UK Metabolic Biochemistry Network recommendations for the investigation of sudden unexplained death in infancy and childhood (SUDIC)

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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

Between 3% and 6% of sudden infant death syndrome (SIDS), sudden unexpected death in infancy (SUDI) and sudden unexpected death in childhood (SUDC) are likely due to inherited metabolic disorders. The most frequently implicated disorders include defects of fatty acid oxidation and carnitine transport, ketogenesis, congenital lactic acidosis (respiratory chain disorders), urea cycle disorders, organic acidurias and carbohydrate disorders. This guideline outlines the key sample requirements for investigation into an inherited metabolic disorder as the cause of death and should be used in conjunction with local procedures which outline investigation of a wider range of causes. Samples should be collected and stored when death is imminent or as soon as possible after death and post mortem in order to reach an accurate diagnosis.

Table 1. Minimum set of samples for investigation of IMD causes of SUDIC

Sample	Container and volume	Storage	Investigations
Blood	Guthrie card 4 filled spots	+4°C or ambient	Acylcarnitines DNA extraction if required
	Retrieval of Newborn Screening Guthrie card if available from NBS lab	+4°C or ambient	For confirmation of any post mortem findings
	Lithium heparin 2 x 1 ml	-20°C	Plasma amino acids Any other relevant metabolic investigations
	EDTA 2 x 1 ml (1 ml minimum)	+4°C as whole blood	DNA extraction and storage
Urine (or bladder wash if urine not available)	Plain universal container 2 - 4 ml (as much as possible)	-20°C	Organic acids
Skin biopsy	Full thickness (4 mm ×4 mm) obtained as soon as possible after death using sterile technique into tissue culture medium (ideal) or sterile saline.	+4°C or ambient (DO NOT FREEZE)	For fibroblast culture and store
Muscle (skeletal plus cardiac/liver/ kidney as indicated)	Snap frozen (local procedures apply) Submitted for staining (i.e. oil red O or Sudan black stains), immunohistochemistry or respiratory chain complexes (pre-mortem, <2 h after death).	-80°C (snap frozen at the bedside)	Respiratory chain enzymes

Biochemical analysis

Acylcarnitine analysis

Post mortem acyl carnitine profiles differ to normal profiles and specific post mortem reference ranges need to be applied. The conditions detected are limited compared to in-life disorders and include:

(1) Disorders of fatty acid oxidation and carnitine transport: primary carnitine deficiency, medium chain acyl-CoA dehydrogenase deficiency (MCADD), very long chain acyl-CoA dehydrogenase deficiency (VLCADD) and long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
(2) Organic acidurias: Methylmalonic aciduria (MMA), proprionic aciduria (PA), isovaleric aciduria (IVA)

Post mortem acyl carnitine analysis should be carried out in a laboratory experienced in the interpretation of post mortem samples.

Organic acid analysis

Urine organic acids are the most informative. However, if urine is not available a bladder wash may be useful but must be interpreted with caution. Gross excretion of lactate and tricarboxylic acid (TCA) cycle metabolites is common secondary to post mortem changes. Moderate increases of other metabolites are often noted which may be secondary to post mortem changes.

Detection of dicarboxylic acids in the absence of ketosis requires follow up investigation for fatty acid oxidation defects. Prominent organic acidurias including MMA, PA and IVA may be picked up by organic acid analysis. MCADD has a typical pattern of increased hexanoyl and suberyl glycine in post mortem urine organic acids. Urine organic acid analysis and interpretation should be carried out by a laboratory experienced in post mortem analysis.

Profiles often contain large amounts of ketones. A potential cause may be undiagnosed diabetes mellitus and, particularly in cases with suggestive clinical history, testing of urine glucose should be considered to investigate this.

Drug metabolites may be detected on organic acid analysis however, samples should be further analysed by a toxicology laboratory specialising in post mortem investigations to determine the significance.

Fatty acid oxidation studies on cultured fibroblasts

A skin biopsy should be set up for subsequent testing e.g. fatty acid oxidation flux analysis to investigate for fatty acid oxidation defects as well as general mitochondrial or respiratory chain defects. Specific enzyme analysis should be requested based on biochemical and clinical findings.

In all cases of suspected non-accidental head injury, specific enzyme analysis of glutarate dehydrogenase should be carried out to rule out Glutaric Aciduria Type 1.

Genetic analysis

Genetic analysis is carried out dependent upon post mortem analysis, biochemical findings and clinical presentation prior to death. This may involve specific genetic panels or whole exome sequencing.

References

Deaths: Sudden Unexpected Death and Inherited Metabolic Disease Pathology. Marta C. Cohen, Sufin Yap, Simon E. Olpin, and Camilla Scott, Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom © 2024 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies. This is an update of M.C. Cohen, S. Yap, S.E. Olpin, Deaths: Inherited Metabolic Disease and Sudden Unexpected DeathdPathology, Editor(s): Jason Payne-James, Roger W. Byard, Encyclopedia of Forensic and Legal Medicine (Second Edition), Elsevier, 2016, Pages 85e95, ISBN 9780128000557, https://doi.org/10.1016/B978-0-12-800034-2.00125-7. Introduction

Definitions

IMD	Inherited metabolic disorder
IVA	Isovaleric aciduria
LCHADD	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
MCADD	Medium chain acyl-CoA dehydrogenase deficiency
MMA	Methylmalonic aciduria
PA	Propionic aciduria
SIDS	Sudden infant death syndrome
SUDC	Sudden unexplained death in childhood
SUDI	Sudden unexplained death in infancy
SUDIC	Sudden unexpected death in infancy and childhood
TCA	Tricarboxylic acid
VLCADD	Very long chain acyl-CoA dehydrogenase deficiency

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