

Acylcarnitine profile analysis

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Disclaimer: These Technical Standards and Guidelines were developed primarily as an educational resource for clinical laboratory geneticists to help them provide quality clinical laboratory genetic services. Adherence to these standards and guidelines is voluntary and does not necessarily assure a successful medical outcome. These Standards and Guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinical laboratory geneticist should apply his or her own professional judgment to the specific circumstances presented by the individual patient or specimen. Clinical laboratory geneticists are encouraged to document in the patient's record the rationale for the use of a particular procedure or test, whether or not it is in conformance with these Standards and Guidelines. They also are advised to take notice of the date any particular standard or guideline was adopted, and to consider other relevant medical and scientific information that becomes available after that date. *Genet Med* 2008;10(2):151–156.

Acylcarnitine profile (ACP) analysis is performed for the biochemical screening of disorders of fatty acid oxidation (FAO) and organic acid metabolism.^{1,2} In some cases, ACP results are diagnostic for a specific disorder, while in other cases, further testing is needed to establish a precise diagnosis.^{1–3} The conditions revealed by acylcarnitine analysis have in common the accumulation of C2–C18 acyl-CoA species, which are substrates for one of several carnitine acyl-CoA transferases expressed in different intracellular compartments. The resulting acylcarnitine species are measured in the following clinical situations:

1. Evaluation of symptomatic patients
2. Evaluation of asymptomatic (at-risk) siblings of known patients
3. Newborn screening and follow-up testing
4. Prenatal diagnosis
5. Postmortem screening

Virtually all laboratories providing this analysis as a clinical service do so using tandem mass spectrometry (MS/MS) as the analytical platform.^{4–6} Less frequently employed methodologies include gas chromatography-mass spectrometry, high-performance liquid chromatography, and capillary electrophoresis. As is the case for all complex metabolic profiles, appropriate acylcarnitine analysis requires both analytical pro-

iciency and in-depth interpretation of results with informative reporting.

BACKGROUND

Clinical description of disease

Inherited FAO disorders are inborn errors of metabolism (IEM) of relatively recent discovery.^{7–9} They may present at any age, from birth to adulthood, frequently leading to life-threatening episodes of metabolic decompensation after a period of inadequate caloric intake and intercurrent illness. Typical manifestations are hypoketotic hypoglycemia, liver disease, skeletal and cardiomyopathy, and sudden unexpected death.

Organic acidemias are a more heterogeneous group of IEM.^{10,11} They typically present with recurrent episodes of acute life-threatening illness, hypo- or hypertonia, failure to thrive, and developmental delay. Common acute manifestations include vomiting, lethargy, coma, and seizures.

With rare exceptions, the diagnosis of these conditions is almost exclusively a laboratory process, of which acylcarnitine analysis is a key component. A comprehensive metabolic evaluation typically also includes the analysis of plasma amino acids, urine organic acids, and plasma carnitine (free and total). Depending on results of these studies, additional testing may also be warranted.

Disorders biochemically detectable by acylcarnitine analysis

ACP analysis detects disorders of FAO and some disorders of organic acid metabolism. Specific disorders detected in a typical acylcarnitine run are shown in Table 1.

Prevalence

The combined incidence of these disorders is between 1:5,000 and 1:10,000 live births.¹²

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Table 1

Inborn errors of metabolism detected by acylcarnitine profile analysis: disorders of fatty acid oxidation and organic acid metabolism

Fatty acid oxidation disorders
Carnitine uptake defect
Carnitine palmitoyltransferase I (CPTI) deficiency
Carnitine-acylcarnitine translocase (CACT) deficiency
Carnitine palmitoyltransferase II (CPTII) deficiency
Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
Long-chain L-3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
Trifunctional protein (TFP) deficiency
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
Medium/short-chain L-3-hydroxyacyl-CoA (M/SCHAD) dehydrogenase deficiency
Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency
Multiple-CoA dehydrogenase (MAD) deficiency (α -ETF, β -ETF, ETF-QO deficiency) (Glutaric acidemia type II)
Dienoyl-CoA reductase deficiency
Organic acid disorders
Propionyl-CoA carboxylase deficiency (Propionic acidemia)
Multiple carboxylase deficiency (Holocarboxylase synthetase deficiency and Biotinidase deficiency)
Methylmalonyl-CoA mutase deficiency (Methylmalonic acidemia)
Disorders of cobalamin metabolism (Cbl A/B/C/D/F deficiencies)
Succinyl-CoA synthetase deficiency (SUCLA2)
Isobutyryl-CoA dehydrogenase deficiency
Ethylmalonic encephalopathy
β -Ketothiolase (2-methylacetoacetyl-CoA thiolase, or 3-oxothiolase) deficiency
Isovaleryl-CoA dehydrogenase deficiency (Isovaleric acidemia)
2-Methylbutyryl-CoA dehydrogenase deficiency (short/branched chain acyl-CoA dehydrogenase (SBCAD) deficiency)
2-Methyl 3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency
3-Methylcrotonyl-CoA carboxylase (3-MCC) deficiency
3-Hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) deficiency
3-Methylglutaconyl-CoA hydratase deficiency
Malonyl-CoA carboxylase deficiency
Glutaryl-CoA dehydrogenase deficiency (Glutaric acidemia type I)
Glutamate formiminotransferase deficiency (Formiminoglutamic aciduria)

Mode of inheritance

All IEM detectable by acylcarnitine analysis are inherited as autosomal recessive traits except 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, which is X-linked.¹³

PREANALYTICAL REQUIREMENTS

Sample types

Carnitine and its esters are found in virtually all biological fluids. The preferred sample type for the testing of symptomatic patients and asymptomatic at-risk individuals is plasma or serum. Some laboratories also prefer testing dried blood spots, an approach that facilitates ease of specimen transport and may increase the sensitivity of detecting disorders of long-chain FAO. ACP is less frequently performed in urine, although this can be a sensitive approach for detecting certain organic acidemias such as glutaric acidemia type I,¹⁴ biotinidase deficiency, and isobutyryl-CoA dehydrogenase deficiency.¹⁵ ACP can also be performed in various tissues including cultured fibroblasts, lymphocytes, and amniocytes, as well as homogenized liver and muscle.^{16–18} Postmortem screening can be performed on dried-blood spots or bile,^{19,20} and amniotic fluid is used for the prenatal diagnosis of selected IEM.²¹

Sample volumes

Sample collection volumes and conditions of sample shipping and handling must be established by the laboratory and made available to referring physicians upon request. Typical sample testing volumes are given in Table 2.

Conditions of sample shipping, handling and storage

Specimens spotted and dried on filter paper can be shipped at room temperature. All other sample types should be frozen as soon as possible and shipped to the testing laboratory on dry ice. Long-term storage at room temperature causes progressive losses of acylcarnitines, with degradation of short-chain species occurring faster than long chain. Compounds are stable indefinitely when stored at -80°C . Criteria for sample rejection should be established and documented by the laboratory.

METHOD VALIDATION

Calibration and quantitation

Stable-isotope internal standards are available from a variety of commercial sources. These standards must be validated by

Table 2
Typical sample testing volumes for acylcarnitine profile analysis

Sample type	Testing volume
Amniotic fluid (cell-free supernatant)	20 μL
Amniocyte culture medium	50 μL^a
Bile (liquid specimen)	20 μL^b
Bile dried spot (postmortem)	one 1/8" punch ^b
Blood dried spot (neonatal, postmortem)	one 1/8" or 3/16" punch
Cell culture medium	50 μL^a
Plasma/serum	20 μL
Urine	Variable; standardized to creatinine

^aSpotted on filter paper.

^bMay require dilution if profile is abnormal.

determining recoveries from weighed, nonisotopic acylcarnitine standards for as many compounds as possible. Internal standards must be periodically revalidated at a frequency determined by the laboratory.

Reference standards are not available for all acylcarnitine species, particularly the hydroxy species. Quantitation of these compounds should be extrapolated by application of the calibration for the nearest species of similar structure.

The laboratory should determine the linear range, analytical measurement range and lower limit of detection for all clinically informative acylcarnitines, when possible. These performance characteristics should be verified on a regular basis as specified by CLIA.

Reference ranges

Reference ranges for all reported acylcarnitines should be established and periodically validated.^{1,2} When literature-based ranges are used, they must be validated by the laboratory before being put into use. For all applications except postmortem screening and tissue analyses, reference ranges should be age-matched. In particular, the comparison of pediatric results to blood spot, plasma, and serum normative ranges derived from an adult population is not appropriate.

Testing personnel

Appropriate training and ongoing competency requirements for laboratory personnel performing ACP analysis must be established and documented. Particularly for MS/MS-based applications, instrument optimization, method validation, and clinical testing must be performed by personnel with specialized training in the operation of MS/MS.

ANALYSIS OF ACYLCARNITINES

Sample preparation

Acylcarnitines are most often analyzed as their butyl-esters,² although the analysis of underivatized specimens is possible and alternative derivatization methods (including methylation) are also occasionally used. A typical procedure for plasma sample preparation for acylcarnitine analysis is summarized below (specific procedures must be determined and validated by each laboratory):

Specimens are diluted with a mixture of deuterium-labeled internal standards dissolved in acetonitrile acidified with 0.3% formic acid or methanol. Internal standards typically include d_3 -C2, d_3 -C3, d_3 -C4, d_9 -C5, d_3 -C8, d_9 -C14, d_3 -C16. Other internal standards can also be used, but care must be taken not to interfere with the signal of a clinically relevant species (e.g., the butyl ester of d_3 -C6 at m/z 319 is only 1 Da from m/z 318, the $[M + 1]^+$ molecular ion of hydroxyisovalerylcarnitine). Samples are centrifuged, and the supernatant containing the extracted acylcarnitines is transferred to another tube and evaporated to dryness under nitrogen. Acylcarnitines are derivatized to their butyl-esters by adding 3N HCl in *n*-butanol and heating at 65°C for 15 minutes. Samples are

again evaporated to dryness under nitrogen, and finally reconstituted in the mobile phase.

Analytical methods

For MS/MS-based testing, acylcarnitines are analyzed without chromatographic separation in the positive-ion mode, using either precursor-ion (also called parent-ion) scan or multiple-reaction monitoring (MRM). Precursor ion scan is preferable, as it allows evaluation of the whole profile and detection of common drug artifacts, presence of interfering compounds, and evidence of poor derivatization. Chromatographic separation can be considered when the separation of isomers is desired and clinically relevant. However, this is more easily achieved by other testing avenues such as urine organic acid or acylglycine analysis.

The liquid sample is introduced into the ion source through a capillary tube and exposed to a strong electric field and a counter flow of nitrogen gas (electrospray ionization, ESI). This causes evaporation of the solvent and desorption of charged ions into the mass analyzer. ESI occurs under atmospheric pressure allowing efficient ionization, while the mass analyzers operate at very low pressure. The combination is possible by introducing the ions into the analyzers through a very small (<1 mm) orifice and using powerful vacuum pumps.

In a standard triple quadrupole system, the first (Q_1) and third (Q_3) quadrupoles can be set either to scan a mass range or to select one or more individual ions. The second quadrupole (Q_2) is utilized as a collision cell where fragmentation of ions in transit is enhanced. In the precursor-ion mode for the analysis of butylated derivatives, all precursors of products m/z 85 within a mass range between 200 and 500 m/z are recorded. For MRM analysis, appropriate parent-product ion pairs must be identified for the unambiguous detection of each reported acylcarnitine species. However, this may not always be possible. For example, the parent-product ion pair of C4-acylcarnitine (288/85) can represent butyrylcarnitine, isobutyrylcarnitine, and formiminoglutamate.²²

Acylcarnitine species are listed in Table 3, along with the molecular weight of $[M+H]^+$ ions corresponding to their butyl-ester derivatives. Tolerance limits for the identification of acylcarnitines by molecular mass must be defined by the laboratory.

Quality control

A positive and negative control sample should be prepared and analyzed with every batch of patients tested. The internal standard mix should also be analyzed separately with each batch.

A quality control (QC) program based on the quantitative analysis of normal and abnormal control specimens should be implemented on a regular basis. Target ranges should be established for each metabolite and used to accept or reject a given QC run. The internal standards in each specimen serve as a QC check for each specimen. The use of Westgard rules for clinical specimen analysis further controls the parameters for quality patient diagnosis and reporting.²³ A QC designee should per-

Table 3
[M+H]⁺ ions of acylcarnitine-butyl-esters

Acyl-carnitine (butyl-esters)	Chain length	[M+H] ⁺
Free carnitine	—	218
Acetyl-	C2	260
Acrylyl-	C3:1	272
Propionyl-	C3	274
Formiminoglutamate (FIGLU)	—	287
Isobutyryl-/butyryl-	C4	288
Tiglyl-	C5:1	300
Isovaleryl-/2-methylbutyryl- (*)	C5	302
3-hydroxybutyryl-	C4-OH	304
Hexanoyl-	C6	316
3-hydroxyisovaleryl- 2-methyl-3-hydroxybutyryl-	C5-OH	318
Benzoyl-	—	322
Dextrose (fragment)	—	325
Heptanoyl-	C7	330
3-hydroxyhexanoyl-	C6-OH	332
Phenylacetyl-	—	336
Salicylyl- (*)	—	338
Octenoyl- (*)	C8:1	342
Octanoyl-	C8	344
Malonyl-	C3-DC	360
Decadienoyl-	C10:2	368
Decenoyl-	C10:1	370
Decanoyl-	C10	372
Methylmalonyl-/succinyl-	C4-DC	374
3-hydroxydecanoyl-	C10:1-OH	386
Glutaryl-/3-hydroxydecanoyl-	C5-DC/C10-OH	388
Dodecenoyl-	C12:1	398
Dextrose (fragment)	—	399
Dodecanoyl-	C12	400
3-hydroxydodecenoyl-	C12:1-OH	414
3-hydroxydodecanoyl-	C12-OH	416
Tetradecadienoyl-	C14:2	424
Tetradecenoyl-	C14:1	426
Tetradecanoyl- (myristoyl-)	C14	428
3-hydroxytetradecenoyl-	C14:1-OH	442
3-hydroxytetradecanoyl-	C14-OH	444
Hexadecenoyl-	C16:1	454
Hexadecanoyl- (palmitoyl-)	C16	456
3-hydroxyhexadecenoyl- ^a	C16:1-OH	470
3-hydroxyhexadecanoyl-	C16-OH	472

(Continued)

Table 3
Continued

Acyl-carnitine (butyl-esters)	Chain length	[M+H] ⁺
Dextrose (fragment)	—	473
Octadecadienoyl-	C18:2	480
Octadecenoyl-	C18:1	482
Octadecanoyl- (stearyl-)	C18	484
3-hydroxyoctadecadienoyl-	C18:2-OH	496
3-hydroxyoctadecenoyl-	C18:1-OH	498
3-hydroxyoctadecanoyl-	C18-OH	500

^aAn apparent elevation could be related to a drug and/or plasticizer interference.

form monthly compilation and review and sign-off of control values.

Proficiency testing

An ongoing proficiency testing (PT) program for acylcarnitine analysis must be implemented and documented. A bi-annual PT program for ACP is offered by the College of American Pathologists (CAP) and supervised by the joint CAP/American College of Medical Genetics Genetic Biochemical and Molecular Genetic Resource Committee.²⁴ A qualitative blood spot acylcarnitine quality assurance program is also offered by the “European Research Network for Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism.”²⁵

TEST INTERPRETATION AND REPORTING

Interpretation

Results should be reviewed and interpreted by an ABMG-certified biochemical geneticist. Informative results are usually characterized by a pattern of one or more elevated acylcarnitine species in comparison with age-matched reference ranges. Interpretation of results is based on pattern recognition and correlation of positive and negative findings, rather than on individual abnormal values. The differential diagnosis of abnormal results of species potentially representing multiple isomers (C4, C5, C5-OH, C5-DC) is critical and cannot be overstated.^{2,3} Basic acylcarnitine patterns associated with various disease states are listed in Table 4. In addition to the primary markers listed, calculation of ratios (for example C8/C10 ratio in MCAD deficiency) is useful in the interpretation of abnormal results. Informative profiles may not always be detected in disorders where the accumulation of diagnostic species is a reflection of the residual activity of the defective enzyme, the dietary load of carnitine and precursors, and the anabolic-catabolic status of the patient. Modest abnormalities should be correlated to the patient’s carnitine levels as a status of carnitine deficiency could affect the outcome of this analysis.

Several drugs (for example, valproic acid, pivalic acid, cefotaxime) may induce abnormal levels of one or more known

Table 4
Basic acylcarnitine patterns associated with various disease states

Designation	Acylcarnitine name	Disorder
C0 ↓	Free carnitine	Carnitine uptake defect Secondary carnitine deficiencies (e.g., in organic acidemias and FAOs)
C0 ↑	Free carnitine	CPTI deficiency (with C16, C18 ↓)
C3 ↑	Propionyl	Propionic acidemia Methylmalonic acidemias Succinyl-CoA synthetase deficiency
C4 ↑	Butyryl	SCAD deficiency Formiminoglutamic aciduria (with more prominent peak at m/z 287) Ethylmalonic encephalopathy (with C5) Multiple acyl-CoA dehydrogenase (MAD) deficiency (with C5, and other longer chain species)
	Isobutyryl	Isobutyryl-CoA dehydrogenase (IBD) deficiency
C5 ↑	Isovaleryl	Isovaleric acidemia
	Methylbutyryl	Methylbutyryl-CoA dehydrogenase (SBCAD) deficiency
C4-OH ↑	3-Hydroxybutyryl	SCHAD deficiency
C5-OH ↑	3-Hydroxyisovaleryl	3-Methylcrotonyl-CoA carboxylase (3-MCC) deficiency Holocarboxylase synthetase deficiency HMG-CoA lyase deficiency (with C6DC) Biotinidase deficiency 3-Methylglutaconyl-CoA hydratase deficiency
	3-Hydroxy-2-methylbutyryl	3-Oxothiolase deficiency (with C5:1) 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency
C8 ↑	Octanoyl	MCAD deficiency (with C6, C10, C10:1)
C3DC ↑	Malonyl	Malonyl-CoA carboxylase deficiency
C4DC ↑	succinyl/methylmalonyl	Succinyl-CoA synthetase (SUCLA2) deficiency
C5DC ↑	Glutaryl	Glutaric acidemia type I
C10-OH ↑	3-Hydroxy decanoyl	M/SCHAD deficiency, MCKAT deficiency
C14:1 ↑	Tetradecenoyl	VLCAD deficiency (with C14, C14:2)
C16 ↑	Palmitoyl	CPTII deficiency (with C18:2, C18:1, C18) Carnitine/acylcarnitine translocase (CACT) deficiency (with C18:2, C18:1, C18)
C16-OH ↑	3-Hydroxypalmitoyl	LCHAD deficiency (with C16:1-OH, C18:1-OH, C18-OH) Trifunctional protein (TFP) deficiency (with C16:1-OH, C18:1-OH, C18-OH)

acylcarnitine species.^{26,27} Other exogenous compounds (drug metabolites, food additives, intravenous fluids containing dextrose) could result in the appearance of atypical species,²⁸ some of them at *m/z* values in close proximity or even overlapping with acylcarnitines of diagnostic significance. Dietary artifacts are also possible, usually related to food intake enriched with fatty acids (MCT-oil, ketogenic diet).²⁹

Reporting

Patient reports must contain appropriate patient and specimen information as contained in Section C 2.4, 2.4.1, and

2.4.2 of these guidelines, and as described previously.³⁰ When abnormal results are detected, the interpretation should include an overview of the results and their significance, quantitative results with age-appropriate reference ranges, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (e.g., enzyme assay, molecular analysis), and a phone number to reach the reporting laboratory with additional questions. Acylcarnitine reference values are age-dependent, requiring that quantitative results be matched against a properly defined age group.

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Lori Oxendine was incorrectly listed as an author of the above referenced article in the January issue's Table of Contents. We regret the error.