fatty acid oxidation flux / in vitro probe assay, VLCAD assay, *ACADVL gene*
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) / Mitochondrial Trifunctional Protein deficiency	HCM	Mixed	Liver disease, hypotonia, hypoketotic hypoglycaemia, neuropathy, lactic acidosis, retinopathy, hypoparathyroidism	ACY, OA, IM	Fibroblast fatty acid oxidation flux / in vitro probe assay, LCHAD & long chain-thiolase assay, *HADHA* & *HADHB* genes
Multiple acyl-CoA dehydrogenase deficiency (MADD) (glutaric aciduria type II)	HCM	Mixed	Facial and cerebral malformations, cystic renal disease, liver disease, hypoketotic hypoglycaemia	ACY, OA, IM	Fibroblast fatty acid oxidation flux / in vitro probe assay, *ETFA*, *ETFB* & *ETFDH* genes
Mitochondrial disorders					
Complexes I - V deficiencies	HCM, mixed	DCM, NC	Heterogeneous disorders, any organ may be affected; lactic acidosis	OA, blood & urine amino acids, blood & CSF lactate	Skeletal and cardiac) muscle respiratory chain complexes, Nuclear and mitochondrial DNA mutations e.g. *SCO2*, complex I nuclear genes, mtDNA mutations/deletions, mtDNA depletion syndromes
Barth syndrome	NC	HCM, mixed	Neutropenia, muscle weakness, growth retardation	OA, cardiolipin profile.	*TAZ* gene

Table 1 (continued)

Disorder	Most prominent cardio-myopathy	Other cardio-myopathy	Supporting clinical signs	First line metabolic tests	Diagnostic test
Lysosomal storage disorders					
Glycogen storage disease type II (Pompe disease)	HCM, mixed		Hypotonia, muscle weakness, progressive respiratory failure	Leukocyte enzymes: α-glucosidase	*GAA* gene
MPS type I (Hurler), other MPS disorders		DCM, mixed	Dysmorphism, coarse facies, hepatosplenomegaly, impaired growth, skeletal abnormalities	GAGs (quantitation and electrophoresis)	Leukocyte MPS enzymes; genetic analysis
Fabry disease		HCM	Limb pain, angiokeratom; HCM is a late complication in adults, also found in female carriers	Leukocyte enzymes (males): α-galactosidase A	*GLA* gene to detect female carriers
Mucolipidoses II & III (I-cell disease & pseudo-hurler polydystrophy		HCM	Dysmorphism, coarse facies, hepatosplenomegaly,skeletal abnormalities, psychomotor retardation	Plasma arylsulphatase A or hexosaminidase (elevated)	Fibroblast N-acetylglucosaminyl-1-phosphotransferase assay
Disorders of glycogen metabolism					
Glycogen storage disease type IIIa (debrancher enzyme deficiency)	HCM	Mixed	Ketotic hypoglycaemia, hyperlipidaemia, raised transaminases	UA, LFTs, cholesterol, lactate, amino acids	Fibroblast / leucocyte enzyme studies, *AGL* gene
Glycogen storage disease type IV (brancher enzyme deficiency), neuromuscular form	DCM	Mixed	hypotonia, exercise intolerance, polyglucosan bodies in affected tissues	Enzyme assay in affected tissue	Histology, *GBE1* gene
Amino and organic acid disorders					
Propionic aciduria	DCM	mixed	Dehydration, hepatomegaly, lethargy, coma, acidosis, high anion gap	OA, ACY	Fibroblast propionyl-CoA carboxlase assay, *PCCA* & *PCCB* genes
Methylmalonic aciduria		DCM, mixed	Dehydration, hepatomegaly, lethargy, coma, acidosis, high anion gap	OA, ACY	Fibroblast MM-CoA mutase activity, cobalamin studies, propionate incorporation assay, *MUT* & *MMACHC* (cblC) genes
Malonic aciduria		HCM, mixed	Mild clinical features. Developmental delay, epilepsy.	OA, ACY	Fibroblast malonyl- CoA decar-boxylase assay, *MLYCD* gene
Tyrosinaemia type 1 (fumarylactoacetase deficiency)		HCM	Liver failure, vomiting, renal tubulopathy	OA, plasma & urine amino acids	*FAH* gene

Table 1 (continued)

Disorder	Most prominent cardio-myopathy	Other cardio-myopathy	Supporting clinical signs	First line metabolic tests	Diagnostic test
Other metabolic disorders					
Congenital Disorders of Glycosylation (CDG)		HCM, DCM, mixed	Any organ can be affected	Transferrin isoelectric focussing	Fibroblast enzyme studies, several genes
Haemochromatosis		HCM, DCM, mixed	Iron overload, liver disease, diabetes, hypogonadism	Ferritin, transferrin saturation	*HFE* gene
Neutral lipid storage disease with myopathy NLSDM	DCM		Lipid myopathy, muscle weakness Jordan's anomaly - neutral lipid-containing vacuoles in leukocytes	increased CK	*PNPLA2 gene*

DCM Dilated cardiomyopathy, *HCM* Hypertrophic cardiomyopathy, *Mixed* Hypertrophic-hypocontractile cardiomyopathy, *NC* Non-compaction cardiomyopathy, *ACY* Acyl carnitine profile, *CK* creatine kinase, *GAGs* Glycosaminoglycans, *IM* intermediary metabolites, *OA* Organic acids, *UA* Uric acid

Table 2. Investigations required for the diagnosis of a metabolic cause of cardiomyopathy.

Sample requirements may vary between laboratories, so please refer to your local laboratory for advice before taking samples for analysis. Information on metabolic investigations can be found in the MetBioNet Metabolic Assay Directory http://www.metbio.net/metbioAssays.asp.

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/serum	
Liver function test	Plasma/serum	
Calcium, magnesium, phosphate	Plasma/serum	
Thyroid function test	Plasma/serum	
Uric acid	Plasma/serum	Raised in some glycogen storage disorders
Cholesterol, triglyceride	Plasma/serum	
FBC and film	EDTA-blood	Vacuolated lymphocytes suggestive of Hurler
Metabolic investigations		
Amino acids	Plasma/urine	
Acyl carnitine profile	Plasma/blood spots	Should include measure of free carnitine
Organic acids	Urine	
Intermediary metabolites	Fluoride plasma	Includes glucose, lactate, free fatty acids & 3-hydroxybutyrate. For majority of disorders most informative when the patient is hypoglycaemic
Glycosaminoglycans (mucopolysaccharide screen)	Urine	Quantitation and electrophoresis
White cell enzymes: α-glucosidase, α-L-iduronidase (if GAGs are abnormal) and α-galactosidase	EDTA whole blood	
CSF lactate	CSF	If mitochondrial disorder suspected
Respiratory chain enzymes	Muscle biopsy snap frozen in liquid nitrogen at bed side	Complexes I-IV , Complex V by blue native gel Fibroblast complexes /ATP production assay
Cardiolipin	Whole blood	For investigation of Barth syndrome in males
Transferrin isoelectric focussing	Plasma/serum	For investigation of glycosylation disorders
Ferritin, transferrin saturation	Plasma/serum	For investigation of haemochromatosis
Confirmation investigations		
Genetic testing	DNA	Sample for DNA and cultured fibroblasts should be stored pending results of other investigations.
Enzyme analysis	Skin biopsy for fibroblast culture	

Table 3. Samples required for the post mortem investigation of a metabolic cause of cardiomyopathy

Sample	Preservation	Storage	Investigation	Examples of disorder detected
Whole blood	Guthrie card blood spots	Dry at room temp	ACY, AA	FAOD, AAO ,OAU
Whole blood	LiHep	Plasma +4°C	ACY, AA	FAOD, AAO, OAU
Whole blood	EDTA	Room temp, then extract DNA and store at -20°C	DNA	Confirmation of findings of other investigations
Bile	Guthrie card blood spots	Dry at room temp	ACY	FAOD, OAU
Urine	Sterile vial	Freeze at -20°C	OA	FAOD and OAU
Skin (punch biopsy) or 3 mm x 3 mm	Sterile medium	Room temp or +4°C. DO NOT FREEZE		FAOD, OAU, AAO , respiratory chain disorders
Skeletal Muscle (fresh)*	Liquid nitrogen	Freeze at -80°C	Respiratory complexes I - V	Respiratory chain disorders
Cardiac muscle (fresh)*	Liquid nitrogen	Freeze at -80°C	Respiratory complexes I - V	Respiratory chain disorders
Liver (fresh)*	Liquid nitrogen	Freeze at -80°C	Enzyme assays	Glycogen storage disorders

OA Organic acids, *AA* Amino acids, *ACY* acyl carnitine profile, *FAOD* fatty acid oxidation disorder, *AAO* amino acidopathy, *OAU* organic aciduria.

*Tissue samples should be collected before death if possible as enzyme activities deteriorate rapidly post mortem.