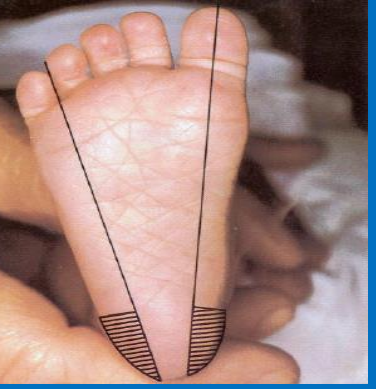

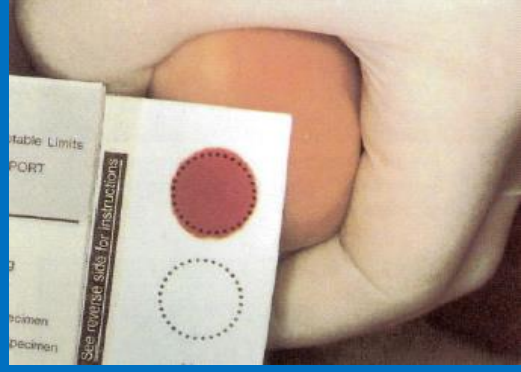

Metabolic screening in newborn

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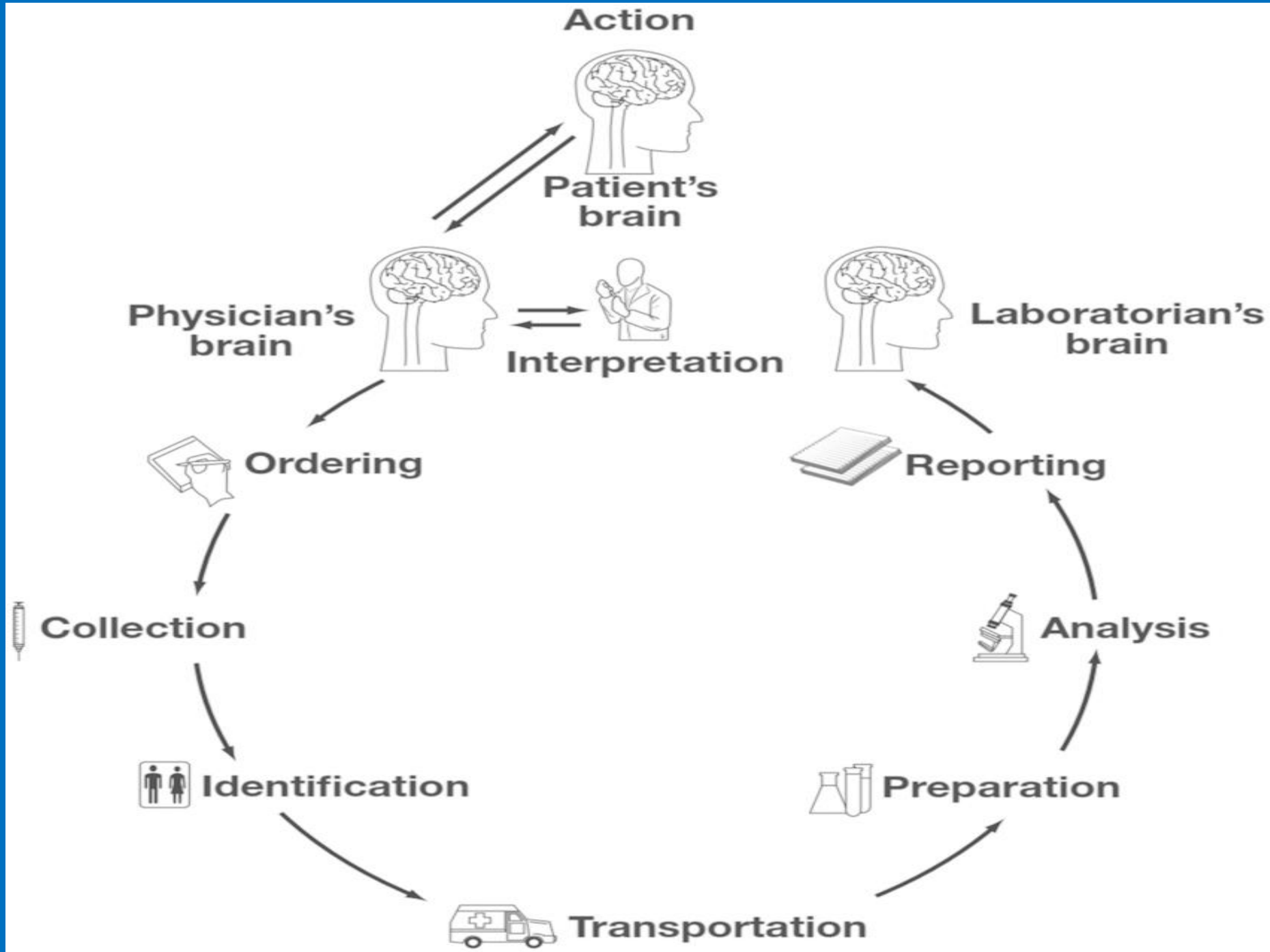
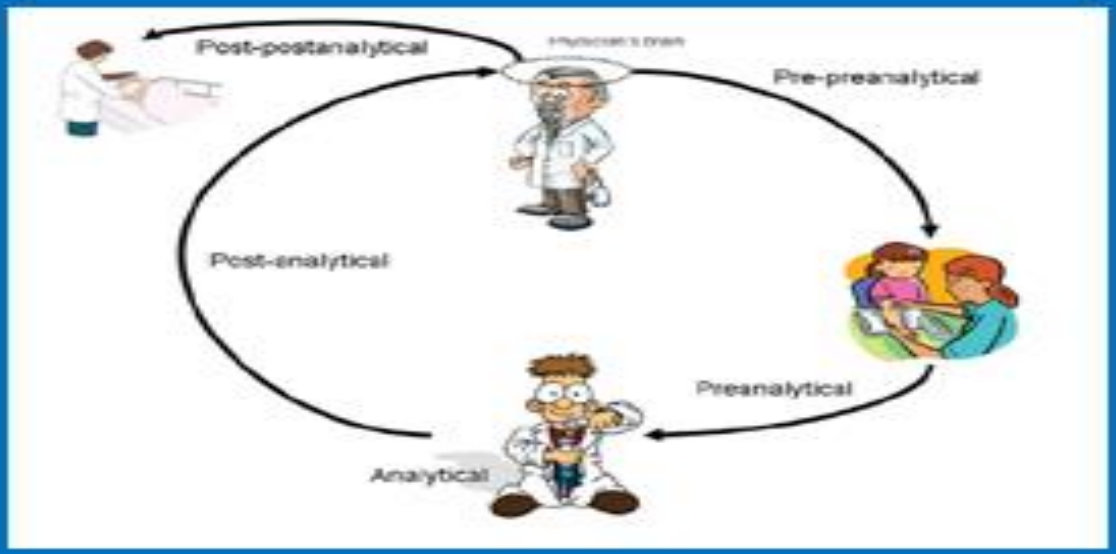
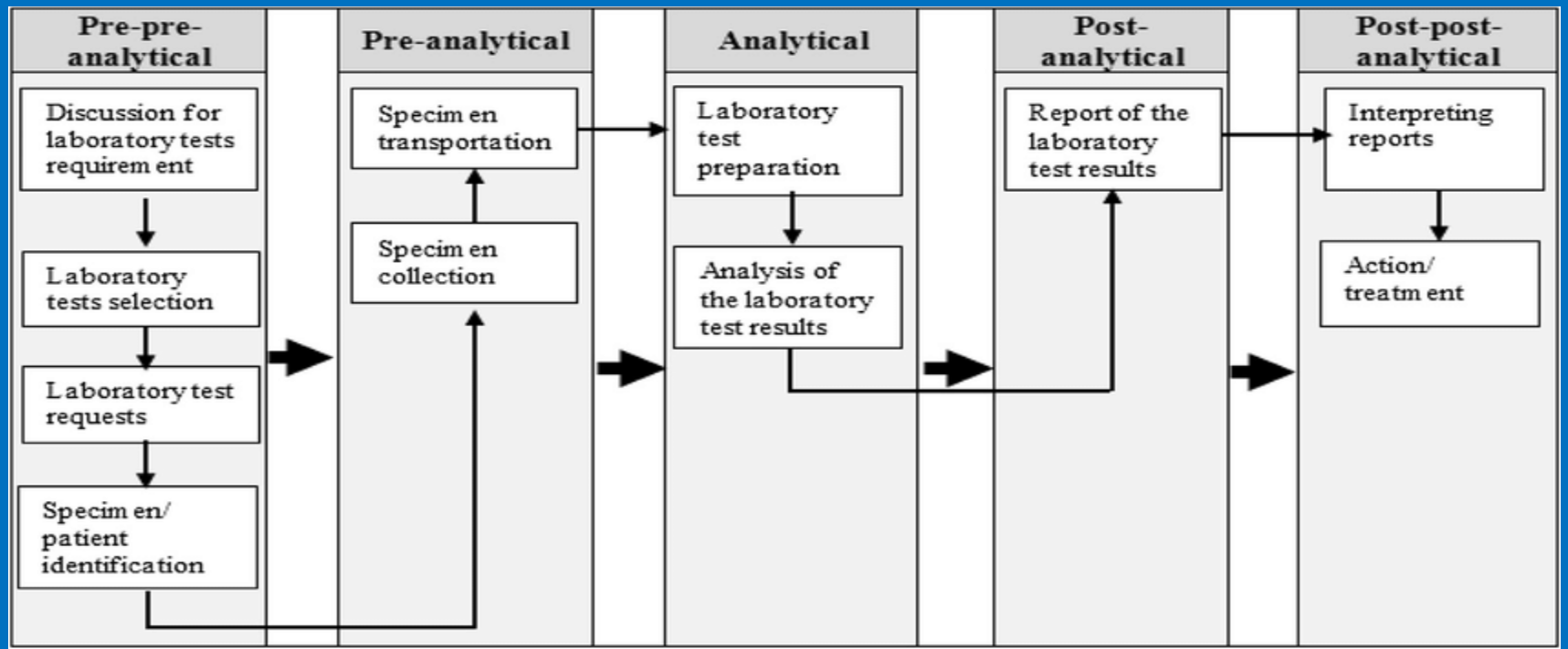
Tehran University of Medical Sciences


Action
Patient's brain
Physician's brain
Interpretation
Laboratorian's brain
Ordering
Reporting
Collection
Analysis
Identification
Preparation
Transportation


Post-postanalytical
Pre-preanalytical
Post-analytical
Preanalytical
Analytical


Pre-pre-analytical
Discussion for laboratory tests requirem ent
Laboratory tests selection
Laboratory test requests
Specim en/ patient identification
Pre-analytical
Specim en transportation
Specim en collection
Analytical
Laboratory test preparation
Analysis of the laboratory test results
Post-analytical
Report of the laboratory test results
Post-post-analytical
Interpreting reports
Action/ treatm ent

- the generation of any laboratory test result consists of 9 steps, including :
- ordering
- collection
- identification (at several stages),
- transportation
- separation (or preparation)
- analysis
- reporting
- interpretation
- action

Non IEM

- There are a range of non-specific causes which include:
- Major illness e.g. organ failure (disorders associated with liver dysfunction) (ie,PHE AND TYROSINE)
- Transient illness
- Premature – liver maturity
- Diet / feed
- Parenteral nutrition /TPN
- Analytical error – unlikely with triplicate testing
- Contamination of card

Table 50.5 Non-IEM organic acids in urine as well as dietary/drug/bacterial artefacts

Compound	Condition
Aromatic acids (4-hydroxyphenyl)	Gut bacterial action
Mandelic acid	Albumin infusion
D-Lactic acid	Short bowel syndrome
D-2-Hydroxyisocaproic acid	Short bowel syndrome
D-Phenyllactic acid	Short bowel syndrome
3-Hydroxyisovaleric acid	Valproate medication
Glutaric acid	Gut bacterial action
3-Hydroxypropionic acid	Gut bacterial action
Methylmalonic acid	Vitamin B_{12} deficiency
Ethylmalonic acid	Vitamin B_2 deficiency
C_{10}>C_8>C_6 dicarboxylic acids	MCT diet
7-Hydroxyoctanoic acid	MCT diet
3-Hydroxydicarboxylic acids	Coeliac disease
Succinic acid	2-Ketoglutarate decomposition.
Glycolic acid	Ethylene glycol poisoning
Pyroglutamic acid	Glutamine decomposition Flucloxacillin toxicity
Di-(2-ethylhexyl)phthalate	Nutramigen feeding Pregestimil feeding
Furane-2,5-dicarboxylic acid	Heated sugars
Furoylglycine	Heated sugars
4-Hydroxycyclohexanecarboxylic acid	Food processing
Homovanillic acid	Neuroblastoma
Vanilmandelic acid	Neuroblastoma, phaeochromocytoma
N-Acetyltyrosine	Parenteral feeding
5-Hydroxyindoleacetic acid	Carcinoid syndrome
Valproate metabolites	Depakine therapy
2-Hydroxyhippuric acid	Salicylate ingestion
Ethosuximide metabolites	Antiepileptic therapy
Keppra metabolites	Antiepileptic therapy
Phenytoin metabolites	Antiepileptic therapy

Abnormalities associated with the inherited organic aci- accumulation in the various organic acidemias. It can be

- Cut off: Gray zone /pathologic zone
- Importance low or high metabolite
- Common metabolite in several diseases specific cut off for each disease
- History clinical status Diet/Formula/medication/Transfusion
- Metabolite base/enzymology(Enzyme assay)
- If initial result is an alert, or abnormal results are obtained on two different NBS specimens, further testing is recommended to establish diagnosis

Definition and Use of Primary and Secondary Markers

- Primary markers (analytes) – used to establish presumptive positives.
- Secondary markers – used in conjunction with primary analyte results to assign risk
- Isolated elevations of secondary markers are considered unimportant

Secondary metabolites and criteria for mild elevation of primary marker

- For PKU: PHE/TYR ratio > 3
- For MSUD: LEU+ILE and VAL
- For PA and MMA: C3/C2 ratio > 0.4
- For MCAD: C8/C10 ratio > 3
- For VLCAD: C14:1/C12:1 ratio > 3
- For LCHAD: C16-OH plus at least one of the following: C18:1-OH, C16, C18:1
- For CPT-II/CAT: C16 and C18:1
- No suitable secondary markers for C3-DC, C4, C5, C5-OH, C5-DC

Action taken by co-ordinator

- Low risk: contact physician of record, check clinical status of pt., request second blood spot specimen,
- recommend follow-up testing if symptomatic
- Moderate risk (includes positive test on repeat specimen from above and/or presence of secondary markers): request follow-up testing; recommend referral to regional metabolic center if child symptomatic
- High risk: recommend immediate referral to metabolic center, follow-up testing and initiate appropriate therapy regardless of clinical status

Initial laboratory tests

- Blood gases/Ph
- CK
- Glucose
- Electrolytes
- Ammonia
- Lactate
- Renal function tests
- Liver function tests
- Urinalysis
- Basic hematological tests/coagulation studies

Elevated lactate

- Lactate concentration: mmol/l = mg/dl × 0.11
- *Normal values*: *Blood* < 2.1 mmol/l (< 19 mg/dl).*CSF* < 1.8 mmol/l (< 16 mg/dl)
- *Blood sample*: Uncuffed vein (scalp, i.v. line) or artery, relaxed child.Na-fluoride sample tube
- *Alanine* (plasma amino acids) reflects the concentration of pyruvate (and indirectly lactate) but is not affected by cuffing. Normal < 450 µmol/l, alanine/lysine ratio < 3.

- A primary metabolic disorder should be considered if there is no convincing secondary cause such as shock, asphyxia or cardiac disease or in particular a difficult venepuncture.

Disorders of the respiratory chain or Krebs cycle

Pyruvate dehydrogenase (PDH) or pyruvate carboxylase deficiency.

primary causes:

- Long-chain fatty acid oxidation disorders
- Organic acidurias, disorders of biotin metabolism
- Glycogen storage diseases, gluconeogenesis disorders

Secondary causes

- Most common: the use of a tourniquet or difficulty in drawing the blood
- Muscular activity, assisted ventilation, seizures (lactate up to 4–6 mmol/l)
- Severe systemic disease: central and peripheral hypoxia or ischaemia, shock, cardiac failure,

cardiomyopathy, liver or renal failure, septicaemia, diabetes mellitus, etc.

- Any severe metabolic disease
- Renal tubular syndrome, hyperchloraemia, urinary tract infection (lactic aciduria)
- Drugs (biguanides); intoxication (e.g. ethanol)
- Consider thiamine deficiency

Lactate

- *Postprandial elevation* of lactate (> 20%)

indicate PDH deficiency or respiratory chain defects, respectively.

- ↑ Lactate after glucose challenge is found also in glycogen storage disease types 0, III, VI.
- *Postprandial decline* of lactate indicate glycogen storage disease type I or gluconeogenesis defects.

Pyruvate

- Indic: Pyruvate should not be routinely measured as values obtained may be spurious and lactate is the more relevant and reliable test.
- Pyruvate is sometimes used to determine

the lactate/pyruvate ratio (redox state, normal < 20)

- Never measure pyruvate without lactate
- Method: Photometric
- Normal: Blood: 50–100 µmol/l; CSF: 70–140; lactate/pyruvate ratio: < 20 (elevated in respiratory chain disorders, typically normal in PDH deficiency)

Finding	*Indicative of (selection)*
Anaemia (macrocytic)	Disturbances in cobalamin and/or folic acid metabolism
Reticulocytosis	Glycolysis defects, disorders of the γ-glutamyl cycle
Vacuolised lymphocytes	Lysosomal storage disorders, juvenile NCL
↑ Alkaline phosphatase	Bile acid synthesis defects, hypoparathyroidism
↓ Alkaline phosphatase	Hypophosphatasia
↓ Cholesterol	Sterol synthesis defects, lipoprotein disorders, glycosylation disorders, peroxisomal disorders
↑ Triglycerides	Glycogen storage disorders, lipoprotein disorders
↑ CK	Dystrophinopathies, fatty acid oxidation disorders, glycogen storage disorders, glycolysis disorders, muscle AMP-deaminase deficiency, mitochondrial disorders
↓ Creatinine	Creatine synthesis disorders
↑ α-Fetoprotein (AFP)	Tyrosinaemia type I, hepatoblastoma, neonatal haemochromatosis, viral hepatitis, ataxia telangiectasia

↑ Uric acid	Glycogen storage disorders (incl. Fanconi-Bickel disease), fructose intolerance, disorders of purine metabolism, fatty acid oxidation defects, mitochondrial disorders
↓ Uric acid	Disorders of purine metabolism, molybdenum cofactor deficiency
↑ Iron, transferrin	Haemochromatosis, peroxisomal disorders
↑ Copper	Peroxisomal disorders, Wilson disease (urine, liver)
↓ Copper, coeruloplasmin	Wilson disease (serum), Menkes disease, acoeruloplasminaemia
Hypo(para)thyroidism	Mitochondrial disorders, CDG
Low CSF glucose	Glucose transport protein 1 (GLUT1) deficiency

- *Obtain urine sample:*
- Check colour and odour
- Perform standard test strip analyses (e.g. ketone bodies, glucose, protein; pH > 5 during acidosis

→ (DD: renal tubular acidosis)

- Store urine sample from the acute phase for organic acids or additional metabolic tests
- *If lumbar puncture is performed:* Store CSF (freeze immediately)

Unusual clinical observations

Urine and body odour

Odour	*Substance*	*Disorder/origin*
Animal-like, mouse-like	Phenylacetate	Untreated phenylketonuria, phenylbutyrate treatment
Maple syrup, "Maggi"	Sotolone	Maple syrup urine disease
Acrid (sweaty feet)	Isovaleric acid	Isovaleric aciduria, glutaric aciduria II
Male cat urine	3-OH-isovaleric acid	3-Methylcrotonylglycinuria, multiple carboxylase deficiency
Cabbage	2-OH-butyric acid	Tyrosinaemia type I
Rancid butter	2-Oxo-4-methiolbutyric acid	Tyrosinaemia type I
Sulphur	Hydrogen sulphide	Cystinuria
	Methionine	Tyrosinaemia type I, cirrhosis
Fish-like	Trimethylamine, dimethylglycine	Trimethylaminuria, dimethylglycinuria

Reducing substances in urine

Method: Test tablets (e.g. Clinitest®, Bayer)

Detects: Any reducing substances, particularly sugars

Substance	*Disorder/origin*
Galactose	Classical galactosaemia, galactokinase deficiency, severe liver disease (secondary galactose intolerance), Fanconi-Bickel disease
Fructose	Fructose intolerance, essential fructosuria
4-Hydroxyphenylpyruvate	Tyrosinaemia types I and II
Homogentisic acid	Alcaptonuria
Xylose, arabinose	Pentosuria, arabinosuria
Glucose	Diabetes mellitus, Fanconi syndrome
Oxalic acid (massive)	Hyperoxaluria
Salicylates, ascorbic acid	Drugs
Uric acid	Hyperuricosuria
Hippuric acid	Na-benzoate treatment of hyperammonaemia, malabsorption

Nitroprusside test (Brand reaction)

Method: 0.5 ml urine + 200 µl 5% Na-cyanide

Detects: Sulphur-containing acids (disulphides). False positive result may occur in severe ketosis, may be false negative in homocystinuria (assess total plasma homocysteine!).

Substance	*Disorder/origin*
Cystine	Cystinuria, hyperargininaemia, generalised hyperaminoaciduria
Homocystine	Classical homocystinuria, cobalamin deficiencies, cystathioninuria (bacterial in urinary tract infections)
Glutathione	Gammaglutamyl transaminase deficiency
Drugs	N-Acetylcysteine, penicillamine, captopril, ampicillin and others

Sulphite test

Method: Dipstick (e.g. Merckoquant® 10013, Merck), *fresh urine at the bedside*

Diagn.: Sulphite oxidase and molybdenum cofactor deficiencies (particularly test early-onset epileptic encephalopathy). Positive result may be caused by various sulphite-containing drugs, false negative results may occur.

Four lab values are important in diagnosis of possible IEM:

A.G> 16: The most specific lab finding suggestive for IEM.

- Anion gap = [Na+] – [Cl– + HCO3] 7–16 mmol/l

D.D →

Shock and lactic acidosis

DKA

Renal failure or CMP

2) **Ketones:**

absence of ketonuria after significant fasting in:

- **FAOD**
- **Hyperinsulinism**
- **HMGL**

Urinary ketones (test strip)

- Ketonuria due to the ketone bodies 3-hydroxybutyrate and acetoacetate is normal during fasting
- pathological in the fed state and in the neonate
- Absence of ketones during fasting is suggestive of a fatty acid oxidation disorder
- Ketosis is a physiological response to fasting, catabolic state or ketogenic diet
- Permanent ketosis may in rare cases indicate a ketolysis defect.
- *Ketosis with fasting hypoglycaemia* indicate adrenal insufficiency or glycogen storage diseases (GSD) type 0.

3) Elevated Ammonia:

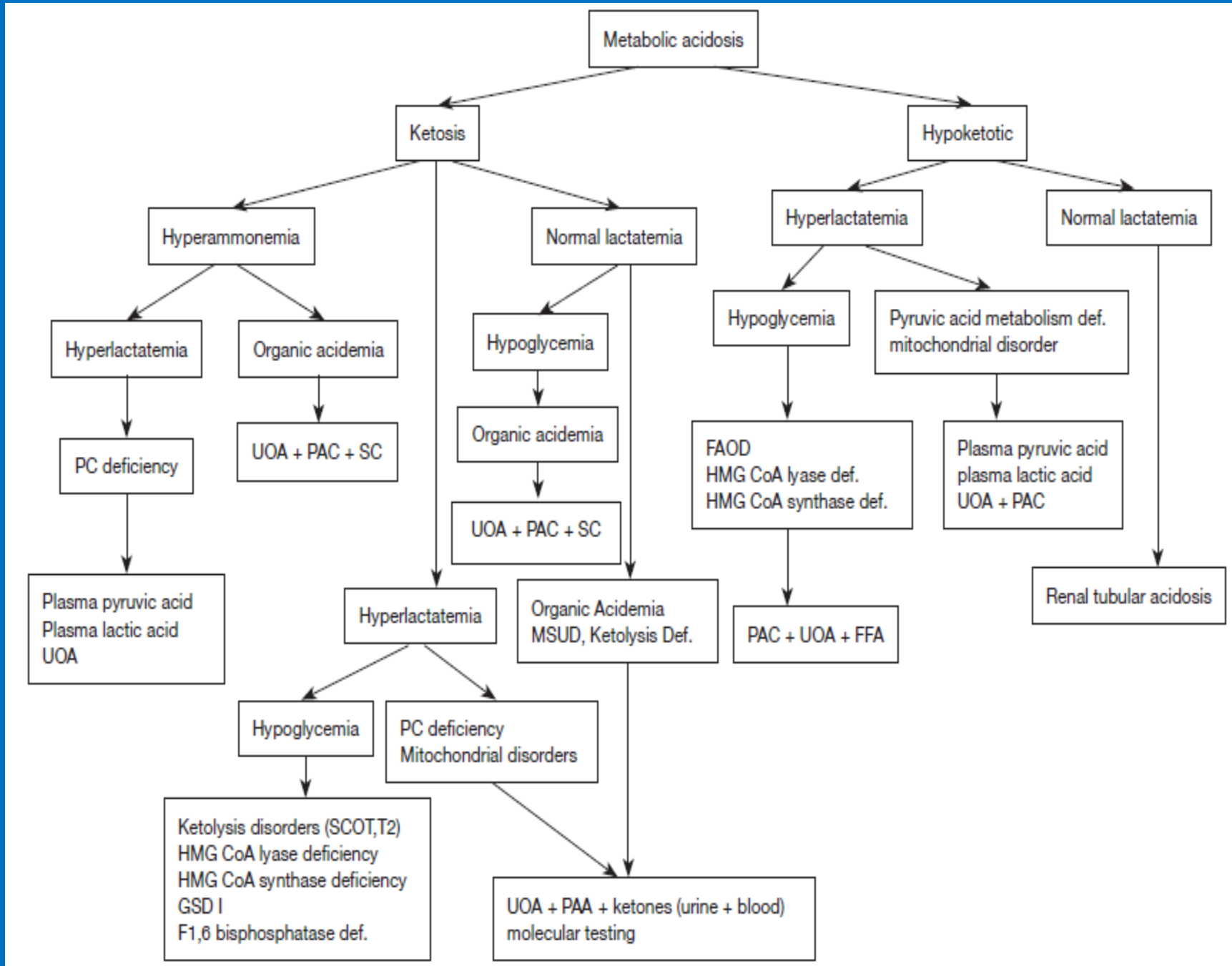
Normal range is age dependent:

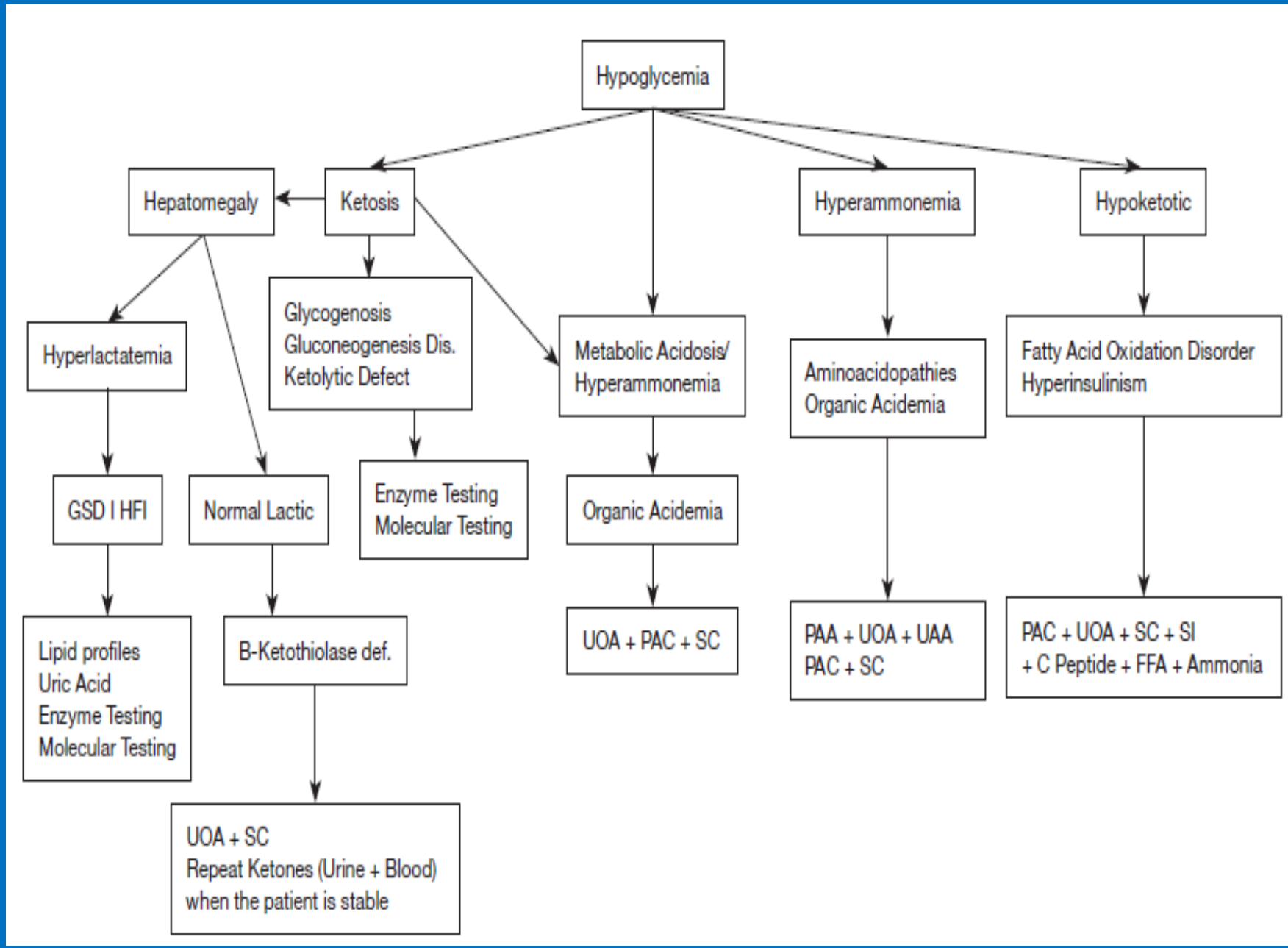
- **Up to 150 µm/L in premature infant**
- **> 50 µm/L is abnormal in older infant and children**

4) Elevated creatine kinase:

IEM with myopathy or CMP or both, such as:

- **FAOD**
- **Electron transport chain disorders**
- **GSD (specially types III and V)**


Metabolic acidosis
Ketosis
Hypoketotic
Hyperammonemia
Normal lactatemia
Hyperlactatemia
Normal lactatemia
Hyperlactatemia
Organic acidemia
Hypoglycemia
Hypoglycemia
Pyruvic acid metabolism def.
mitochondrial disorder
PC deficiency
UOA + PAC + SC
Organic acidemia
FAOD
HMG CoA lyase def.
HMG CoA synthase def.
Plasma pyruvic acid
plasma lactic acid
UOA + PAC
Plasma pyruvic acid
Plasma lactic acid
UOA
UOA + PAC + SC
Renal tubular acidosis
Hyperlactatemia
Organic Acidemia
MSUD, Ketolysis Def.
PAC + UOA + FFA
Hypoglycemia
PC deficiency
Mitochondrial disorders
Ketolysis disorders (SCOT,T2)
HMG CoA lyase deficiency
HMG CoA synthase deficiency
GSD I
F1,6 bisphosphatase def.
UOA + PAA + ketones (urine + blood)
molecular testing


Hypoglycemia
Hepatomegaly
Ketosis
Hyperammonemia
Hypoketotic
Hyperlactatemia
Glycogenosis
Gluconeogenesis Dis.
Ketolytic Defect
Metabolic Acidosis/
Hyperammonemia
Aminoacidopathies
Organic Acidemia
Fatty Acid Oxidation Disorder
Hyperinsulinism
GSD I HFI
Normal Lactic
Enzyme Testing
Molecular Testing
Organic Acidemia
PAA + UOA + UAA
PAC + SC
PAC + UOA + SC + SI
+ C Peptide + FFA + Ammonia
Lipid profiles
Uric Acid
Enzyme Testing
Molecular Testing
B-Ketothiolase def.
UOA + PAC + SC
UOA + SC
Repeat Ketones (Urine + Blood)
when the patient is stable

- Which diseases are diagnosed by LC/Mass
- a)Diagnostic for:
- FAOD
- Aminoacidopathies
- UCD
- b)Suggestive for
- Organic acidemia
- Mithocondrial disorders
- In suspicion to organic acidemia, differention and confirmation by urine GCMS is necessary.

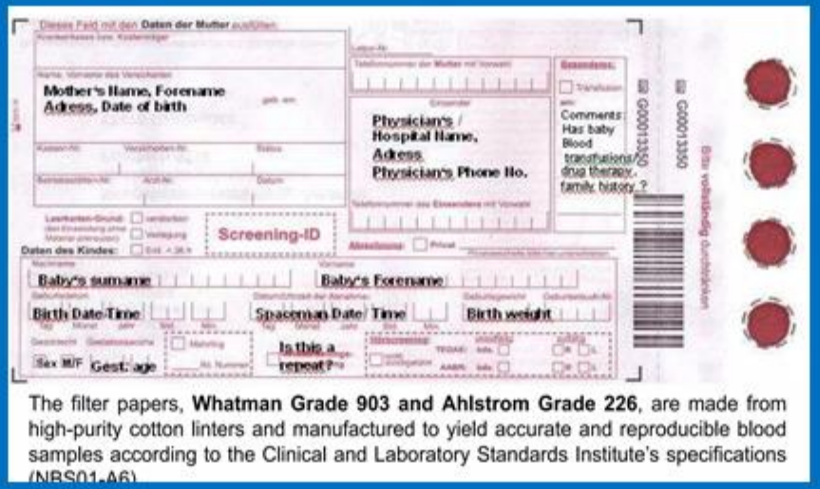
- **Diagnosable Components:**
  - **LC Mass: 48 Components**
  - **GCMS: 135 Components (To 178)**

Newborn Screening: Common Diseases Detected

	FATTY ACID OXIDATION DISORDERS	ORGANIC ACIDEMIAS	AMINOACIDOPATHIES	UREA CYCLE DISORDERS
Metabolism	**Fat** Defect in β-oxidation of fatty acids.	**Protein** Defect in amino acid breakdown leads to accumulation of organic acid byproducts	**Protein** Defect in amino acid breakdown leads to accumulation of certain intact amino acids	**Protein** Defect in making urea (blood urea nitrogen) from ammonia that results from amino acid breakdown
Disorders	Medium-chain acyl CoA dehydrogenase Long-chain 3-hydroxy acyl CoA dehydrogenase Very long-chain acyl CoA dehydrogenase	Propionic Methylmalonic Isovaleric	Maple syrup urine Phenylketonuria Homocystinuria tyrosinemia	Ornithine transcarbamylase (X-linked) Citrullinemia Arginosuccinic aciduria
Presentation	**Hypoketotic Hypoglycemia** Lethargy, vomiting Sudden infant death syndrome, Reye syndrome Long-chain disorders have cardiomyopathy and rhabdomyolysis	**Metabolic Acidosis With Anion Gap** Neonatal lethargy, vomiting, coma, strokes, death	**No Acidosis or Hyperammonemia** Elevations in specific amino acids See text for clinical features	**Hyperammonemia Without Acidosis** Neonatal lethargy, vomiting, coma, death
Laboratory Tests	Newborn Screen **Plasma acylcarnitines** Hypoglycemia No or inappropriately low ketones	Newborn Screen **Urine organic acids** Plasma acylcarnitines	Newborn Screen **Plasma amino acids**	Newborn Screen (not for ornithine transcarbamylase) **Hyperammonemia** **Plasma amino acids** **Urine orotic acid**

Expanded NBS – 29 conditions

- 20 inborn errors of metabolism
- 3 hemoglobinopathies
- 2 endocrine disorders
  - Congenital hypothyroidism
  - Congenital adrenal hyperplasia
- 3 other metabolic disorders
  - Cystic fibrosis
  - Galactosemia
  - Biotinidase deficiency
- Hearing loss



What are we screening for?

9 OA	5 FAO	6 AA	3 Hb Pathies	6 Others
CORE PANEL				
IVA GA I HMG MCD MUT 3MCC Cbl A,B PROP BKT	MCAD VLCAD LCHAD TFP CUD	PKU MSUD HCY CIT ASA TYR I	Hb SS Hb S/ßTh Hb S/C	CH BIOT CAH GALT HEAR CF

Test	Specimen	Method
Amino Acid & Acylcarnitine Profile	DBS	ESI-MS/MS
Amino Acid & Acylcarnitine Profile	Plasma	LC-MS/MS
Organic Acid Profile	Urine	GC/MS
Single analytes of organic acid (VMA/HVA, Succinyl acetone, Homogentisic, Orotic acid, …)	Urine	GC/MS
Amino Acid Profile	Plasma	HPLC
Amino Acid Profile	Urine	HPLC
Homocysteine	Plasma	HPLC

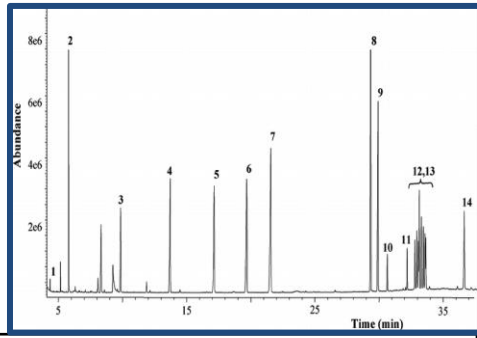
Amino Acid & Acylcarnitine Profile in Plasma

LC-MS/MS

Alanine,
Aspartic Acid,
Arginine,
Citrulline,
Glutamic Acid,
Glycine,
Leucine + Isoleucine,
Methionine,
Ornithine,
Phenylalanine,
Tyrosine,
Valine,
Threonine,
Serine,
Histidine,
Lysine,
Tryptophane,
Proline

Free Carnitine(C0)
Acetylcarnitine(C2) ,
Propionylcarnitine(C3) ,
Malonylcarnitine(C3DC) ,
Butyrylcarnitine(C4)
Hydroxybutyrylcarnitine(C4OH) ,
Ethylmalonylcarnitine(C4DC) ,
Isovalerylcarnitine(C5) ,
Tyglylcarnitine(C5:1) ,
Hydroxyisovalerylcarnitine(C5OH) ,
Glutarylcarnitine(C5DC) ,
Hexanoylcarnitine(C6) ,
HydroxyHexanoylcarnitine(C6OH) ,
Methylglutarylcarnitine(C6DC) ,
Octanoylcarnitine(C8) ,
Decanoylcarnitine(C10) ,
Decenoylcarnitine(C10:1) ,
Dodecanoylcarnitine(C12) ,
Dodecenoylcarnitine(C12:1) ,
Tetradecanoylcarnitine(C14) ,
Tetradecenoylcarnitine(C14:1) ,
Tetradecadienoylcarnitine(C14:2),
Hydroxytetradecanoylcarnitine(C14OH),
Hexadecanoylcarnitine(C16),
Hydroxyhexadecanoylcarnitine(C16OH),
Hexadecenoylcarnitine(C16:1),
Hedroxyhexadecenoylcarnitine(C16:1OH),
Octadecanoylcarnitine(C18),
Octadecenoylcarnitine(C18:1),
Octadecadienylcarnitine(C18:2),
Hydroxystearoylcarnitine(C18OH),
Hydroxyoctadecenoylcarnitine(C18:1OH),
Hydroxylinoleoylcarnitine(C18:2OH).

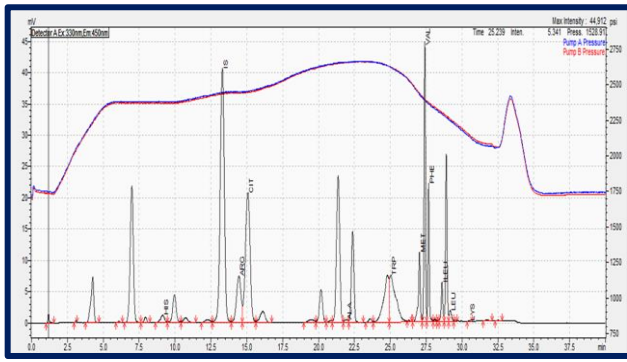
Organic Acid Profile

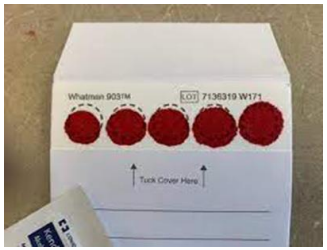


GC/MS

Lactic acid , 2-Hydroxyisobutyric acid , Caproic acid , Glycolic acid , Glyoxylic acid-oxime , Oxalic acid , 2-Hydroxybutyric acid , 3-Hydroxypropionic acid , Pyruvic acid-oxime , Valproic acid , 3-Hydroxybutyric acid , 3-Hydroxyisobutyric acid , 2-Hydroxyisovaleric acid , 2-Methyl-3-hydroxybutyric acid , Malonic acid , 3-Hydroxyisovaleric acid , 2-Keto-isovaleric acid-oxime , Methylmalonic acid , 2-ethyl-3-OH-propionic , Urea , 4-Hydroxybutyric acid , 2-Hydroxyisocaproic acid , 3-Hydroxyvaleric acid , Acetoacetic acid , 2-Hydroxy-3-Methylvaleric acid , Benzoic acid , Acetoacetic acid-oxime , Octanoic acid , 2-Methyl-3-hydroxyvaleric acid , Glycerol , Phosphoric acid , Acetylglycine , Ethylmalonic acid , 2-Methyl-3-hydroxyvaleric acid , 2-Ketoisocaproic acid-oxime , Phenylacetic acid , Maleic acid , Succinic acid , Methylsuccinic acid , Glyceric acid , Fumaric acid , Uracil , Propionylglycine , Acetylglycine , Mevalonolactone , mevalonolactone-origin fragment , Isobutyrylglycine , 2-propyl-3-hydroxy-pentanoic acid , Mesaconic acid , Glutaric acid , 3-Methylglutaconic acid , 3-Methylglutaric acid , 2-Propyl-3-ketopentanoic acid , Propionylglycine , Isobutyrylglycine , 2-Deoxytetronic acid , Butyrylglycine , 3-Methylglutaconic acid(E) , Glutaconic acid , succinylacetone , decanoic , 2-Propyl-5-OH-pentanoic(VPA) , 3-methylglutaconic , isovalerylglycine , Butyrylglycine , Malic acid , Adipic acid , Phenyllactic acid , Isovalerylglycine , 2-Hexenedioic acid , 5-Oxoproline , Thiodiglycolic acid , 3-Methyladipic acid , 2-Propyl-glutaric acid , 7-Hydroxoctanoic acid , 5-Hydroxy-2-furoic acid , Tiglylglycine , 3-Methylcrotonoylglycine , Tiglylglycine , 3-Methylcrotonoylglycine , 3-Hydroxyglutaric acid , 2-Hydroxyglutaric acid , Pimelic acid , 3-Hydroxy-3-methylglutaric acid , 3-Hydroxyphenylacetic acid , 4-Hydroxybenzoic acid , 2-Ketoglutaric acid-oxime , 4-Hydroxyphenylacetic acid , 2-Ketoglutaric acid-oxime , Hexanoylglycine , Phenylpyruvic acid-oxime , N-Acetylaspartic acid , 2-Hydroxyadipic acid , Octenedioic acid , 3-Hydroxyadipic acid , Suberic acid , 3-Methylglutaconic acid , 2-Keto-adipic-OX , Aconitic acid , Orotic acid , Vanillic-2 (3-Methoxy-4-hydroxybenzoic acid) , Homovanillic acid , Azelaic acid , Hippuric acid , Isocitric acid , Citric acid , Hippuric acid , Homogentisic acid , Methylcitric acid , 3-(3-Hydroxyphenyl)-3-hydroxypropionic acid , Methylcitric acid , 3-Hydroxyoctenedioic acid , 3-Hydroxysuberic acid , Vanilmandelic acid , Sebacic acid , Decadienedioic acid , 4-Hydroxyphenyllactic acid , 4-Hydroxyphenylpyruvic acid-oxime , 2-Hydroxyhippuric acid , 3-Indoleacetic acid , Palmitic acid , 2-Hydroxysebacic acid , 3-Hydroxysebacic acid , 2-Hydroxyhippuric acid , Dodecanedioic acid , N-Acetyltyrosine , Uric acid , 3,6-Epoxydodecanedioic acid , Suberylglycine , 3-hydroxydodecanedioic acid , 3,6-Epoxytetradecanedioic acid.

Amino Acid Profile





HPLC

Homocysteine

- Aspartic Acid,
- Glutamic Acid ,
- Asparagine ,
- Serine ,
- Glutamine ,
- Histidine ,
- Glycine ,
- Threonine ,
- Citrulline ,
- Arginine ,
- Alanine ,
- Tyrosine ,
- Tryptophane ,
- Methionine ,
- Valine ,
- Phenylalanine ,
- Isoleucine ,
- Leucine ,
- Ornithine ,
- Lysine
- ~~Proline~~

Aminoacidopathies

Disorders	Primary metabolite in MS/MS	Confirmatory tests / follow-up	Findings in confirmatory tests
Argininemia	↑ Arginine	Plasma NH3, PAA, enzyme assay	↑ NH3, ↑ arginine on PAA, ↓ hepatic arginase activity
Argininosuccinic aciduria (ASA)	↑ Citrulline	Plasma NH3, UAA, PAA, enzyme assay	↑ NH3, ↑ argininosuccinic acid on UAA and PAA, ↓ fibroblast/liver ASL activity
Citrullinemia Type 1 "Neonatal" citrullinemia	↑ Citrulline	Plasma NH3, PAA	↑ NH3, ↑ citrulline on PAA, ↓ fibroblast/liver ASS activity
Homocystinuria	↑ Methionine	PAA, Hcy in P, UAA, UOA	↑ Blood and urine homocyst(e)ine on PAA and UAA; ↑ urine methylmalonic acid on UOA in cobalamin C, D, F synthesis defects
Maple syrup urine disease (MSUD)	↑ total "Leucine, isoleucine, alloisoleucine ↑ Valine	PAA, Urine DNPH, UOA	↑ Leucine, isoleucine, alloisoleucine and valine on PAA; positive DNPH; ↑ branched chain α-keto and hydroxyl acids on UOA
Phenylketonuria	↑ Phenylalanine ↑ phenylalanine tyrosine ratio	PAA, urine and/or blood or CSF neopterin and biopterin studies	↑ Phenylalanine on PAA, ↑ phenylalanine/ tyrosine ratio; abnormal urinary and/or blood or CSF pterins in BH4 synthesis defects
Tyrosinemia type 1	↑ Tyrosine	PAA, UOA	↑ Tyrosine and methionine on PAA; ↑ succinylacetone and tyrosine metabolites on UOA
Tyrosinemia type 2 Oculocutaneous tyrosinemia	↑ Tyrosine	PAA, UOA	↑ Tyrosine on PAA; ↑ tyrosine metabolites without increased succinylacetone on UOA

Samples for measurement of amino acids

- **Whole blood spotted on filter paper**: screens newborns for:
  - Many amino acidopathies
  - Urea cycle defects
- **Plasma**: identify patients with a suspected disorder of:
  - Amino acid metabolism
  - Monitoring treatment
- **Urine**: screen for:
  - Disorders of amino acid transport (cystinuria, lysinuric protein intolerance, or hartnup disease)
  - Generalized renal tubular dysfunction.
- **CSF** (usually in addition to plasma amino acids): evaluation of patients with:
  - Neurometabolic disorders (such as glycine encephalopathy)
  - Disorders of serine metabolism

Specimen Collection

The timing of the specimen collection is important in the detection of metabolic disorders.

- Acutely ill patients → Blood and urine specimens on admission
- Diagnosis of most amino acid disorders → Overnight fast or at least 3 h after meal
- Young infants → Immediately before the next scheduled feeding (at least 2–3 h after the last feeding)
- Hyperammonemia screening → Postprandial samples
- TPN patient → Intravenous hyperalimentation should be discontinued for at least 2–3 h prior to specimen collection

Hemolyzed samples

- The concentration of the majority of the physiological amino acids is the same in red blood cells and in plasma, with exception of taurine, glutamate, aspartate, and argininosuccinate
- The enzyme arginase converts arginine into ornithine and urea and is expressed in red blood cells. Hemolysis will release arginase in the plasma causing hydrolysis of arginine.
  - Therefore, in hemolyzed samples:
    - ↓ Arginine
    - ↑ Orn, Taurine, Glu, Asp, Argininosuccinate

Handling and storage of samples

- Whole blood collected for amino acids analysis should be spun down as soon as possible.
- Plasma should be kept frozen during transport and until analysis is performed.
- Refrigerated conditions may be acceptable for a short period of time.
- Improper handling of specimens can result in artifactual changes in the amino acid contents.

Table 1.Collection, handling, and storage artifacts

Factor/condition	Source	Amino acid(s) affected	Value
Contamination, bacterial	U	Ala, Gly, Pro	↑ H
Contamination, bacterial	U	Trp, aromatic amino acids, Ser	↓ L
Contamination, fecal	U	Pro, Glu, Leu, Ile, Val, OH-pro-line	↑ H
Contamination, protein	U	Cys	↓ L
Contamination, RBC	U	Orn	↑ H
Contamination, unwashed skin	B	Most amino acids	↑ H
Contamination, WBC	U	Tau	↑ H
Contamination, WBC	B	Asp, Glu, Tau	↑ H
Hemolysis	B	Asp, Glu, Gly, Orn	↑ H
Hemolysis	B	Arg, Gln	↓ L
Serum vs. plasma	B	Serum Tau > plasma Tau	
Storage	U	Glu, Asp, GABA	↑ H
Storage	U	Gln, Asn, phosphoethanolamine	↓ L
Storage	B	Gln, Cys, homocystine	↓ L
Storage	B	Glu	↑ H
Tube artifact, thrombin	B	Gly	↑ H
Tube artifact, EDTA	B	Ninhydrin positive artifact	
Tube artifact, metasulfite	B	*S*-sulfocysteine	↑ H
Unspun blood left at rm. temp.	B	Orn, total homocysteine	↑ H
Unspun blood left at rm. temp.	B	Arg, Cys, homocystine	↓ L

Table 2. Nutritional status and amino acid values

Factor/condition	Source	Amino acid(s) affected	Value
Diet, canned formula or milk	U	Homocitrulline	↑ H
Diet, gelatin	U	Gly	↑ H
Diet, high protein (infants)	B	Met, Tyr	↑ H
Diet, shellfish	U	Taurine	↑ H
Diet, white meat from fowl	U	Anserine, 1-methylhistidine, carnosine	↑ H
Folate deficiency	B	Total Homocyst(e)ine	↑ H
Kwashiorkor	B	Pro, Ser, Gly, Phe	↑ H
Kwashiorkor	B	Leu, Ile, Val, Trp, Met, Thr, Arg	↓ L
Obesity	B	Branched chain amino acids, Phe,Tyr	↑ H
Obesity	B	Gly	↓ L
Starvation, 1–2 days (with or without vomiting)	B	Branched chain amino acids, Gly	↑ H
Starvation, 1–2 days (with or without vomiting)	B	Alanine	↓ L
Vitamin B12 deficiency	B	Total homocyst(e)ine	↑ H
Vitamin B6 deficiency	U	Cystathionine	↑ H

Table 3. Effects of illness/disease on amino acid values

Factor/condition	Source	Amino acid(s) affected	Value
Burn >20% of surface area (0–7 days after injury)	B	Phe	↑ H
Burn >20% of surface area (0–7 days after injury)	U	Ala, Gly, Thr, Ser, Glu, Gln, Orn, Pro	↓ L
Diabetes	B	Leu, Ile, Val	↑ H
Hepatic disease	B	Tyr, Phe, Met, Orn, GABA	↑ H
Hepatic disease	B	Branched chain amino acids	↓ L
Hepatoblastoma	U	Cystathionine	↑ H
Hyperinsulinism	B	Leu, Ile, Val	↓ L
Hypoparathyroidism, primary	U	All amino acids	↑ H
Infection	B	All amino acids	↓ L
Infection	B	Phe/Tyr ratio	↑ H
Infection	U	All amino acids	↑ H
Ketosis	B	Leu, Ile, Val	↑ H
Ketotic hypoglycemia	B	Ala	↓ L
Leukemia, acute	U	Advanced disease: all amino acids	↑ H
Leukemia, acute	U	On therapy: gly, asp, thr, ser	↑ H
Neuroblastoma	U	Cystathionine	↑ H
Renal failure	U	Phe, Val	↓ L
Renal failure	U	His	↑ H
Renal failure	B	Phe, Cit, Cys, Gln, homocyst(e)ine	↑ H
Renal failure	B	Leu, Val, Ile, Glu, Ser	↓ L
Respiratory distress on oxygen	B	Cystine	↓ L
Rickets	U	Gly	↑ H

P plasma, *U* urine, *CSF* cerebrospinal fluid, *H* high, *L* low

Table 4. Effect of medications on amino acid values

Factor/condition	Source	Amino acid(s) affected	Value
Arginine infusion	B	Arg	↑ H
Arginine infusion	U	Arg, Lys, Orn, Cys	↑ H
Bile acid sequestrants (colestipol, niacin)	B	Homocyst(e)ine	↑ H
Cyclosporin A	B	Total homocysteine	↑ H
2-Deoxycoformycin	B	Homocyst(e)ine	↓ L
Lysine aspirin	U	Lys	↑ H
Methotrexate therapy	B	Homocyst(e)ine	↑ H
Methotrexate therapy	B	Phe/Tyr ratio	↑ H
Nitrous oxide anesthesia	B	Homocyst(e)ine	↑ H
Oral contraceptives	B	Pro, Gly, Ala, Val, Leu, Tyr	↓ L
D-Phenylalanine	U	Phe	↑ H
Tamoxifen	B	Homocyst(e)ine	↓ L
Tetracycline, renal toxicity	U	All amino acids	↑ H
Valproate	B,U	Gly	↑ H
Vigabatrin/ vinyl-GABA	U	β-alanine, β-aminoisobutyrate, GABA	↑ H
Vigabatrin/ vinyl-GABA	CSF	GABA, β-alanine	↑ H
Vigabatrin/ vinyl-GABA	B,U	2-Aminoadipic acid	↑ H

P plasma, *U* urine, *CSF* cerebrospinal fluid, *H* high, *L* low

Urine sample

- Urine is not the fluid of choice in the diagnostic investigation of an aminoacidopathy (phenylketonuria, maple syrup urine disease, homocystinuria, etc.) as plasma is a better sample type.
- Urine amino acids analysis is the diagnostic test for disorders of amino acid transport (cystinuria, lysinuric protein intolerance, Hartnup) or in prolidase deficiency.
- Although a random specimen is usually sufficient for diagnostic purposes, a timed urine collection may be required for reabsorption studies in conjunction with a plasma sample collected at mid-point.
- The interpretation of urine amino acids relies on patterns of amino acids more than on absolute values.

Interpretation of Amino Acids Results and Reference Values

Circadian rhythm

- Circadian rhythm is a physiological basis for higher amino acid concentrations, up to 10–15%, in the blood in the afternoon.
- A mild generalized increase in urine amino acids is a relatively common finding in hospitalized children.
- Vomiting and poor oral intake for 1–2 days may cause mild elevations (two- to threefold) of the plasma branched-chain amino acids.

In a patient with MSUD and metabolic decompensation, the pattern of branched-chain amino acids will show a disproportionately high leucine compared to isoleucine and valine and a markedly reduced alanine in addition to the presence of alloisoleucine.

Interpretation of Amino Acids Results and Reference Values

Secondary amino acid changes

- Secondary amino acid changes can be a clue to other types of metabolic disorders such as:
  - Galactosemia
  - Organic acidemias
  - Disorders of pyruvate metabolism
- Gross elevations of many amino acids, particularly glutamine and alanine in blood, have been reported in moribund children.
- Elevations of the branched-chain amino acids, citrulline, and arginine can be secondary to hypoxia and liver failure.

Table 5. Pathologic conditions associated with abnormal amino acids concentrations

Amino acid	Source	Disorder(s)	Value
All amino acids	U	Classic galactosemia, Renal Fanconi syndrome, Lowe syndrome	↑ H
All amino acids	U	Tyrosinemia type 1, hereditary fructose intolerance	↑ H
All amino acids	U	Vitamin D-dependent rickets, mitochondrial disorders	↑ H
Neutral amino acids	U	Hartnup disorder	↑ H
Alanine	P	Lactic acidosis, disorders of pyruvate metabolism, mitochondrial disorders, hyperammonemic syndromes, glucagon receptor defect	↑ H
Alanine	P	Maple syrup urine disease	↓ L
β-Alanine	P/U	β-Alaninemia	↑ H
β-Alanine	CSF	GABA-transaminase deficiency	↑ H
β-Alanine	U	Pyrimidine disorders, methylmalonate semialdehyde dehydrogenase deficiency	↑ H
Allo-isoleucine	P/U/ CSF	Maple syrup urine disease, E_3 deficiency	↑ H
α-Aminoadipic	U	α-Aminoadipic/α-Ketoadipic aciduria	↑ H
β-Aminoisobutyric acid	U	β-Alaninemia, β-Aminoisobutyric acid aminotransferase deficiency (benign)	↑ H
δ-Aminolevulinic acid	U	Tyrosinemia type I, porphyria	↑ H
Arginine	U	Cystinuria, dibasic aminoaciduria, lysinuric protein intolerance	↑ H
Arginine	P	Arginase deficiency, glucagon receptor defect	↑ H
Arginine	P	HHH syndrome, ornithine aminotransferase deficiency, urea cycle defects (except arginase deficiency)	↓ L
Argininosuccinate	P/U/ CSF	Argininosuccinate lyase deficiency	↑ H
Asparagine	P/CSF	Asparagine synthase deficiency	↓ L
Aspartic acid	U	Dicarboxylic aminoaciduria	↑ H
Aspartic acid	U	Pyruvate carboxylase deficiency type B	↓ L
Aspartylglucosamine	P/U	Aspartylglucosamidase deficiency	↑ H
Carnosine	U	Carnosinemia	↑ H
Citrulline	P	Citrullinemia type I (argininosuccinate synthase deficiency), Citrullinemia type II (citrin deficiency), argininosuccinate lyase deficiency, pyruvate carboxylase deficiency type B	↑ H

Table 5. (continued)

Amino acid	Source	Disorder(s)	Value
Citrulline	P	Δ-pyrroline-5-carboxylate synthase deficiency, lysinuric protein intolerance, NAGS, CPS, OTC deficiencies, mitochondrial disorders	↓ L
Cystathionine	P/U	Cystathionase deficiency	↑ H
Cystine	U	Cystinuria, hyperlysinemia, hyperornithinemia	↑ H
Cystine	P	Molybdenum cofactor deficiency, sulfite oxidase deficiency	↓ L
Formiminoglutamic acid (FIGLU)	U	Formiminoglutamic aciduria	↑ H
GABA	P/U	β-Alaninemia	↑ H
GABA	P/U/ CSF	GABA transaminase deficiency	↑ H
Glutamic acid	U	Dicarboxylic aminoaciduria	↑ H
Glutamic acid	P	Glutamic acidemia, glutamine synthase deficiency	↑ H
Glutamine	P/U/ CSF	Urea cycle defects	↑ H
Glutamine	P	Glutaminase deficiency (normal ammonia)	↑ H
Glutamine	P	Glutamine synthase deficiency, propionic acidemia, methylmalonic acidemia, maple syrup urine disease, pyruvate carboxylase deficiency	↓ L
Glycine	P/U/ CSF	Glycine encephalopathy, glycine transporter deficiency, propionic acidemia, methylmalonic acidemia, D-Glyceric aciduria	↑ H
Glycine	U	Familial renal iminoglycinuria, hyperprolinemia type I and II	↑ H
Glycine	P/CSF	Serine deficiency disorders	↓ L
Glycylproline	U	Prolidase deficiency	↑ H
Hawkinsin	U	Hawkinsinuria	↑ H
Histidine	P/U	Histidinemia	↑ H
Homoarginine	P/U	Hyperlysinemia	↑ H
Homocarnosine	CSF	Homocarnosinosis	↑ H
Homocitrulline	P/U	HHH syndrome, saccharopinuria	↑ H
Homocyst(e)ine	P/U	Cystathionine-β-synthase deficiency, cobalamin disorders, folate disorders, methionine synthase (MS) and MS reductase deficiency	↑ H
Homocyst(e)ine	P	Methionine adenosyltransferase deficiency, *S*-Adenosylhomocysteine hydrolase deficiency, glycine-*N*-methyltransferase deficiency, adenosine kinase deficiency	↑ H
Homocysteine-cysteine disulfide	P	Cystathionine-β-synthase deficiency	↑ H
Total Homocysteine	P	Molybdenum cofactor deficiency, sulfite oxidase deficiency	↓ L
Hydroxylysine	U	Hydroxylysinuria	↑ H
Hydroxyproline	U	Familial renal iminoglycinuria, hyperprolinemia type I and II	↑ H
Hydroxyproline	P/U	Hydroxyprolinemia	↑ H
Imidodipeptides	U	Prolidase deficiency	↑ H
Isoleucine	P/U	Maple syrup urine disease, E3 deficiency	↑ H
Leucine	P/U	Maple syrup urine disease, E3 deficiency	↑ H
Lysine	U	Cystinuria, lysinuric protein intolerance, dibasic aminoaciduria	↑ H
Lysine	P/U	Hyperlysinemia, saccharopinuria	↑ H
Lysine	P	HHH syndrome, ornithine aminotransferase deficiency, lysinuric protein intolerance	↓ L
Lysine	P	Urea cycle defects, pyruvate carboxylase deficiency type B	↑ H
Methionine	P/CSF	Homocysteine remethylation disorders	↓ L
Methionine	P/U	Cystathionine-β-synthase deficiency, hypermethioninemias	↑ H
Methionine sulfoxide	P	Cystathionine-β-synthase deficiency, hypermethioninemias	↑ H
Ornithine	U	Cystinuria, dibasic aminoaciduria, hyperlysinemia, lysinuric protein intolerance	↑ H
Ornithine	P	HHH syndrome, ornithine aminotransferase deficiency	↑ H
Ornithine	P	Δ-pyrroline-5-carboxylate synthase deficiency	↓ L
Phenylalanine	P/U	Phenylketonuria, hyperphenylalaninemias, pterin disorders	↑ H
Phenylalanine	P	Tyrosinemia type I	↑ H
Phosphoethanolamine	U	Hypophosphatasia	↑ H
Pipecolic acid	P	Hyperlysinemia, antiquitin deficiency (pyridoxine responsive seizures)	↑ H
Pipecolic acid	U	Hyperprolinemia type II	↑ H
Pipecolic acid	P/U	Peroxisomal disorders	↑ H
Proline	P	Δ-pyrroline-5-carboxylate synthase deficiency	↓ L

Table 5. (continued)

Amino acid	Source	Disorder(s)	Value
Proline	U	Familial renal iminoglycinuria	↑ H
Proline	P/U	Hyperprolinemia type I and II, lactic acidosis, multiple acyl-CoA dehydrogenase deficiency	↑ H
Saccharopine	P/U	Saccharopinuria	↑ H
Sarcosine	P/U	Sarcosinemia, mitochondrial disorders, glutaric acidemia type II, Betaine therapy	↑ H
Serine	P/CSF	Serine deficiency disorders	↓ L
S-Sulfocysteine	P/U	Molybdenum cofactor deficiency, sulfite oxidase deficiency	↑ H
Taurine	U	Molybdenum cofactor deficiency, sulfite oxidase deficiency, β-Alaninemia	↑ H
Threonine	P/CSF	Pyridoxal phosphate-dependent seizures, citrullinemia type II (citrin deficiency)	↑ H
Tryptophan	U	Tryptophanuria	↑ H
Tyrosine	P/U	Tyrosinemia type I, II, III, transient tyrosinemia of the newborn	↑ H
Tyrosine	P	Phenylketonuria, pterin disorders	↓ L
Valine	P/U	Maple syrup urine disease, E3 deficiency, branched chain amino transferase 2 deficiency	↑ H

P plasma, *U* urine, *CSF* cerebrospinal fluid, *H* high, *L* low

Table V: Maternal conditions affecting the newborn screening results

Maternal conditions	NBS analyte affected	Results in	Additional information/ duration of interference
Hyperthyroidism treated with Propylthiouracil (PTU)	Low thyroxine (T4), high TSH	Transient hypothyroidism	Until drug clears, typically 7–14 days
^{161}I (radioactive iodine) treatment during pregnancy: Before 8 weeks' gestation.	none	Euthyroid (but may cause birth defects)	Will cause maternal hypothyroidism (potential effect on fetal brain development if not treated in first trimester)
^{161}I (radioactive iodine) treatment during pregnancy: After 8 weeks' gestation (when fetal thyroid matures and traps iodine)	Low T4, high TSH	Permanent hypothyroidism	Lifelong
Steroids: prednisone, betamethasonel/ dexamethasone	Low or normal 17-0HP	Suppresses fetal adrenal function and causes false-negative results for CAH	Unknown - depends on class of steroid and dose; estimate 1–2 weeks
CAH	Elevated 17-0HP	False-positive result	Unknown-estimate 3-7 days
PKU or moderate hyperphenylalaninemias uncontrolled by diet or medications	Elevated phenylalanine; although ratio of phenylalanine - to - tyrosine (Phe/Tyr) should be normal; false-positive result	Transient hyperphenylalaninemia	12–24 hours unless infant has PKU
3-MCC deficiency	Elevated C50H	False-positive result	Unknown
Fatty liver of pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)	May have elevated even chain acylcarnitines	False-positive result	Unknown
Carnitine deficiency	May have low carnitine levels	False-positive result	Unknown
Vitamin B12 deficiency	Elevated propionylcarnitine (C3)	False-positive result	A number of days depending on nutrition provided

Table VI: Treatments used in special care baby unit and effects on newborn screening results

Treatment	Effect on newborn screening results	Duration of effect
Parenteral Nutrition (PN)	Elevation of multiple amino acids	4–24 hours after PN discontinued
Carnitine supplementation	Elevations of acylcarnitines; can mask carnitine transport disorders	For duration of supplementation and weeks later
Red cell transfusion and Extra Corporeal Life Support (ECLS) (pre- and postnatal transfusions)	Can mask the absence of enzymes and proteins intrinsic to the red blood cell (RBC), thereby negating results for hemoglobinopathies and galactosemia (when testing is for galactose 1 phosphate uridyl transferase (GALT) enzyme activity)	120 days after last transfusion ECLS invalidates all NBS results for analyte-specific periods of time
Dopamine	False-negative testing for CH, because levels of TSH are suppressed	Until drug therapy is stopped
Steroids	Suppressed TSH and T4; possible false-negative result for CH. May suppress 17-OHP resulting in false-negative testing for CAH	Unknown - depends on class of steroid and dose; estimate 1–2 weeks
Iodine exposure with povidone/ iodine preps	Transient hypothyroidism; lowT4, elevated TSH	Once exposure to topical iodine discontinued, resolution may take 2–6 weeks (depending on dose absorbed and other factors)
Pivalic acid antibiotic therapy	May cause elevated isovaleryl 2-methylbutyryl carnitine	Unknown

Table VII: Conditions of the infant affecting newborn screening tests

Condition of the infant	Effect on newborn screening	Duration of effect
Immature hypothalamic-pituitary thyroid axis	Low T4, normal TSH, infants with congenital hypothyroidism (CH) can be missed	Up to 6 weeks of age
Hypothyroxinemia of preterm birth	Transient hypothyroidism, lowT4; normal TSH followed by elevated TSH	Up to 6 weeks of age
Liver enzyme immaturity	Transient elevations of tyrosine, methionine, and galactose, occasionally other amino acids	A few weeks
Iodine deficiency	Transient hypothyroidism low T4, elevated TSH	Until supplemented
Acute illness	Transient hypothyroidism; low T4, elevated TSH, elevated immunoreactive trypsinogen (IRT)	Until recovered
Hypoxia	Elevated IRT	Until recovered
Liver disease	Elevated tyrosine, methionine, galactose Depression of biotinidase enzyme	Until recovered
Renal immaturity	Elevated 17-OHP, amino acids	Until recovered
Preterm	Lower biotinidase levels inversely related to gestational age	40 weeks gestational age

تفسیر آزمایشات متابولیک

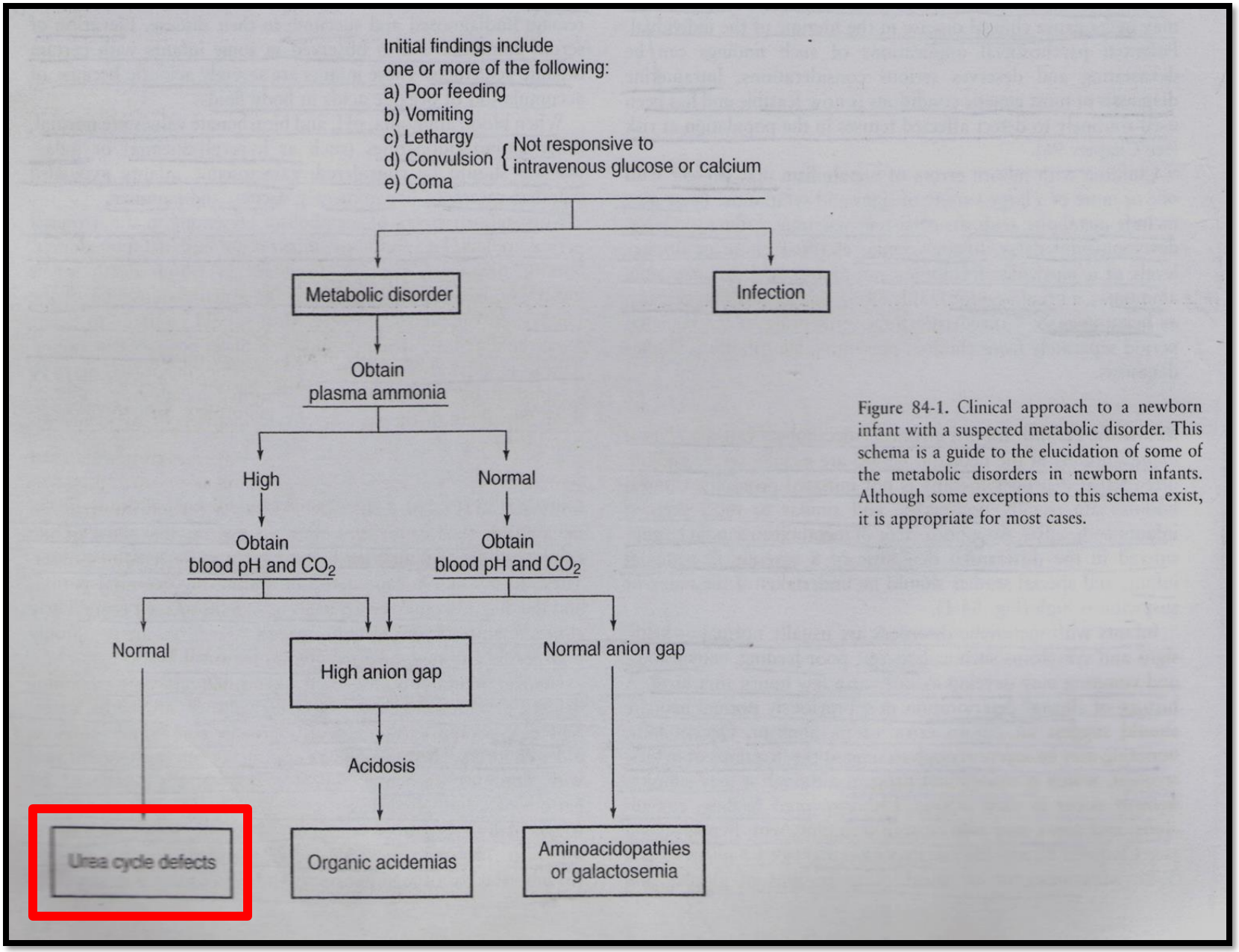
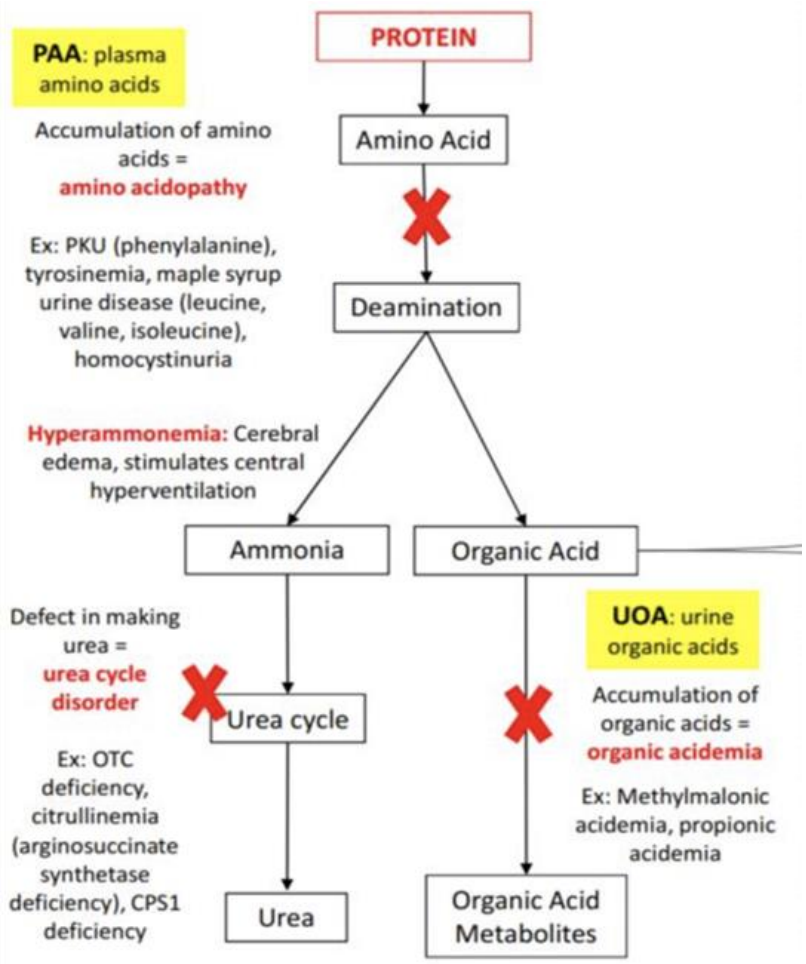


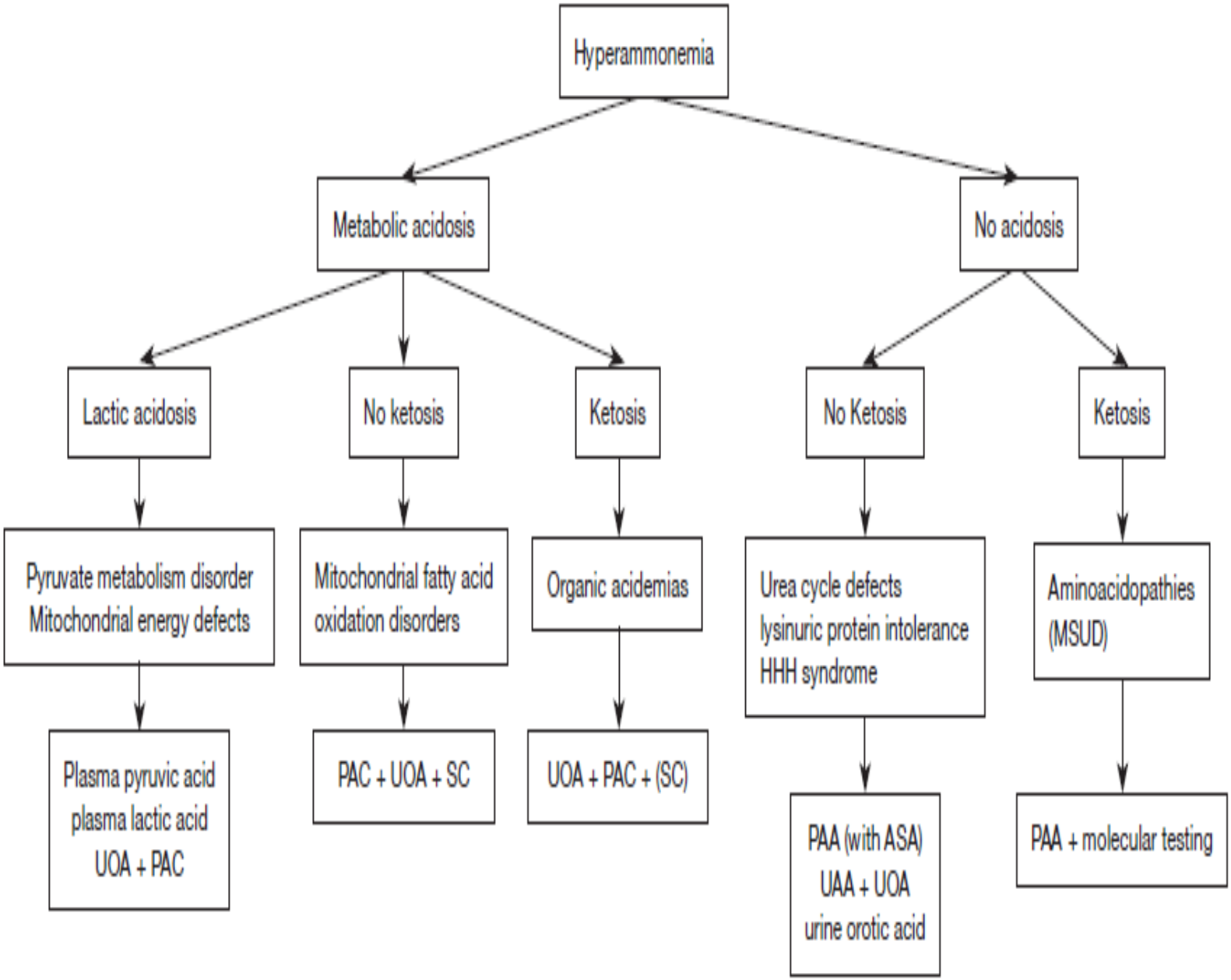
Figure 84-1. Clinical approach to a newborn infant with a suspected metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

Amino acid disorders



Hyperammonemia: Neos: > 50…> 100; Kids/Adults: >100…>150

- Level of hyperammonemia: 1) urea cycle defect 2) organic acidemia 3) amino acidopathy
- Central hyperventilation → respiratory alkalosis
- Why is it bad? Cerebral edema → herniation


Hyperammonemia
Metabolic acidosis
No acidosis
Lactic acidosis
No ketosis
Ketosis
No Ketosis
Ketosis
Pyruvate metabolism disorder
Mitochondrial energy defects
Mitochondrial fatty acid oxidation disorders
Organic acidemias
Urea cycle defects
lysinuric protein intolerance
HHH syndrome
Aminoacidopathies (MSUD)
Plasma pyruvic acid
plasma lactic acid
UOA + PAC
PAC + UOA + SC
UOA + PAC + (SC)
PAA (with ASA)
UAA + UOA
urine orotic acid
PAA + molecular testing

1) **UCD:** elevation of ammonia without metabolic acidosis (sometimes respiratory alkalosis)

Normal Level of ammonia:

- Fulterm < 100 μmol/L (< 1.7 μg/ml)
- Preterm < 150 μmol/L (< 2.6 μg/ml)
- Children < 35 μmol/L (< 0.6 μg/ml)

Pathologic Level of ammonia:

Neonate: > 150 μmol/L (> 2.6 μg/ml)

Ch.-Ad: > 100 μmol/L (> 1.7 μg/ml)

MS/MS: Increased level of

- Citruline
- Glutamic acid
- Aspartic acid
- Alanine

Urine GCMS: Increased level of:

- orotic acid
- uracil

Orotic acid

- Indic.: Suspected heterozygous OTC deficiency, urea cycle defects carbamyl phosphate disorder, disorders of pyrimidine

metabolism, mitochondrial disorders, allopurinol test

- Method: HPLC, MS-MS, capillary electrophoresis
- unexplained elevations also in other disorders, e.g. Rett syndrome, Lesch-Nyhan syndrome,
- “benign orotic aciduria

Elevation of other amino acids

- **Citrulline:** DD: citrullinaemia:↑ Cit; argininosuccinic aciduria:↑ Cit,↑ Asa,

Renal disease

- Confirmation: AA plasma and urine
- **Arginine:** Argininaemia; low sensitivity, Arg frequently normal in newborns
- Confirmation: AA plasma and urine
- **Glycine:**Non-ketotic hyperglycinaemia
- Confirmation: AA plasma (if symptomatic: plasma + CSF)

Follow-up testing for elevated citrulline

- *Possible diagnosis: citrullinemia (ASD);*
- *argininosuccinic aciduria(ASLD)*Plasma amino acids - elevated Cit, also Asa in ASLyase
- Urine amino acids (grossly elevated arginino-succinic acid (Asa) is diagnostic of ASL def)
- Urine organic acids - orotic acid may be elevated
- Confirmation:
- Argininosuccinate synthetase (ASS) activity in liver or cultured fibroblasts
- Argininosuccinate lyase (ASL) deficiency is confidently diagnosed from Asa levels

(فرم جواب به پیوست غلظت آنالیت‌ها در برنامه کشوری غربالگری نوزادان)

Report Form for Derivatized Sample Analysis by MS-MS Assay

تاریخ : ۱۴۰۰/۰۷/۲۹

نام نوزاد : امیررضا میرزائی | نام مادر:سمیرا | نام آزمایش: آنالیز نمونه خون خشک شده روی کاغذ از نظر بیماریهای

تاریخ تولد ۱۴۰۰/۰۷/۰۳ | تاریخ نمونه گیری:۱۴۰۰/۰۷/۲۴ | روش آزمایش: تاندم مس اسپکتروفتومتری مشتق سازی sciex 3200

جنسیت نوزاد : مرد | تاریخ دریافت نمونه : ۱۴۰۰/۰۷/۲۷ | کد پذیرش۲۴ رقمی کشوری نمونه

مرکز ارسال کننده : شهید احمدی - تهران جنوب | تاریخ پذیرش : ۱۴۰۰/۰۷/۲۷ | ۰۱۱۰۰۰۷۲۷۰۰۰۰۲۱۰۲۱۰۴۳۲۲۱

شماره کاغذ گاتری از مرکز بهداشتی : ۱۰۵۰-۷/۱۸ | تاریخ گزارش : ۱۴۰۰/۰۷/۲۹

Analyte Abbreviation	Analyte Full name	Result (µM)	reference interval	pathologic border	Description
Ala	Alanine	189.00	<362	>514	Normal
Asp	Aspartic Acid	30.50	<84	>95	Normal
Glu	Glutamic Acid	203.00	<427/00	>461	Normal
Arg	Arginine	13.50	4/00-34	<4 , >42	Normal
Cit	Citrulline	48.40	5.0-21.0	<4 , >30	*
Gly	Glycine	214.00	<417	>486	Normal
Leu+Ile	Leucine+Isoleucine	107.00	<170	>191	Normal
Met	Methionine	20.60	9.0-32	<9 , >36	Normal
Orn	Ornithine	49.60	<133	>148	Normal
Phe	Phenylalanine	34.30	<69	>112	Normal
Pro	Proline	89.80	<292	>314	Normal
Tyr	Tyrosine	43.90	<264	>303	Normal
Val	Valine	73.20	<156	>166	Normal
C0	Free Carnitine	14.90	8/0-40	<6/5 , >45	Normal
C2	Acetylcarnitine	6.94	7-38	<5, >40	*
C3	Propionylcarnitine	0.39	0.3-4/6	<0.3 , >5/0	Normal
C3DC & C8OH	Malonylcarnitine & 3-Hydroxyoctanoylcarnitine	0.02	<0/05	>0/15	Normal
C4	Butyrylcarnitine	0.14	<0.55	>0/75	Normal
C4OH	Hydroxybutyrylcarnitine	0.03	<0.3	>0.5	Normal
C4DC	Methylmalonylcarnitine	0.15	<0/25	>0.34	Normal
C5	Isovalerylcarnitine	0.13	<0.36	>0.45	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.03	<0/15	>0.16	Normal
C5:1	Tiglylcarnitine	0.01	<0.03	>0.09	Normal
C5OH	Hydroxyisovalerylcarnitine	0.10	<0/27	>0.47	Normal
C6	Hexanoylcarnitine	0.01	<0.09	>0.12	Normal
C6DC	Adipoylcarnitine	0.01	<0.05	>0.06	Normal
C8	Octanoylcarnitine	0.02	<0.08	>0.28	Normal

کد پذیرش : ۵۳۷۱۱۴۱ پزشک معالج: دکتر طالع - علی نوع بیمه: آزاد تاریخ چاپ : ۱۴۰۲/۰۶/۰۶ ۱۴:۴۵

HPLC

Test	Result	Unit	Reference Value
Aspartic Acid	7.8	uMol/L	0-20
Glutamic Acid	106.7	uMol/L	10-120
Asparagine	28.0	uMol/L	24-60
Serine	120.0	uMol/L	60-200
Glutamine	286.2	uMol/L	396-746
Histidine	58.7	uMol/L	50-130
Glycine	233.6	uMol/L	140-490
Threonine	89.9	uMol/L	40-240
Citrulline	78.5	uMol/L	8-47
Arginine	29.0	uMol/L	40-160
Taurine	52.1	uMol/L	19-216
Alanine	134.5	uMol/L	240-600
Tyrosine	90.6	uMol/L	30-120
a-Aminobutric Acid	4.1	uMol/L	6-38
Tryptophane	33.4	uMol/L	15-73
Methionine	17.7	uMol/L	6-49
Valin	90.1	uMol/L	140-350
Phenylalanine	58.7	uMol/L	30-80
Isolucine	22.3	uMol/L	30-130
leucine	51.8	uMol/L	60-230
Ornitine	50.3	uMol/L	20-135
Lysine	56.5	uMol/L	80-250

Comment : پلاسما ایکتر

* *Recheked*

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-00-091482

date:00/09/18

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Amirreza Mirzaei	Lab number:9337	Patient's ID:012000917000213014041482
Sample type: urine	Gender: male	age:2m, 13d
Physician/referred by: CMC	Reception Date:00/09/17	Reporting date: 00/09/18

Result:

Abnormal Compound	Cut off	measure
Ethylmalonic acid	7.45%	8.24%
Octanoic acid	0.59%	0.64%

Comment:
The urine organic acid analysis shows increased level of Ethylmalonic acid and Octanoic acid, that may be due to fasting. MCT oil consumption or carnitine deficiency.

Approved and interpreted by: Dr. Sedigheh shams

Differential diagnosis

Plasma citrulline	*Other features*	*Diagnosis*
Low (usually)	↑↑ Orotic acid	Ornithine transcarbamylase deficiency
	Specific acylcarnitines and organic acids	Organic aciduria, e.g. propionic or methylmalonic aciduria
	↓–n Orotic acid	Carbamylphosphate synthase deficiency N-acetylglutamate synthase deficiency Ornithine aminotransferase deficiency (newborns)
>30 µM	↑ Orotic acid	Lysinuric protein intolerance
>50 µM	↓–n Orotic acid, ↑ lactate	Pyruvate carboxylase deficiency (neonatal)
100–300 µM	↑ Argininosuccinate	Argininosuccinic acidaemia
>1,000 µM	↑ Orotic acid	Citrullinaemia

HD-IMC-LA-Rs-01-120646

تاریخ : 1401/12/10

فرم جوابدهی آزمایشگاه شناسایی و تشخیص بیماری های متابولیک ارثی

(فرم جواب به پیوست فلفت آنالیت‌ها در برنامه کشوری غربالگری نوزادان)

نام نوزاد : سیده ملکا رضایی

نام مادر : سمیرا

نام آزمایش: آنالیز نمونه خون خشک شده روی کاغذ از نظر بیماری متابولیک ارثی

تاریخ تولد 1401/11/24

تاریخ نمونه گیری : 1401/11/30

روش آزمایش: تاندم مس اسپکترومتری جرم مشق سازی

جنسیت نوزاد : زن

تاریخ دریافت نمونه : 1401/12/08

مرکز ارسال کننده : ثلاث ـ تهران جنوب

کد پذیرش24 رقمی کشوری نمونه

تاریخ پذیرش : 1401/12/08

شماره کاغذ گاتری از مرکز بهداشتی : 7

01101120800000602102064 6

تاریخ گزارش : 1401/12/10

Analyte Abbreviation	Analyte Full name	Result (µM)	reference interval	pathologic border	Description
Ala	Alanine	237.71	83-332	>467	Normal
Arg	Arginine	16.53	3.39-51.31	<2.80 , >62.07	Normal
Cit	Citrulline	68.66	4.4-27	<3 , >50	*
Glu	Glutamic Acid	331.88	172.2-645.1	>723	Normal
Gly	Glycine	172.90	69.3-308.5	>336.6	Normal
Leu+Ile	Leucine+Isoleucine	113.25	48-201	>215	Normal
Met	Methionine	22.08	7.06-27.84	<6.37, >34.25	Normal
Orn	Ornithine	71.09	48.55-182	>202	Normal
Phe	Phenylalanine	45.74	25.21-79.94	>119	Normal
Pro	Proline	211.93	81-374	>404	Normal
Tyr	Tyrosine	188.21	40.1-267.6	>296.4	Normal
Val	Valine	104.64	42.3-148	>159	Normal
C0	Free Carnitine	16.191	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	7.551	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	1.087	0.37-4.30	<0.2 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.021	<0.25	>0.44	Normal
C4	Butyrylcarnitine	0.152	0.085-0.7	>0.97	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.125	<0.31	>1.14	Normal
C5	Isovalerylcarnitine	0.127	<0.53	>0.63	Normal
C5:1	Tiglylcarnitine	-	<0.074	>0.23	
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.201	<0.45	>0.49	Normal
C6	Hexanoylcarnitine	0.033	<0.10	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.166	<0.46	>0.5	Normal
C8	Octanoylcarnitine	0.027	<0.10	>0.38	Normal
C8:1	Octenoylcarnitine	0.068	<0.19	>0.24	Normal
C10	Decanoylcarnitine	0.035	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.063	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.018	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.034	<0.146	>0.26	Normal
C12:1	Dodecenoylcarnitine	0.019	<0.09	>0.15	Normal
C14	Tetradecanoylcarnitine	0.101	<0.36	>0.58	Normal
C14:1	Tetradecenoylcarnitine	0.023	<0.13	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.009	<0.025	>0.042	Normal

END OF KESHAVARZ BLVD.-DR.GHARIB ST. بیمارستان دکتر حسن اهری انتهای بلوار کشاورز خیابان دکتر غریب ۳-۶۶۹۲۰۹۸۱

شماره آزمایشگاه : L011216141	نام : سیده ملکا رضائی حور	جنس : زن	OPD	تاریخ پذیرش	۱۴۰۱/۱۲/۲۷ ۱۱:۱۹	چاپ دوم
کد برگه : ۲۶۱۶۲۴۵	نام پدر : سیداحمد	سن : ۱. ماه		تاریخ جواب :	۱۴۰۲/۰۱/۰۹ ۰۹:۴۳	
کد پذیرش : ۶۰۰۷۹۹۳	پزشک معالج: ---------- دکتر	نوع بیمه: آزاد		تاریخ چاپ :	۱۴۰۲/۰۶/۰۶ ۱۴:۴۴	

HPLC(plasma)

Test	Result	Unit	Reference Value
Aspartic Acid	9.4	uMol/L	0-20
Glutamic Acid	308.8	uMol/L	10-120
Asparagine	49.4	uMol/L	24-60
Serine	177.4	uMol/L	60-200
Glutamine	614.2	uMol/L	396-746
Histidine	121.7	uMol/L	50-130
Glycine	279.3	uMol/L	140-490
Threonine	216.8	uMol/L	40-240
Citrulline	173.2	uMol/L	8-47
Arginine	213.6	uMol/L	40-160
Taurine	46.7	uMol/L	19-216
Alanine	298.9	uMol/L	240-600
Tyrosine	151.5	uMol/L	30-120
a-Aminobutric Acid	15.0	uMol/L	6-38
Tryptophane	39.9	uMol/L	15-73
Methionine	38.1	uMol/L	6-49
Valin	169.7	uMol/L	140-350
Phenylalanine	62.6	uMol/L	30-80
Isolucine	62.6	uMol/L	30-130
leucine	90.8	uMol/L	60-230
Ornitine	52.0	uMol/L	20-135
Lysine	123.1	uMol/L	80-250

* *Recheked*

Dr Signature :

نام: سیده ملکا رضائی حور	نام پزشک: دکتر علی طالع
سن: 4 ماهه	تاریخ پذیرش: 02/03/24
شماره: 40824	تاریخ جواب: 02/04/07

Amino Acids profile in plasma by LC-MS/MS

Amino Acid	Result (µM)	Normal Value	Description
Alanine	228.1	139-474	Normal
Allo-isoleucine	0.3	< 2	Normal
Alpha-aminoadipic acid	0.7	<4	Normal
Arginine	35.5	19-136	Normal
Argininosuccinic acid	15.5	< 0.2	Abnormal
Asparagine	51.6	25-91	Normal
Aspartic acid	6.8	< 20	Normal
Beta-aminoisobutyric acid	2.7	< 5	Normal
Beta-alanine	4.9	<28	Normal
Citrulline	91.3	9-45	Abnormal
Cystathionine	0.0	<1	Normal
Cystine	6.5	2-25	Normal
Gamma-aminobutyric acid	0.2	<1.5	Normal
Glutamic acid	109.3	31-202	Normal
Glutamine	759.2	316-850	Normal
Glycine	195.8	111-426	Normal
Glycylproline	0.0	<0.5	Normal
Histidine	46.8	10-116	Normal
Homocitrulline	0.1	<1	Normal
Homocystine	0.0	<0.2	Normal
Hydroxylysine	0.1	<0.5	Normal
Hydroxyproline	35.8	8-61	Normal
Isoleucine	33.6	25-105	Normal
Leucine	53.8	48-195	Normal
Lysine	108.0	49-283	Normal
Methionine	19.8	11-44	Normal
Ornithine	47.9	20-130	Normal
Phenylalanine	45.5	28-102	Normal
Proline	159.8	85-303	Normal
Serine	126.5	69-271	Normal
Sulfocysteine	0.0	<1	Normal
Threonine	137.2	47-237	Normal
Tryptophan	64.5	17-134	Normal
Tyrosine	76.8	26-115	Normal
Valine	96.0	83-312	Normal

Interpretation: This result is compatible with biochemical diagnosis of "Argininosuccinate Lyase Deficiency.

This test has been done with cooperation with Farzanegan Lab.

Follow-up testing for elevated arginine

- *Possible diagnosis: arginase deficiency*
- Plasma amino acids - marked elevation of Arg
- Urine amino acids - elevated Arg, Lys, Cys ,Orn
- Urine organic acids - orotate
- Confirmation: Arginase activity (RBC)

Follow-up testing for elevated ornithine

- *Possible diagnosis: HHH syndrome; gyrate atrophy*
- Plasma amino acids - markedly elevated Orn
- • Urine amino acids - elevated Orn, homoCit
- • Urine organic acids - orotic acid
- • Confirmation:
- elevated ammonia in addition to Orn and increased
- excretion of homocitrulline (homoCit) are diagnostic of
- HHH syndrome - a mitochondrial membrane
- transporter defect (ORNT1)
- • ornithine aminotransferase activity in lymphocytes
- (gyrate atrophy)

تفسیر آزمایشات متابولیک

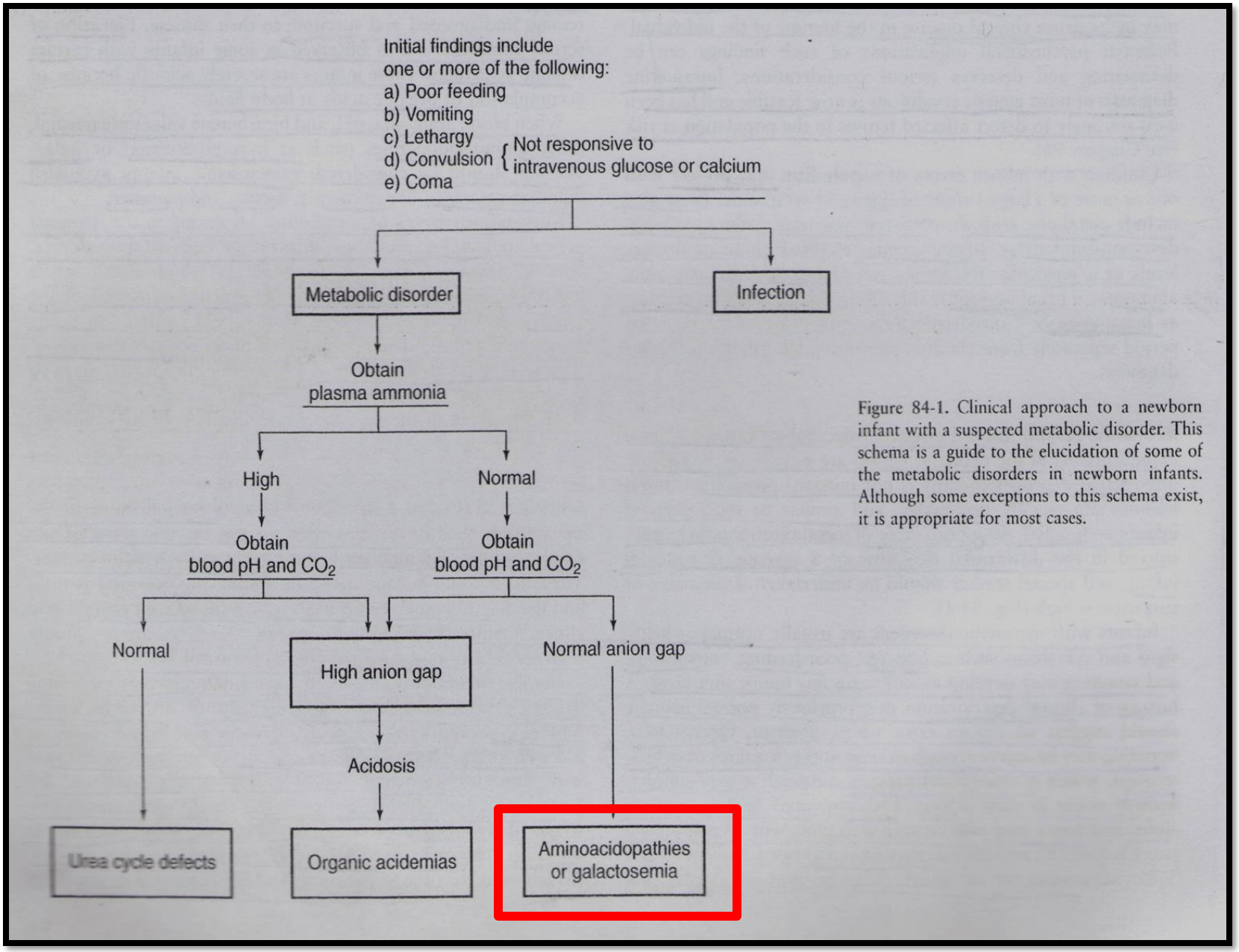


Figure 84-1. Clinical approach to a newborn infant with a suspected metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

- The most common abnormality in NBS for amino acids is elevated tyrosine; most cases are NOT tyrosinemia I, II or III (these are very rare)
- The most common urea cycle defect, OTC deficiency, is not currently detectable by MS/MS (possibility of low citrulline?)
- It is not clear that Tyr-I, NKH, HHH, Hyperprolinemia or Arginase deficiency are detectable in the neonate (< 5d of age)

Aminoacidopathies

2/A) PKU:

High blood level of phenylalanine (usually above than 10mg/dl) is diagnostic in:

- **HPLC method**
- **MS/MS method** **(mass spectrometry/ mass spectrometry)**

GCMS: Increased level of metabolites:

- Phenyl acetate
- Phenyl lactate
- Phenyl pyrovate

Phenylketonuria (PKU;)

- Metab.: ↑ Phe, ↓ Tyr, ↑ Phe/Tyr ratio
- Confirm.: AA plasma; exclude cofactor deficiency pterines in urine, DHPR activity in DBS; consider BH4 test
- DD: Prematurity, liver disease/hepatic failure, parenteral nutrition; ↑ Phe + ↑ Tyr: tyrosinaemia type 2 or 3, transient hypertyrosinaemia (premature neonates
- Neonatal Presentation: None

Pre-analytical aspects PHE

- **Potential for false negatives PHE**

Missing sample spot in the plate well
Transfusions at least 72h
Delays in transit
Physiological reasons
Potential for false positives
Contamination of the sample
Non-sample source contamination
Physiological reasons

2/B) Tyrosinemia: Blood level elevation of tyrosine:

- HPLC method ,MS/MS method **(mass spectrometry/mass spectrometry)**
  - **GCMS:** Elevation of:
  - Succcinylacetone
  - N-acetyltyrosine
  - 4 -HPPA
  - 4 -HPLA
  - 4 -HPAA

Follow-up testing for elevated tyrosine
Possible diagnosis: tyrosinemia type I, II or III

- Plasma amino acids - elevated Tyr
- Urine organic acids (elevated tyrosine metabs;
- succinylacetone is diagnostic of type I)
- **TYR II or III - Elevated TYR with normal SUAC**
- Clinical history (hepatorenal phenotype - type I; oculocutaneous phenotype - type II)
- DD:types 2 and3, transient hypertyrosinaemia (mainly premature neonates)
- *Note: transient tyrosinemia of the newborn is by far the most common cause of elevated Tyr*

کد پذیرش24 رقمی کشوری نمونه	تاریخ پذیرش : 1401/01/28	مرکز ارسال کننده : اسماعیل آباد - تهران جنوب
01101012800000402104345 7	تاریخ گزارش : 1401/01/31	شماره کاغذ گاتری از مرکز بهداشتی : 670

Analyte Abbreviation	Analyte Full name	Result (µM)	reference interval	pathologic border	Description
Ala	Alanine	253.08	<332	>467	Normal
Arg	Arginine	11.42	3.39-51.31	<2.80 , >62.07	Normal
Cit	Citrulline	11.54	5.2-27	<3 , >50	Normal
Glu	Glutamic Acid	409.16	<593	>723	Normal
Gly	Glycine	146.37	<308.46	>336.58	Normal
Leu+Ile	Leucine+Isoleucine	172.56	<201	>215	Normal
Met	Methionine	19.67	6.97-24.8	<6.34, >28.5	Normal
Orn	Ornithine	75.26	<182	>202	Normal
Phe	Phenylalanine	52.02	<68	>109	Normal
Pro	Proline	230.34	<374	>404	Normal
Tyr	Tyrosine	1185.51	<292.74	>336.58	*
Val	Valine	152.32	<131	>143	*
C0	Free Carnitine	37.080	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	25.997	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	3.933	0.37-4.30	<0.31 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.113	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.369	<0.49	>0.67	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.177	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.274	<0.39	>0.47	Normal
C5:1	Tiglylcarnitine	0.019	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.325	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.048	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.238	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.040	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.096	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.039	<0.139	>0.16	Normal

END OF KESHAVARZ BLVD.-DR.GHARIB ST.

شماره آزمایشگاه : L010508814	نام : لیانا رستمی نصیرآباد	جنس : زن	OPD	تاریخ پذیرش	۱۴۰۱/۰۵/۱۵ ۰۸:۵۷		
کد برگه : ۲۴۷۸۶۹۵	نام پدر : مرتضی	سن : ۴. ماه		تاریخ جواب :	۱۴۰۱/۰۵/۲۳ ۱۲:۲۹		
کد پذیرش : ۵۶۹۴۲۲۴	پزشک معالج: دکتر طالع - علی	نوع بیمه: آزاد		تاریخ چاپ :	۱۴۰۲/۰۶/۰۶ ۱۴:۳۸		

HPLC

Test	Result	Unit	Reference Value
Aspartic Acid	2.9	uMol/L	0-20
Glutamic Acid	87.4	uMol/L	10-120
Asparagine	38.2	uMol/L	24-60
Serine	142.3	uMol/L	60-200
Glutamine	679.8	uMol/L	396-746
Histidine	53.7	uMol/L	50-130
Glycine	159.0	uMol/L	140-490
Threonine	92.4	uMol/L	40-240
Citrulline	20.9	uMol/L	8-47
Arginine	51.9	uMol/L	40-160
Taurine	31.7	uMol/L	19-216
Alanine	188.6	uMol/L	240-600
Tyrosine	387.4	uMol/L	30-120
a-Aminobutric Acid	29.2	uMol/L	6-38
Tryptophane	70.7	uMol/L	15-73
Methionine	19.0	uMol/L	6-49
Valin	167.0	uMol/L	140-350
Phenylalanine	50.8	uMol/L	30-80
Isolucine	53.2	uMol/L	30-130
leucine	76.2	uMol/L	60-230
Ornitine	42.2	uMol/L	20-135
Lysine	96.5	uMol/L	80-250

* *Recheked*

Dr Signature :

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-01-052263

date:01/05/19

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Liana Rostami nasir abad	Lab number:8814	Patient's ID:012010518000325014022263
Sample type: urine	Gender: female	age:3m,25d
Physician/referred by: cmc	Reception Date:01/05/18	Reporting date: 01/05/19

Result:

Abnormal Compound	Cut off	measure
4-Hydroxyphenyllactic acid	12.51%	2683.98%
4-Hydroxyphenylacetic acid	139.99%	450.46%
4-Hydroxyphenylpyruvic acid	1.90%	348.46%

Comment:

The urine organic acid analysis shows significantly increased level of 4-Hydroxyphenyllactic acid, 4-Hydroxyphenylacetic acid and 4-Hydroxyphenylpyruvic acid, that is related to Tyrosinemia Type II. This patient is a known case of Tyrosinemia Type II.

Follow-up testing for elevated glycine

- *Possible diagnosis: NKH (nonketotic hyperglycinemia)*
- CSF amino acids - elevated glycine
- Plasma amino acids - elevated glycine
- Urine organic acids - rules out other metabolic causes for elevated glycine
- Confirmation:
- Ratio of CSF: plasma glycine > 0.08
- Reduced activity of the glycine cleavage system (liver)

Follow-up testing for elevated proline

- *Possible diagnosis: hyperprolinemia type I or type II*
- Plasma amino acids - elevated proline
- Urine organic acids (to rule out lactic acidosis and check for P5C)
- Confirmation:
- Type II - P5C dehydrogenase deficiency - by marked elevation of D1-pyrroline 5-carboxylate (P5C) in urine and plasma
- Type I - proline oxidase deficiency - by exclusion of type II

Follow-up testing for elevated methionine

- *Possible diagnosis: homocystinuria or hypermethioninemia*
- Plasma amino acids - elevated methionine and/or total plasma homocysteine
- Confirmation:

Cystathionine ß-synthase activity in lymphocytes or fibroblasts (if Hcys and Met elevated)

- Methionine adenosyl transferase activity (if Met only elevated) in liver

Potential for false negatives MET

Transfusions

Delays in transit / sample deterioration

Physiological reasons

Potential for false positives :

Liver disease (for example due to tyrosinaemia type I or galactosaemia), parenteral nutrition, and methionine adenosyl transferase (MAT) deficiency can give rise to an elevated methionin concentration in the newborn period.

Homocystinuria

- Metab.: ↑ Hcy; more common: ↑ Met (2nd tier Hcy from DBS, where available)
- **Abnormal Screen Result: Elevated MET**
- Elevated MET/PHE
- DD: Liver failure (↑ Met and Tyr); MAT I/III (↑ Met only)
- Confirm.: AA plasma, Hcy
- Neonatal Presentation: None

- Homocystinuric patients can be sub-divided into two important biochemical phenotypes:
- Pyridoxine responsive (screen undetectable)
- Pyridoxine unresponsive (screen detectable)

Raised total homocysteine concentrations are also seen in some rarer inborn errors of metabolism (MTHFR deficiency and defects of vitamin B12 metabolism) and in maternal B12 deficiency but these would not be detected by screening as they are associated with low, rather than high, methionine concentrations.

Total homocysteine (tHcy)

- Blood should be centrifuged within 45 min to obtain EDTA or heparin plasma or serum. For exact

measurement it is important to treat plasma or serum with a reducing agent that converts all Hcy species into the reduced form, HcyH, which is measured either directly or after derivatisation.

- *Normal values* (*fasting*): children < 10 yrs: 3.5–9 µmol/l; > 10 yrs: 4.5–11 µmol/l; women premenopausal 6–15 µmol/l; post-menopausal 6–19 µmol/l; men 8–18 µmol/l.

Maple syrup urine disease

- Metab.: ↑ XLE (= Leu + Ile + Allo-Ile + OH-Pro), ↑ Val, ↑ XLE/Ala
- **Abnormal Screen Result:**

Elevated LEU+ILE

- Elevated VAL
- Elevated LEU+ILE/PHE
- Elevated VAL/PHE
- DD: Total parenteral nutrition, hydroxyprolinaemia, probably non-disease
- Confirm.: AA plasma (Allo-Ile)

Pre-analytical aspects MSUD

- **Potential for false negatives**

Delays in transit / sample deterioration

Physiological reasons

transfusions

Potential for false positives :

MS/MS analysis does not differentiate leucine from isoleucine or hydroxyproline. While elevation of leucine and isoleucine both result from MSUD, increased hydroxyproline may indicate the rare benign condition hydroxyprolinaemia.

increased leucine concentration in galactosaemia or other severe liver disease

تفسیر آزمایشات متابولیک

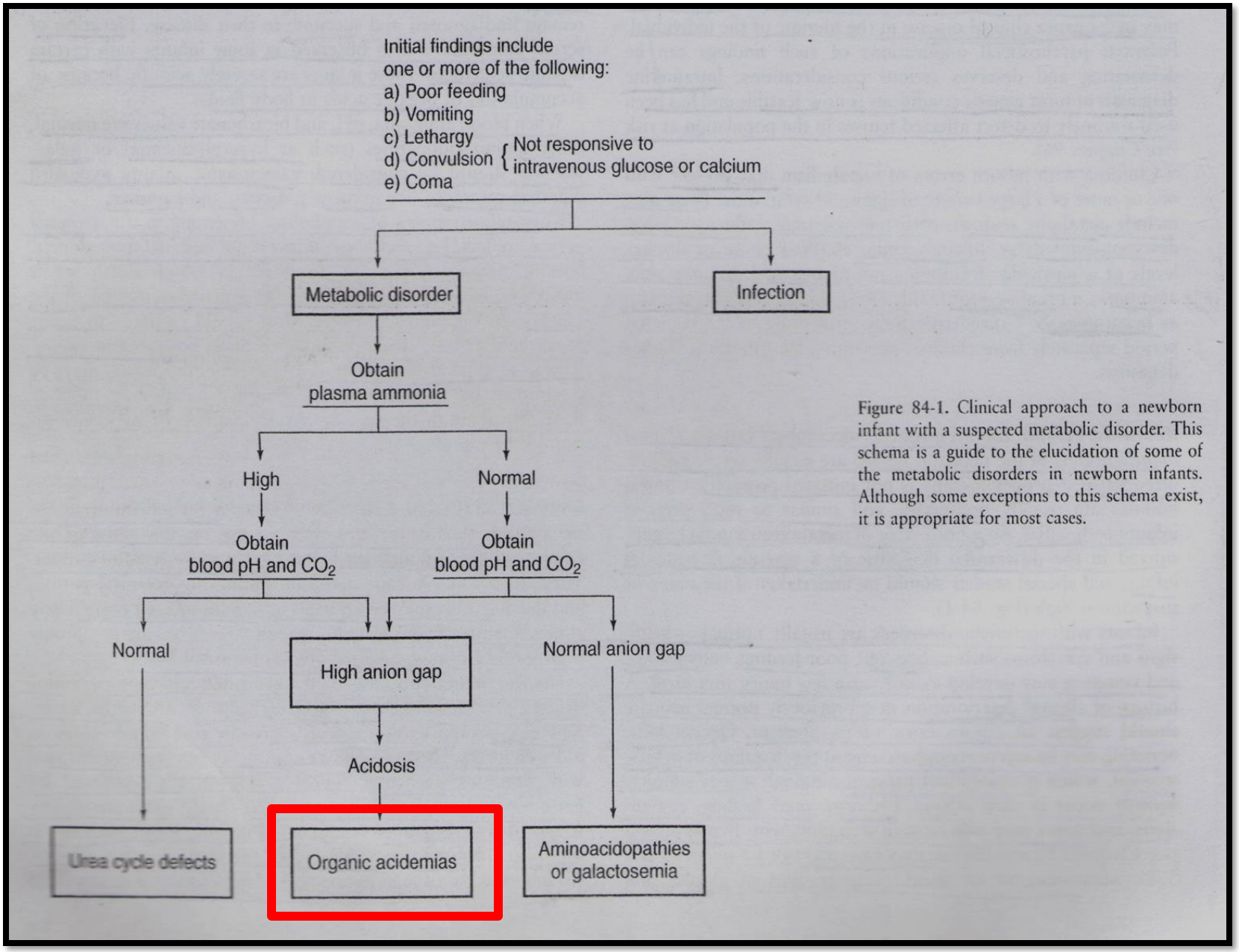
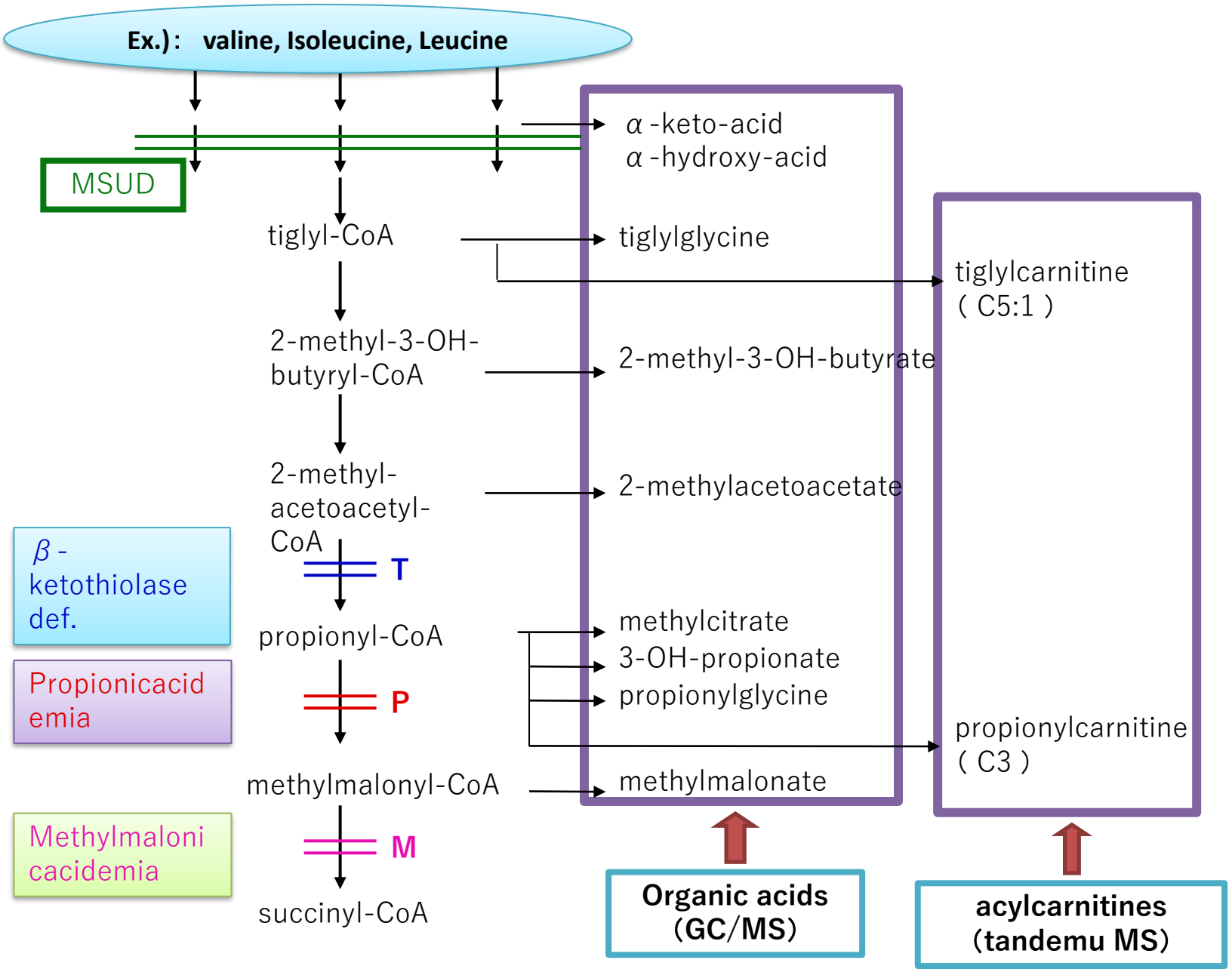


Figure 84-1. Clinical approach to a newborn infant with a suspected metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

Organic acidemias

Disorders	Primary metabolite in MS/MS	Confirmatory tests / follow-up	Findings in confirmatory tests
Glutaric aciduria 1 (GA I)	↑ Glutarylcarnitine (C5-dicarboxylic)	UOA, PACP	↑ Glutaric acid, 3-hydroxygluratic acid, glutaconic acid on UOA; ↑Glutarylcarnitine (C5-dicarboxylic) on PACP
HMG- CoA lyase deficiency	↑ 3- Hydroxyisovalerylcarnitine (C5-OH)	UOA, PACP	↑ 3-Hydroxyisovaleric, 3-methylglutaconic, 3-methylglutaric, 3-hydroxy-3-methylglutaric acids on UOA; ↑ C5- Hydroxyisovalerylcarnitine (C5-OH), 3 methylglutarylcarnitine (C6DC) on PACP
Isovaleric acidemia	↑ Isovalerylcarnitine (C5)	UOA, PACP	↑ Isovalerylglycine, 3-hydroxyisovaleric acid on UOA; ↑ isovalerylcarnitine (C5) on PACP
3-Keto(oxo) thiolase deficiency	↑ Tiglylcarnitine (C5:1), ↑ 3-hydroxy-2-methylbutyrylcarnitine (C5-OH)	UOA, PACP	↑ 2-Methyl-3- hydroxybutyrate, 2 methylacetoacetic, tiglylglycine on UOA; ↑ tiglylcarnitine (C5:1), ↑ 3-hydroxy-2-methylbutyrylcarnitine (C5-OH) on PACP
3-MCC deficiency	↑ 3- Hydroxyisovalerylcarnitine (C5-OH)	UOA, PACP	↑ 3-Hydroxyisovaleric, 3-methylcrotonylglycine on UOA; ↑ 3- hydroxyisovalerylcarnitine (C5-OH) on PACP
2-Methylbutyryl CoA dehydrogenase	↑ 2-Methylbutyrylcarnitine (C5)	UOA	↑ 2-Methylbutyrylglycine on PACP
3-Methylglutanoyl CoA hydratase deficiency	↑ 3 Hydroxyisovalerylcarnitine (C5-OH)	UOA, PACP	↑ 3-Hydroxyisovaleric, 3-methylglutaconic, 3-methylglutaric on UOA; ↑ 3 hydroxyisovalerylcarnitine (C5-OH) on PACP
Methylmalonic acidemia	↑ Propionylcarnitine (C3)	UOA, PACP	Methylmalonic, 3-hydroxypropionate, methylcitrate, propionylglycine on UOA; ↑propionylcarnitine (C3) on PACP
Multiple CoA carboxylase deficiency	↑ Propionylcarnitine (C3), ↑ 3-hydroxyisovalerylcarnitine (C5-OH)	UOA, PACP	↑ 3-OH-isovaleric, 3-methylcrotonylglycine, methylcitrate, 3-OH-propionic, lactate, pyruvate, acetoacetate, 3-OH-butyrate on UOA; ↑ propionylcarnitine (C3),↑ 3 hydroxyisovalerylcarnitine (C5-OH) on PACP
Propionic acidemia	↑ Propionylcarnitine (C3)	UOA, PACP	↑ 3-Hydroxypropionate, methylcitrate, propionylglycine; ↑ propionylcarnitine (C3) on PACP


Ex.) : valine, Isoleucine, Leucine
MSUD
α -keto-acid
α -hydroxy-acid
tiglyl-CoA
tiglylglycine
tiglylcarnitine
(C5:1)
2-methyl-3-OH-
butyryl-CoA
2-methyl-3-OH-butyrate
2-methyl-
acetoacetyl-
CoA
2-methylacetoacetate
β -
ketothiolase
def.
T
propionyl-CoA
methylcitrate
3-OH-propionate
propionylglycine
Propionicacid
emia
P
propionylcarnitine
(C3)
methylmalonyl-CoA
methylmalonate
Methylmaloni
cacidemia
M
succinyl-CoA
Organic acids
(GC/MS)
acylcarnitines
(tandemu MS)

- Acylcarnitine profile is helpful:
  - ↑ **C_3** (propionyl carnitine)→ *P.A
    *MMA
    *MCD
  - ↑ **C_5** (Isovaleryl carnitine): IVA
  - ↑ **C_5OH** (3-hydroxy isovaleryl carnitine)→
    - BKT
    - MCD
    - MCC
    - HMGL
    - IVA
    - 2M-3HBA
  - ↑ **C_4DC** (Methyl malonyl carnitine): MMA
  - ↑ **C_5DC** (Glutaryl carnitine): GA_1

Acylcarnitines in Organic Acidemias: Primary Markers

- **Acylcarnitine species Disorder to be considered**
- **C3 PA, MMA, MCD**
- **C4 IBCD, (SCAD, MAD)**
- **C5 IVA, 2MBCD ,(MAD)**
- **C5:1 (with C5-OH) SKAT, 3-MCC**
- **C5-OH 3-MCC, HMGL, SKAT, MCD, 3-methylglutaconyl hydratase def**
- **C3-DC MA**
- **C5-DC GA-I,**
- **C6-DC (with C5-OH) HMG**

- **Urine organic acid analysis is diagnostic for differentiation:**

P.A→
- MC
- PG
- 3HPA

- **MMA→**
  - MC
  - PG
  - MMA
  - 3HPA

- **MCD→**
  - MC
  - 3HPA
  - methyl crotonylglycine

- **Biotinidase deficiency→**
  - ↓ Biotinidase enzyme
  - GCMS: ↑ MCG- 3HPA- MC

- **IVA→** ↑ IVG
- **BKT:** 2M 3HBA, TG
- **GA_1:** GA, 3HGA
- **HMGL:** 3-hydroxy 3-methylglutaric acid,

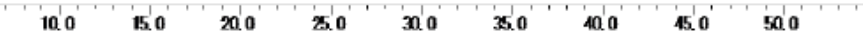
  3-methylglutaconic acid

- **MSUD→**
  - HPLC, MS/MS : ↑ leucine, valine, isolucine
  - U.GCMS: ↑ ketoisoralerate, α keto 3-methylvalerate,α ketoisocaproate

- **Elevated C3 (C3/C0, C3/C2, C4DC)**
- **Abnormal Screen Result: Elevated C3 (propionyl carnitine)**
- Elevated C3/C2 Elevated C3/C16
- **when the C3 is greater than 10 µM and the C3/C2 and/or C3/C16 is elevated or when the C3 is greater than 15 µM, regardless of the ratio levels**
- DD: Propionic aciduria ,methylmalonic aciduria; cobalamin disorders, FIGLU(Glutamate formiminotransferase deficiency),Succinyl CoA synthase deficiency
- many false positive cases
- Confirm.: Acylcarnitines (plasma), OA (urine)

Phe	Phenylalanine	20.15	<68	>109	Normal
Pro	Proline	128.72	<374	>404	Normal
Tyr	Tyrosine	34.36	<292.74	>336.58	Normal
Val	Valine	58.60	<131	>143	Normal
C0	Free Carnitine	11.922	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	12.743	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	20.304	0.37-4.30	<0.31 , >5	•
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.105	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.116	<0.49	>0.67	Normal
C4DC & C5OH	ethylmalonylcarnitine & Hydroxyisovalerylcarnit	0.229	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.081	<0.39	>0.47	Normal
C5:1	Tiglylcarnitine	0.051	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.323	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.048	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.184	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.024	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.014	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.020	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.016	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.008	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.025	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.008	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.090	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.016	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.006	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.002	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	1.000	0.41-6.09	<0.33 ,>7.13	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.005	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.040	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.046	<0.11	>0.134	Normal
C18	Octadecanoylcarnitine	0.577	0.19-1.71	<0.16 , >1.89	Normal
C18:1	Octadecenoylcarnitine	0.814	0.32-2.33	<0.27 , >2.55	Normal
C18:2	Octadecadienylcarnitine	0.325	0.059-0.56	<0.05 ,>0.66	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.011	<0.07	>0.14	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.008	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.003	<0/022	>0/11	Normal

Leu+Ile	Leucine+Isoleucine	43.04	<201	>252	Normal
Met	Methionine	6.89	6.97-22	<4.90, >31	*
Orn	Ornithine	36.25	<177	>193	Normal
Phe	Phenylalanine	14.96	<64	>111	Normal
Pro	Proline	116.16	<351	>371	Normal
Tyr	Tyrosine	28.74	<120	>401	Normal
Val	Valine	30.63	<131	>171	Normal
C0	Free Carnitine	9.612	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	17.225	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	13.234	0.38-4.24	<0.27 , >5.82	*
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.219	<0.17	>0.38	*
C4	Butyrylcarnitine	0.070	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.272	<0.19	>0.78	*
C5	Isovalerylcarnitine	0.049	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.069	<0.08	>0.33	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.345	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.039	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	0.245	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.027	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.017	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.028	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.020	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.006	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.021	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.012	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.073	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.017	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.009	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.002	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.994	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.005	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.042	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.042	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.550	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.762	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.287	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.012	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.010	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.002	<0/022	>0/063	Normal



Result

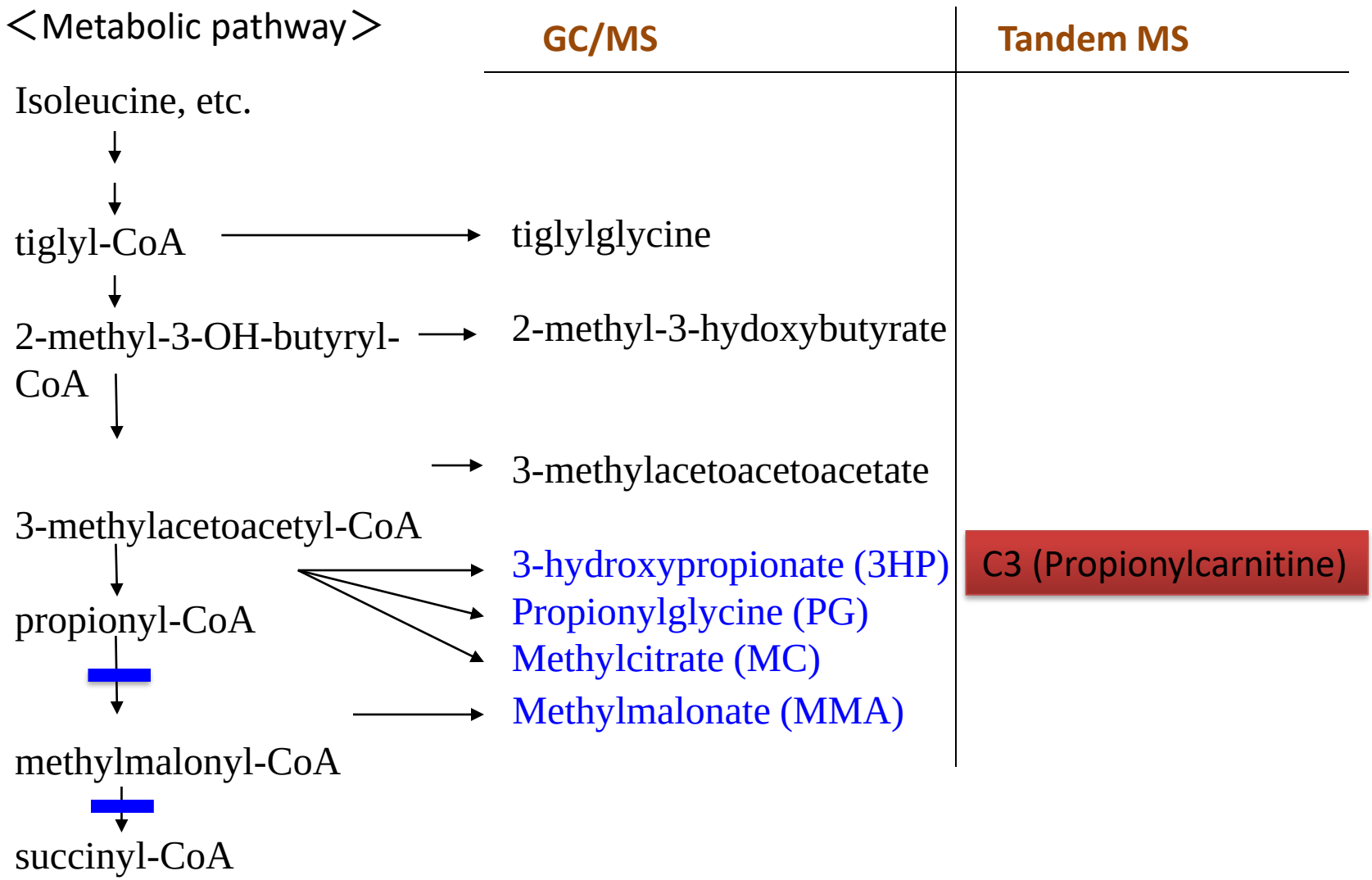
	Compound Name	Cut-off	measure	Error
11	3-Hydroxybutyric acid-2TMS	5/28%	6256/46%	*
3	Caproic acid-TMS	0/50%	0/99%	*
68	Adipic acid-2TMS	13/00%	23/65%	*
1	Lactic acid-2TMS	6/70%	36/22%	*
22	2-Hydroxyisocaproic acid-2TMS	0/50%	90/23%	*
14	2-Methyl-3-hydroxybutyric acid-2	7/65%	45/95%	*
97	Suberic acid-2TMS	11/51%	11/71%	*
17	2-Keto-isovaleric acid-oxime-2TM	0/50%	0/71%	*
59	3-Methylglutaconic acid(E)-2TMS	5/12%	15/01%	*
110	Methylcitric acid-4TMS	1/81%	23/91%	*
112	Methylcitric acid-4TMS	1/49%	10/00%	*
77	Tiglylglycine-2TMS	0/50%	436/62%	*
79	Tiglylglycine-TMS	0/53%	99/30%	*
4	Glycolic acid-2TMS	3/99%	8/94%	*
21	4-Hydroxybutyric acid-2TMS	0/50%	75/53%	*
55	Propionylglycine-2TMS	0/50%	38/23%	*
5	Oxalic acid-2TMS	1/00%	9/46%	*
62	decanoic-1	0/50%	0/68%	*
78	3-Methylcrotonoylglycine-TMS	1/05%	2/38%	*
8	3-Hydroxypropionic acid-2TMS	1/95%	686/19%	*
27	Acetoacetic acid-oxime-2TMS	0/10%	282/62%	*
75	7-Hydroxoctanoic acid-2TMS	0/06%	6/58%	*
89	4-Hydroxyphenylacetic acid-2TMS	139/99%	200/50%	*
23	3-Hydroxyvaleric acid-2TMS	0/50%	359/46%	*
16	3-Hydroxyisovaleric acid-2TMS	6/10%	37/49%	*
123	Palmitic acid TMS	23/34%	78/24%	*
44	Propionylglycine-TMS	0/50%	19/10%	*
36	Acetylglycine-TMS	0/50%	20/41%	*
19	2-ethyl-3-OH-propionic-2TMS	6/22%	14/17%	*
6	2-Hydroxybutyric acid-2TMS	0/50%	4/16%	*
43	Fumaric acid-2TMS	10/36%	20/20%	*
38	Maleic acid-2TMS	0/55%	4/69%	*
30	2-Methyl-3-hydroxyvaleric acid-2	0/50%	1/79%	*
56	Isobutyrylglycine-2TMS	0/50%	0/57%	*
67	Malic acid-3TMS	1/20%	2/74%	*

Methylmalonic Acidemia with Homocystinuria (CBL C, D, F)

- Abnormal Screen Result: Elevated C3 (propionyl carnitine)
- Decreased MET (Methionine)
- Elevated C3/C2

Ex1）elevation of C3 in tandem MS

Methylmalonicacidemia



Elevated C5 (C5/C2)

(isovaleryl carnitine) Isovaleric acidemia is a disorder of leucine (LEU)

DD: Isovaleric aciduria ,2-methylbutyric aciduria ,possibly non-disease,

- Confirm: Acylcarnitines plasma, OA urine
- In OA:Lactic, 3OH-BUTYRIC, **ISOVALERYLGLYCINE,** HIPPURIC, CITRIC, ISOVALERYLGLUTAMATE

Pro	Proline	137.46	<374	>404	Normal
Tyr	Tyrosine	74.06	<292.74	>336.58	Normal
Val	Valine	63.55	<131	>143	Normal
C0	Free Carnitine	20.698	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	18.350	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	3.352	0.37-4.30	<0.31 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.074	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.196	<0.49	>0.67	Normal
C4DC & C5OH	ethylmalonylcarnitine & Hydroxyisovalerylcarnit	0.169	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	2.448	<0.39	>0.47	*
C5:1	Tiglylcarnitine	0.044	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.350	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.044	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.266	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.043	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.031	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.047	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.045	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.008	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.046	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.027	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.152	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.055	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.013	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.006	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	3.154	0.41-6.09	<0.33 , >7.13	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.013	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.137	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.043	<0.11	>0.134	Normal
C18	Octadecanoylcarnitine	1.126	0.19-1.71	<0.16 , >1.89	Normal
C18:1	Octadecenoylcarnitine	1.511	0.32-2.33	<0.27 , >2.55	Normal
C18:2	Octadecadienylcarnitine	0.161	0.059-0.56	<0.05 , >0.66	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.017	<0.07	>0.14	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.008	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.013	<0/022	>0/11	Normal

C0	Free Carnitine	15.335	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	5.538	6.2-40.5	<4.3, >44.8	*
C3	Propionylcarnitine	0.569	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.029	<0.17	>0.38	Normal
C4	Butyrylcarnitine	0.075	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.100	<0.19	>0.78	Normal
C5	Isovalerylcarnitine	0.981	<0.39	>0.57	*
C5:1	Tiglylcarnitine	0.028	<0.08	>0.33	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.175	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.030	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	0.228	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.039	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.063	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.049	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.052	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.013	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.027	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.020	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.039	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.027	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.014	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.003	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.543	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.004	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.026	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.022	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.385	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.401	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.129	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.006	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.004	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.004	<0/022	>0/063	Normal

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-00-081883

date:00/08/18

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Elena Mirzamohammadi	Lab number:8532	Patient's ID:012000817000010014021883
Sample type: urine	Gender: female	age:10d
Physician/referred by: CMC	Reception Date:00/08/17	Reporting date: 00/08/18

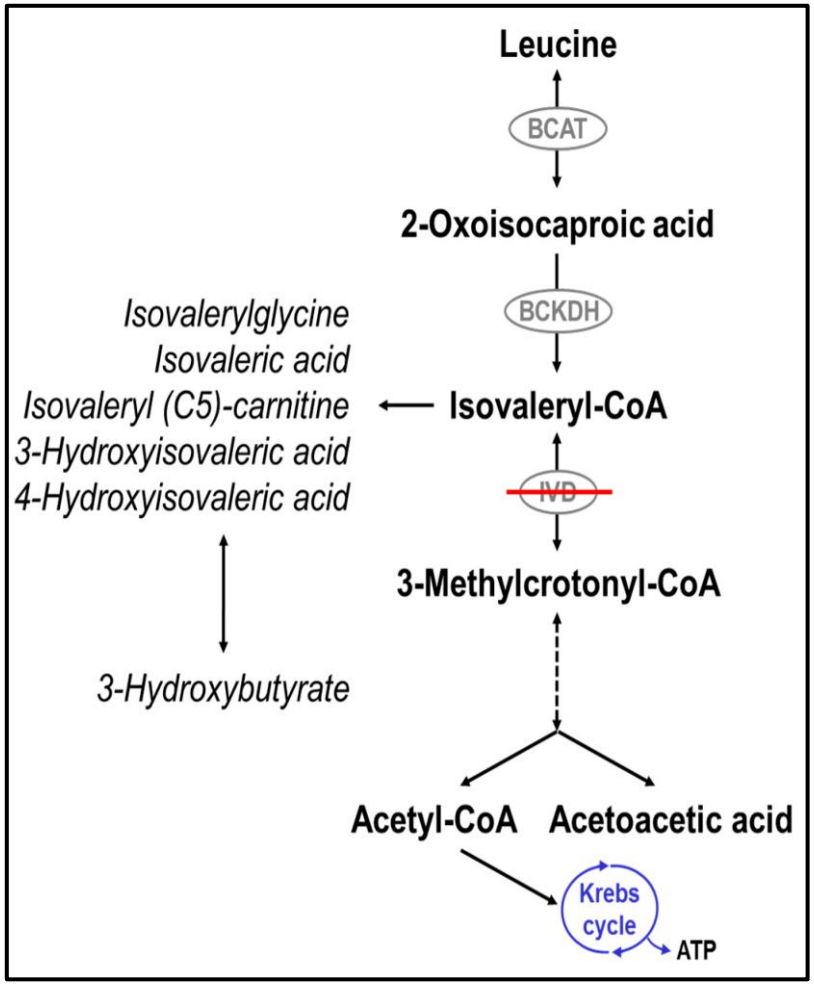
Result:

Abnormal Compound	Cut off	measure
isovalerylglycine-1	0.69%	11.82%

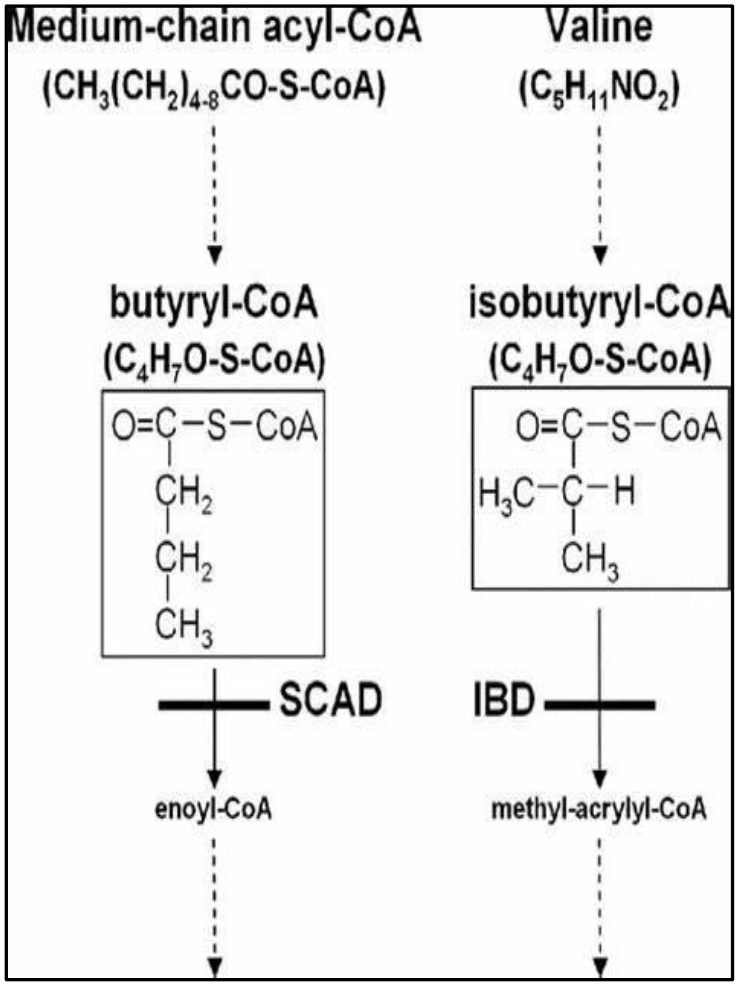
Comment:

The urine organic acid analysis shows increased level of isovalerylglycine. That is indicative of isovaleric acidemia.

Isovaleric acidemia



Isobutyryl-CoA dehydrogenase deficiency



Pre-analytical aspects C5

- **Potential for false negatives :**

Transfusions

Delays in transit / sample deterioration

Physiological reasons

Potential for false positives :

Pivaloylcarnitine is isobaric with isovaleryl carnitine and can result in false positive results

pivalic derivatives present in nipple creams and AB

Glutaric aciduria type 2 is often associated with an increase in C5, C8 and C5-DC

2-methylbutyryl carnitine is elevated in short/branched chain acyl-CoA dehydrogenase deficiency (SBCAD) ,2-methyl butyryl co A dehydrogenase deficiency and is isobaric with isovalerylcarnitine and causes a positive screening result

OA:**2-METHYLBUTYRYLGLYCINE,**2-ETHYL-3OH-PROPIONIC, ALPHA-KG, HIPPURIC, CITRIC

Arg	Arginine	14.76	3.39-51.31	<2.80 , >62.07	Normal
Cit	Citrulline	9.55	5.2-27	<3 , >50	Normal
Glu	Glutamic Acid	493.01	<593	>723	Normal
Gly	Glycine	83.47	<308.46	>336.58	Normal
Leu+Ile	Leucine+Isoleucine	88.44	<201	>215	Normal
Met	Methionine	10.19	6.97-24.8	<6.34, >28.5	Normal
Orn	Ornithine	55.35	<182	>202	Normal
Phe	Phenylalanine	28.01	<68	>109	Normal
Pro	Proline	136.65	<374	>404	Normal
Tyr	Tyrosine	64.40	<292.74	>336.58	Normal
Val	Valine	54.35	<131	>143	Normal
C0	Free Carnitine	25.362	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	16.150	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	1.539	0.37-4.30	<0.31 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.049	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.154	<0.49	>0.67	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.177	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.712	<0.39	>0.47	*
C5:1	Tiglylcarnitine	0.024	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.149	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.068	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.142	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.047	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.076	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.055	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.032	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.007	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.046	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.016	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.136	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.034	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.007	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.004	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	1.998	0.41-6.09	<0.33 , >7.13	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.009	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.067	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.133	<0.11	>0.134	*
C18	Octadecanoylcarnitine	1.284	0.19-1.71	<0.16 , >1.89	Normal

gn Window Help

Mohamadtaha Abd... ×

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Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-001-083325

date:01/08/28

e of Lab Center: Iran Metabolic Center
ress and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical er ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

ent's name: Mohamadtaha Abdi	Lab number:15737	Patient's ID:01201082500010501402332 5
ple type: urine	Gender: male	age:1m, 5d
sician/referred by: CMC	Reception Date:01/08/25	Reporting date: 01/08/28

Result:

Abnormal Compound	Cut off	measure
-	-	-

Comment: **2 methylbutyrilglycine**

No distinct abnormality was seen.

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Follow-up testing for elevated C5

- *Possible diagnosis: isovaleryl-coA dehydrogenase deficiency,2-methylbutyryl-coA dehydrogenase deficiency (2-MBCD),multiple acyl-coA dehydrogenase(MAD deficiency)*
- **Plasma acylcarnitine analysis - elevated C5 (+ others in MAD deficiency)**

Follow-up testing for elevated C5-DC

- *Possible diagnosis: Glutaryl-coA dehydrogenase deficiency (GA-I)(* Glutaric aciduria type 1)
- Metab.: ↑ C5DC (= glutaryl-CoA
- **Elevated C5DC (glutaryl carnitine) + C6OH (3-OH hexanoyl carnitine)**

Urine OA analysis - glutaric acidemia“classical”:3OH-GLUTARIC,GLUTARIC

- **Urine organic acids analysis - glutaric acidemia“low excretor” - glutaric acid not observed! :3OH-GLUTARIC**

Pre-analytical aspects C5-DC

- **Potential for false negatives :**

Transfusions

Delays in transit / sample deterioration

Physiological reasons

Potential for false positives :

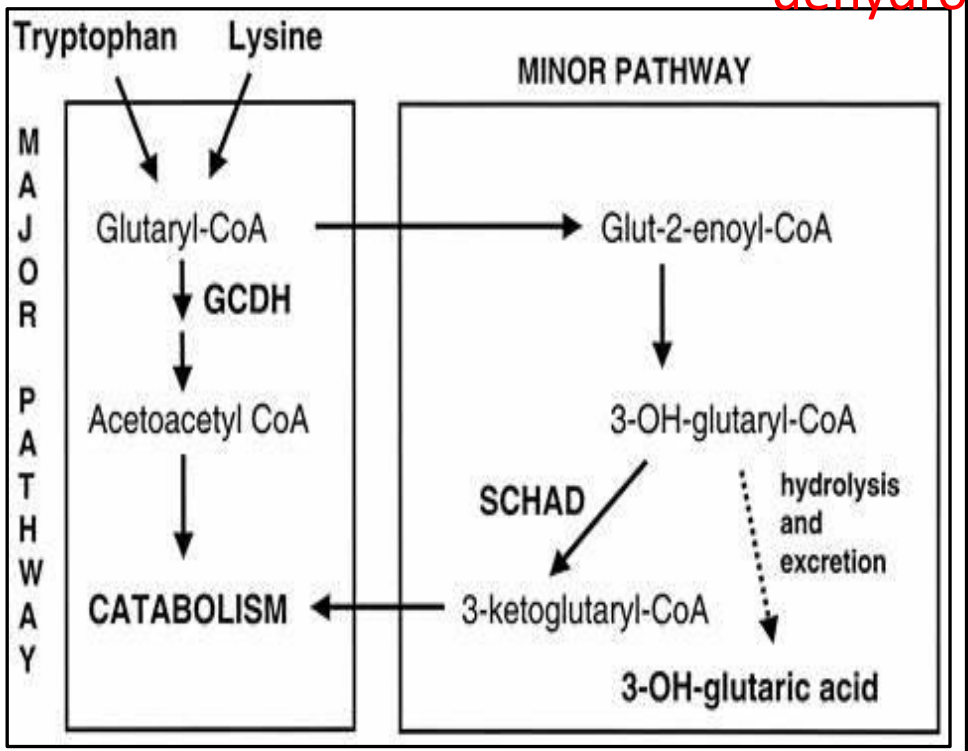
C6OH acylcarnitine is isobaric with C5-DC acylcarnitine

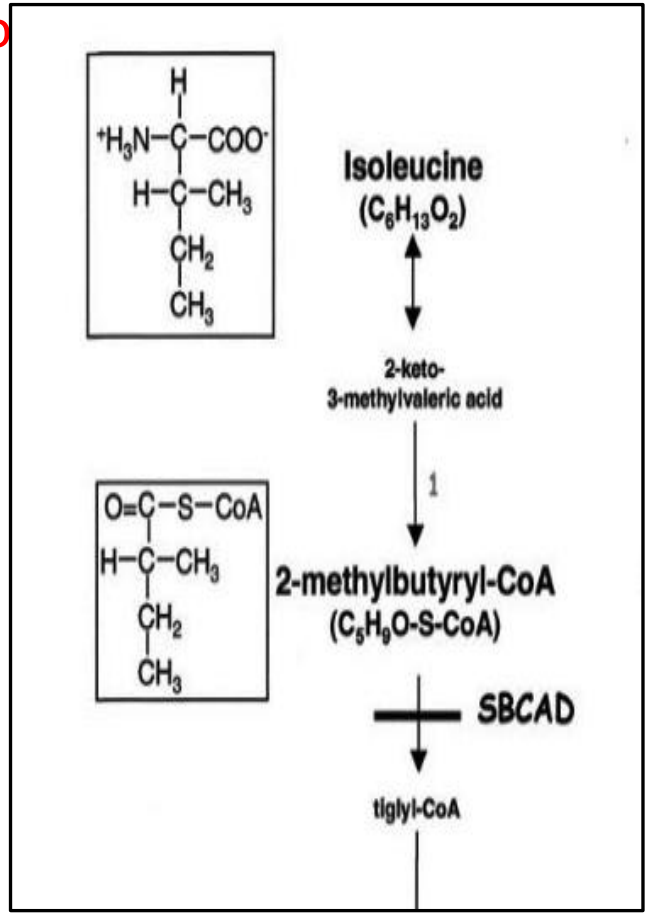
- elevated C6OH acylcarnitine is seen in association with ketosis

Glutaric aciduria type 2 is often associated with an increase in C5, C8 and C5-DC acylcarnitines,

Glutaric acidemia type I

Short/branched chain acyl-CoA dehydrogenase (SBCAD) deficiency (also known as 2-methylbutyryl-CoA dehydro





Elevated C5OH+C4DC

- **Elevated C5OH &C4DC(methyl malonyl carnitine)**
- DD:1. Multiple carboxylase deficiency ,C3 Elevate
- 2.HMG-CoA lyase deficiency ,also ↑ C6DC
- 3.3-Methylcrotonylglycinuria(3MCC) (possibly non-disease) ***Maternal 3-MCC:*** In some newborns, the elevated C4DC+C5OH is reflective of maternal 3-MCC levels.
- 4.3-Methylglutaconic aciduria I (probably non-disease in childhood)also C6:1
- 5.3-Oxothiolase deficiency, also ↑ C5:1
- Confirm.: Acylcarnitines plasma, OA urine

C2	Acetylcarnitine	21.20	7-38	<5, >40	Normal
C3	Propionylcarnitine	2.06	0.3-4/6	<0.3 , >5/0	Normal
C3DC & C8OH	Malonylcarnitine & 3-Hydroxyoctanoylcarnitine	0.00	<0/05	>0/15	Normal
C4	Butyrylcarnitine	0.24	<0.55	>0/75	Normal
C4OH	Hydroxybutyrylcarnitine	0.15	<0.3	>0.5	Normal
C4DC	Methylmalonylcarnitine	0.22	<0/25	>0.34	Normal
C5	Isovalerylcarnitine	0.18	<0.36	>0.45	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.03	<0/15	>0.16	Normal
C5:1	Tiglylcarnitine	0.04	<0.03	>0.09	*
C5OH	Hydroxyisovalerylcarnitine	7.01	<0/27	>0.47	*
C6	Hexanoylcarnitine	0.03	<0.09	>0.12	Normal
C6DC	Adipoylcarnitine	0.01	<0.05	>0.06	Normal
C8	Octanoylcarnitine	0.04	<0.08	>0.28	Normal
C8:1	Octenoylcarnitine	0.05	<0/18	>0.19	Normal
C10	Decanoylcarnitine	0.03	<0.14	>0.15	Normal
C10:2	Decadienoylcarnitine	0.01	<0.03	>0.05	Normal
C10:1	Decenoylcarnitine	0.04	<0.12	>0.17	Normal
C12	Dodecanoylcarnitine	0.06	<0.3	>0.55	Normal
C12:1	Dodecenoylcarnitine	0.10	<0.2	>0.3	Normal
C14	Tetradecanoylcarnitine	0.14	<0/35	>0.55	Normal
C14:2	Tetradecadienoylcarnitine	0.01	<0.05	>0.08	Normal
C14:1	Tetradecenoylcarnitine	0.04	<0.17	>0.31	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.01	<0/03	>0/04	Normal
C16	Hexadecanoylcarnitine	2.28	0/55-7/08	<0/55 ,>8/68	Normal
C16:1	Hexadecenoylcarnitine	0.15	<0/47	>0.51	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.04	<0/14	>0.15	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.01	<0.05	>0.14	Normal
C18	Octadecanoylcarnitine	0.84	0.22-1/67	<0.2 , >1.9	Normal
C18:2	Octadecadienoylcarnitine	0.43	0/07-0/68	<0.07 , >0/82	Normal
C18:1	Octadecenoylcarnitine	1.56	0/35-2/5	<0.2 , >2.76	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.0363	<0/09	>0/1	Normal
C18:1OH	Hydroxyoleoylcarnitine	0.0201	<0/04	>0.05	Normal
C18OH	Hydroxystearoylcarnitine	0.0201	<0/03	>0.05	Normal

C2	Acetylcarnitine	5.92	7-38	<5, >40	*
C3	Propionylcarnitine	0.64	0.3-4/6	<0.21 , >6	Normal
C3DC & C8OH	Malonylcarnitine & 3-Hydroxyoctanoylcarnitine	0.01	<0/05	>0/15	Normal
C4	Butyrylcarnitine	0.09	<0.55	>0/862	Normal
C4OH	Hydroxybutyrylcarnitine	0.04	<0.3	>0.64	Normal
C4DC	Methylmalonylcarnitine	0.17	<0/25	>0.5	Normal
C5	Isovalerylcarnitine	0.09	<0.36	>0.54	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.01	<0/15	>0.16	Normal
C5:1	Tiglylcarnitine	0.02	<0.03	>0.143	Normal
C5OH	Hydroxyisovalerylcarnitine	12.60	<0/27	>0.6	*
C6	Hexanoylcarnitine	0.00	<0.09	>0.16	Normal
C6DC	Adipoylcarnitine	0.01	<0.05	>0.087	Normal
C8	Octanoylcarnitine	0.01	<0.08	>0.34	Normal
C8:1	Octenoylcarnitine	0.02	<0/18	>0.19	Normal
C10	Decanoylcarnitine	0.01	<0.14	>0.18	Normal
C10:2	Decadienoylcarnitine	0.00	<0.03	>0.07	Normal
C10:1	Decenoylcarnitine	0.01	<0.12	>0.22	Normal
C12	Dodecanoylcarnitine	0.02	<0.3	>0.75	Normal
C12:1	Dodecenoylcarnitine	0.10	<0.2	>0.39	Normal
C14	Tetradecanoylcarnitine	0.04	<0/35	>0.64	Normal
C14:2	Tetradecadienoylcarnitine	0.01	<0.05	>0.11	Normal
C14:1	Tetradecenoylcarnitine	0.02	<0.17	>0.36	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.01	<0/03	>0/04	Normal
C16	Hexadecanoylcarnitine	0.44	0/55-7/08	<0/324 , >10	*
C16:1	Hexadecenoylcarnitine	0.02	<0/47	>0.51	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.01	<0/14	>0.19	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.00	<0.05	>0.2	Normal
C18	Octadecanoylcarnitine	0.22	0.22-1/67	<0.142 , >2.18	Normal
C18:2	Octadecadienoylcarnitine	0.25	0/07-0/68	<0.046 , >1.08	Normal
C18:1	Octadecenoylcarnitine	0.31	0/35-2/5	<0.156 , >3.09	*
C18:2OH	Hydroxylinoleoylcarnitine	0.019	<0/09	>0/1	Normal
C18:1OH	Hydroxyoleoylcarnitine	0.00527	<0/04	>0.07	Normal
C18OH	Hydroxystearoylcarnitine	0.00527	<0/03	>0.08	Normal

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-00071031

date:00/07/12

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Mohadese Hosseini	Lab number:	Patient's ID:01200071000001701404103l
Sample type: urine	Gender: female	age:17d
Physician/referred by: CMC	Reception Date:00/07/10	Reporting date: 00/07/12

Result:

Abnormal Compound	Cut off	measure
3-Methylcrotonoylglycine	0.52%	209.69%
3-Hydroxyisovaleric acid	6.10%	559.14%

Comment:
The urine organic acid analysis shows increased level of 3-Methylcrotonoylglycine and 3-Hydroxyisovaleric acid. That is indicative of 3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC). Enzyme assay and genetic study is recommended, for definitive diagnosis. Maternal 3-Methylcrotonyl-CoA Carboxylase Deficiency should also be considered.

Follow-up testing for elevated C5-OH (3-OH isovaleryl carnitine)

- **Plasma acylcarnitine analysis –**
- **elevated C5-OH; also with C5:1 in 3-MCC and SKAT,**
- **or with C6DC in HMG;**
- **or with C3** (propionyl carnitine) **in MCD (holocarboxylase synthetase def).**

Orn	Ornithine	99.50	<133	>148	Normal
Phe	Phenylalanine	49.60	<69	>112	Normal
Pro	Proline	304.00	<292	>314	*
Tyr	Tyrosine	35.50	<264	>303	Normal
Val	Valine	164.00	<156	>166	*
C0	Free Carnitine	29.50	8/0-40	<6/5 , >45	Normal
C2	Acetylcarnitine	35.10	7-38	<5, >40	Normal
C3	Propionylcarnitine	2.26	0.3-4/6	<0.3 , >5/0	Normal
C3DC & C8OH	Malonylcarnitine & 3-Hydroxyoctanoylcarnitine	0.03	<0/05	>0/15	Normal
C4	Butyrylcarnitine	0.30	<0.55	>0/75	Normal
C4OH	Hydroxybutyrylcarnitine	0.14	<0.3	>0.5	Normal
C4DC	Methylmalonylcarnitine	0.17	<0/25	>0.34	Normal
C5	Isovalerylcarnitine	0.26	<0.36	>0.45	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.22	<0/15	>0.16	*
C5:1	Tiglylcarnitine	0.02	<0.03	>0.09	Normal
C5OH	Hydroxyisovalerylcarnitine	3.22	<0/27	>0.47	*
C6	Hexanoylcarnitine	0.08	<0.09	>0.12	Normal
C6DC	Adipoylcarnitine	0.18	<0.05	>0.06	*
C8	Octanoylcarnitine	0.09	<0.08	>0.28	*
C8:1	Octenoylcarnitine	0.07	<0/18	>0.19	Normal
C10	Decanoylcarnitine	0.15	<0.14	>0.15	*
C10:2	Decadienoylcarnitine	0.01	<0.03	>0.05	Normal
C10:1	Decenoylcarnitine	0.06	<0.12	>0.17	Normal
C12	Dodecanoylcarnitine	0.23	<0.3	>0.55	Normal
C12:1	Dodecenoylcarnitine	0.16	<0.2	>0.3	Normal
C14	Tetradecanoylcarnitine	0.33	<0/35	>0.55	Normal
C14:2	Tetradecadienoylcarnitine	0.03	<0.05	>0.08	Normal
C14:1	Tetradecenoylcarnitine	0.14	<0.17	>0.31	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.02	<0/03	>0/04	Normal
C16	Hexadecanoylcarnitine	7.53	0/55-7/08	<0/55 , >8/68	*
C16:1	Hexadecenoylcarnitine	0.41	<0/47	>0.51	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.07	<0/14	>0.15	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.04	<0.05	>0.14	Normal
C18	Octadecanoylcarnitine	1.89	0.22-1/67	<0.2 , >1.9	*
C18:2	Octadecadienoylcarnitine	0.38	0/07-0/68	<0.07 , >0/82	Normal
C18:1	Octadecenoylcarnitine	2.52	0/35-2/5	<0.2 , >2.76	*
C18:2OH	Hydroxylinoleoylcarnitine	0.062	<0/09	>0/1	Normal
C18:1OH	Hydroxyoleoylcarnitine	0.0361	<0/04	>0.05	Normal
C18OH	Hydroxystearoylcarnitine	0.0361	<0/03	>0.05	*

Gly	Glycine				
Leu+Ile	Leucine+Isoleucine	148.83	<201	>252	Normal
Met	Methionine	14.55	6.97-22	<4.90, >31	Normal
Orn	Ornithine	100.91	<177	>193	Normal
Phe	Phenylalanine	36.57	<64	>111	Normal
Pro	Proline	287.23	<351	>371	Normal
Tyr	Tyrosine	166.61	<120	>401	*
Val	Valine	130.54	<131	>171	Normal
C0	Free Carnitine	20.673	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	7.432	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	0.483	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.029	<0.17	>0.38	Normal
C4	Butyrylcarnitine	0.090	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	2.238	<0.19	>0.78	*
C5	Isovalerylcarnitine	0.180	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.087	<0.08	>0.33	*
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.290	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.039	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	1.464	<0.52	>0.56	*
C8	Octanoylcarnitine	0.068	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.092	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.071	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.094	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.033	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.033	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.025	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.053	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.025	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.019	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.003	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	1.110	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.004	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.031	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.036	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.638	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.594	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.268	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.005	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.007	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.003	<0/022	>0/063	Normal

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-0010-3128

date:00/11/16

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Karen Rezayat	Lab number:17374	Patient's ID:012001030000019014043128
Sample type: urine	Gender: male	age:19d
Physician/referred by: CMC	Reception Date:00/10/30	Reporting date: 00/11/16

Result:

Abnormal Compound	Cut off	measure
Adipic acid	13.00%	14.64%
4-Hydroxyphenyllactic acid	12.51%	31.71%
3-Methylglutaconic acid(E)	5.12%	803.74%
Glutaric acid	8.44%	23.73%
3-methylglutaconic-2(3)	14.15%	392.99%
Tiglylglycine	0.53%	9.10%
3-Methylcrotonoylglycine	1.05%	3.60%
3-Methylglutaconic acid	0.50%	10.58%
3-Hydroxy-3-methylglutaric acid	30.52%	156.96%

Urine organic acids analysis

- moderate or marked elevation of 3OH-isovalerate, with 3-methylcrotonylglycine(3-MCC);

or with 3-methylglutaconic and 3Methyl-3OH-glutaric acids , 3-METHYLGLUTARIC(HMG);

or with 3-methylglutaconic acid (glutaconic aciduria type I);

or with metabolites of propionic acidemia in MCD.

- In ß-ketothioase deficiency (SKAT), there is marked elevation of 2-methyl-3-OH-butyric and 2-methylacetoacetic acids, with tiglylglycine.

Biotinidase deficiency

- Method: Determination of biotinidase activity (% normal); residual activity < 10% = severe deficiency,
- 10–20(–30)% = partial deficiency
- Exposure of test card to humid heat may cause denaturation of enzymes and consecutively a false positive result
- Confirm.: Biotinidase analysis in serum/plasma

Beta Ketothiolase Deficiency

- **Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)**
- C5:1 Tiglyl- BKT, MCC, MHBD,MCD
- C4-DC Methylmalonyl-/succinyl- MMA a , SUCLA2
- In SUCLA2 C3 &C4DC Increase&methylmalonic in OA

2-Methyl 3-OH Butyric Aciduria (2M3HBA)

- **Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)**
- Elevated C5:1 (tiglyl carnitine)
- Neonatal Presentation: Usually none

Elevated C4(butyryl carnitine)

- DD: SCAD deficiency ,IBD deficiency

(Isobutyryl Glycinuria)Ethylmaonic Enchephalopathy also C5

- Probably non-diseases (→ C4-acylcarnitine is excluded from NBS programmes in several

countries):

- outpatient assessment, continue breast feeding
- Confirm.: Acylcarnitines (plasma), OA (urine
- Neonatal Presentation: None
- OA In EE:Ethylmalonic acid,isovaleryl glycine

Follow-up testing for elevated C-4

- *Possible diagnosis: isobutyryl-coA dehydrogenase deficiency(IBCD), (SCAD deficiency, MAD deficiency)*
- **Urine organic acids analysis - elevated isobutyrylglycine in IBCD**
- LACTIC, ALPHA-KG, ACONITIC, CITRIC, 4OH-HIPPURIC

- Urine organic acids analysis - marked elevation of ethylmalonic and 2-methylsuccinic acids,butyrylglycine (“classical” SCAD);

modest elevation of ethylmalonic (“mild variant” SCAD); one or more of the following modestly elevated: ethylmalonic acid, adipic acid, glutaric acid, butyrylglycine, isobutyrylglycine,

isovalerylglycine, hexanoylglyine,

suberylglycine (MAD)

Mitochondrial β-oxidation

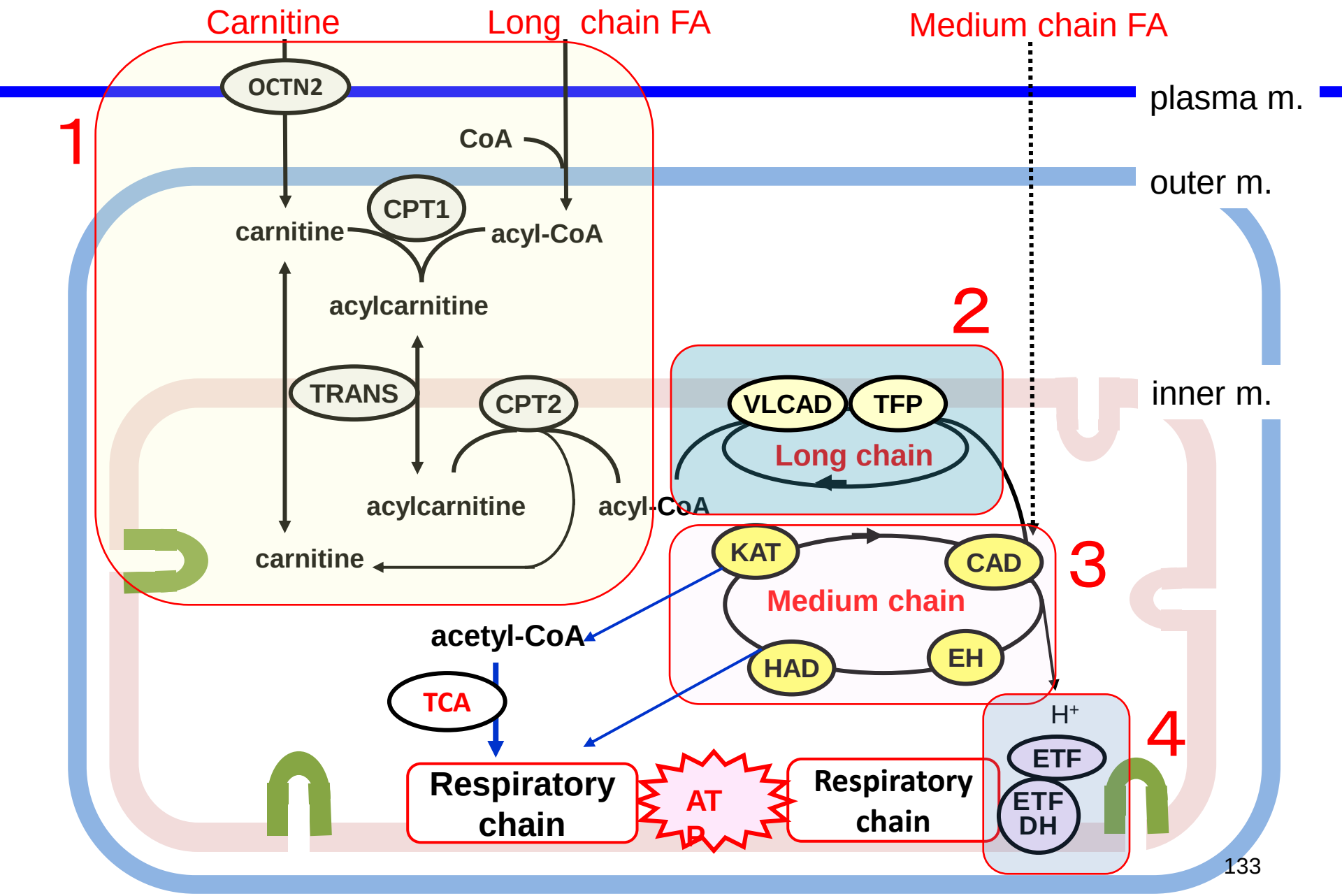


Table 1. The currently identified members of the human acyl-CoA dehydrogenase protein family with their primary metabolic function and optimal substrates.

Gene	ACAD#	Protein name	Catabolic pathway	Optimal substrate	Structure
ACADM	ACAD1	Medium-chain acyl-CoA dehydrogenase/MCAD	Fatty acids	C4:0-C12:0	Soluble matrix homo-tetramer
IVD	ACAD2	Isovaleryl-CoA dehydrogenase/IVD	Leucine	Isovaleryl-CoA	Soluble matrix homo-tetramer
ACADs	ACAD3	Short-chain acyl-CoA dehydrogenase/SCAD	Fatty acids	C4:0-C6:0	Soluble matrix homo-tetramer
ACADL	ACAD4	Long-chain acyl-CoA dehydrogenase/LCAD	Fatty acids	C10:0-16:0	Membrane bound homo-dimer
GCD	ACAD5	Glutaryl-CoA dehydrogenase/GCD	Lysine/tryptophan	Glutaryl-CoA	Soluble matrix homo-tetramer
ACADVL	ACAD6	Very-long-chain acyl-CoA dehydrogenase/VLCAD	Fatty acids	C12:0-C22:0	Membrane-bound homo-dimer
ACADSB	ACAD7	Short/branched-chain acyl-CoA dehydrogenase/SBCAD	Isoleucine	2-Me-butyryl-CoA	Soluble matrix homo-tetramer
ACAD8	ACAD8	Isobutyryl-CoA dehydrogenase/IBD	Valine	Isobutyryl-CoA	Soluble matrix homo-tetramer
ACAD9	ACAD9	ACAD family member 9	(Fatty acids)	?	Membrane-bound homo-dimer
ACAD10	ACAD10	ACAD family member 10	N/A	N/A	
ACAD11	ACAD11	ACAD family member 11	N/A	N/A	

Fatty acid oxidation defects

Disorders	Primary metabolite in MS/MS	Confirmatory tests / follow-up	Findings in confirmatory tests
Carnitine acylcarnitine translocase (CACT) deficiency	↑ C16–C18 acylcarnitines, ↓ Free carnitine	PACP, CK, glucose, NH3	↑ C16–C18 acylcarnitines on PACP; ↓ free carnitine, ↑ CK, ↓ glucose, ↑ NH3 on plasma
Carnitine palmitoyl transferase type 1 (CPT-1) deficiency	↓ C16–C18 acylcarnitines, ↕–↑ free carnitine	PACP, CK, glucose, NH3	↓ C16–C18 acylcarnitines on PACP; ↕–↑ free carnitine, ↑ CK, ↓ glucose, ↑ NH3 on plasma
Carnitine palmitoyl transferase type 2 (CPT-2) deficiency	↑ C16–C18 acylcarnitines, ↓ free carnitine	PACP, CK, glucose, NH3	↑ C16–C18 acylcarnitines on PACP; ↓ free carnitine, ↑ CK, ↓ glucose, ↑ NH3 on plasma
Carnitine uptake/ transporter defect	↓ C16–C18 acylcarnitines, ↓ free carnit	PACP, urine carnitine, CK, glucose, NH3	↓ C16–C18 acylcarnitines on PACP; ↑ urine carnitine; ↓ free carnitine, ↑ CK, ↓ glucose, ↑ NH3 on plasma
3-Hydroxy long chain acyl-CoA dehydrogenase deficiency (LCHAD/MTP)	↑ Long chain 3-hydroxy acylcarnitines	PACP, UOA, CK, glucose, NH3	↑ Long chain 3-hydroxy acylcarnitines on PACP; ↑ 3-OH dicarboxylic acids on UOA; ↑ CK, ↓ Glucose, ↑ NH3 on plasma
Medium chain acyl-CoA dehydrogenase (MCAD) deficiency	↑ C8–C10 acylcarnitines	PACP, UOA, CK, glucose, NH3	↑ C8–C10 acylcarnitines on PACP; ↑ dicarboxylic acids, hexanoylglycine, phenylpropionylglycine and suberylglycine on UOA; ↑ CK, ↓ glucose, ↑ NH3 on plasma
Multiple acyl-CoA dehydrogenase deficiency (MADD) or glutaric acidemia-type 2	↑ Multiple acylcarnitines	PACP, UOA, CK, glucose, NH3	↑ Multiple acylcarnitines on PACP; ↑ glutaric, ethylmalonic, dicarboxylic acids, hexanoylglycine, phenylpropionylglycine and suberylglycine on UOA; ↑ CK, ↓ glucose, ↑ NH3 on plasma
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	↑ Butyrylcarnitine (C4)	PACP, UOA	↑ Butyrylcarnitine on PACP; ↑ ethylmalonic, methylsuccinic, butyrylglycine on UOA
Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	↑ C14, C14:1, C14:2 acylcarnitines, ↓ Free carnitine	PACP, CK, glucose, NH3	↑ Long chain acylcarnitines on PACP; ↑ CK, ↓ glucose, ↑ NH3 on plasma

Acylcarnitines in FAO defects: Summary

Acylcarnitine species	Disorder to be considered
C0	Transporter defect
C4	SCAD, MAD
C5 (with C4)	MAD
C6 (with C8; C10:1)	MCAD
C8	MCAD
C10 (with C8, C10:1)	MCAD
C10:1 (with C8)	MCAD
C14:1	VLCAD

Acylcarnitines in FAO defects: Summary

Acylcarnitine species	Disorder to be considered
C14:1-OH (with C16-OH)	LCHAD/TFP
C16 (usually with C18:1)	CPT-II, CAT
C18:1 (with C16)	CPT-II, CAT
C16-OH	LCHAD, TFP
C18:1-OH (with C16-OH)	LCHAD, TFP
C16 Low (with C18:1)	CPT-I
C18:1 Low (with C16)	CPT-I

- Assessment of acylcarnitine profile with MS/MS method is diagnostic:
- In urine GCMS, findings is nonspecific→
  - **Dicarboxylic aciduria:** ↑ suberate, sebacate, adipate
  - **Non ketosis:** ↓ A.A- ß HB

- **PCD:**
  - ↓ Co (Free carnitine)
  - ↓ Long chains (↓ C16 - C18)

- C16 (Hexadecanoyl carnitine)
- C 18 (octadecanoyl carnitine)

- **CPT_1:**
  - ↑ Co
  - ↓ Long chains (↓ C16- C18)

- **SCAD:**
  - ↑ C_4 (Butyryl carnitine)
  - ↑ EM- M.S
- **MCAD:**
  - ↑ C_8 (octanoyl carnitine)
  - ↑ H.G, S.G
- **SCHAD:** ↑ C_4OH (3-hydroxy butyryl carnitine)
- **VLCAD:** ↑ $C_{14:1}$ (tetradecenoyl carnitine)

01101102600000402102193 6	تاریخ گزارش : 1401/10/29		شماره کاغذ گاتری از مرکز بهداشتی : 61		
Analyte Abbreviation	Analyte Full name	Result (µM)	reference interval	pathologic border	Description
Ala	Alanine	136.56	83-332	>467	Normal
Arg	Arginine	23.28	3.39-51.31	<2.80 , >62.07	Normal
Cit	Citrulline	14.80	4.4-27	<3 , >50	Normal
Glu	Glutamic Acid	403.36	172.2-645.1	>723	Normal
Gly	Glycine	150.30	69.3-308.5	>336.6	Normal
Leu+Ile	Leucine+Isoleucine	117.52	48-201	>215	Normal
Met	Methionine	19.58	7.06-27.84	<6.37, >34.25	Normal
Orn	Ornithine	87.66	48.55-182	>202	Normal
Phe	Phenylalanine	46.91	25.21-79.94	>119	Normal
Pro	Proline	147.82	81-374	>404	Normal
Tyr	Tyrosine	676.00	40.1-267.6	>296.4	*
Val	Valine	100.03	42.3-148	>159	Normal
C0	Free Carnitine	30.367	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	31.255	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	1.956	0.37-4.30	<0.2 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.000	<0.25	>0.44	Normal
C4	Butyrylcarnitine	1.764	0.085-0.7	>0.97	*
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.182	<0.31	>1.14	Normal
C5	Isovalerylcarnitine	0.194	<0.53	>0.63	Normal
C5:1	Tiglylcarnitine	0.121	<0.074	>0.23	*
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.699	<0.45	>0.49	*
C6	Hexanoylcarnitine	0.043	<0.10	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.220	<0.46	>0.5	Normal
C8	Octanoylcarnitine	0.056	<0.10	>0.38	Normal
C8:1	Octenoylcarnitine	0.049	<0.19	>0.24	Normal
C10	Decanoylcarnitine	0.073	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.063	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.019	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.087	<0.146	>0.26	Normal
C12:1	Dodecenoylcarnitine	0.060	<0.09	>0.15	Normal
C14	Tetradecanoylcarnitine	0.180	<0.36	>0.58	Normal
C14:1	Tetradecenoylcarnitine	0.086	<0.13	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.014	<0.025	>0.042	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.008	<0.016	>0.02	Normal
C16	Hexadecanoylcarnitine	2.718	0.32-5.22	<0.23 , >6.47	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.011	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.198	<0.29	>0.31	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.031	<0.12	>0.3	Normal
C18	Octadecanoylcarnitine	0.756	0.17-1.56	<0.14 , >1.76	Normal
C18:1	Octadecenoylcarnitine	1.244	0.27-2.32	<0.23 , >2.53	Normal
C18:2	Octadecadienylcarnitine	0.104	0.055-0.54	<0.048 , >0.62	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.014	<0.03	>0.11	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.007	<0.07	>0.14	Normal

Ala	Alanine	98.40	<338	>580	Normal
Arg	Arginine	31.96	2.45-43	<1.27, >75	Normal
Cit	Citrulline	20.94	5.77-27	<1.69 , >60	Normal
Glu	Glutamic Acid	251.48	<532	>940	Normal
Gly	Glycine	93.71	<307	>417	Normal
Leu+Ile	Leucine+Isoleucine	92.51	<201	>252	Normal
Met	Methionine	16.24	6.97-22	<4.90, >31	Normal
Orn	Ornithine	93.88	<177	>193	Normal
Phe	Phenylalanine	26.95	<64	>111	Normal
Pro	Proline	142.28	<351	>371	Normal
Tyr	Tyrosine	552.69	<120	>140	*
Val	Valine	73.57	<131	>171	Normal
C0	Free Carnitine	27.470	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	8.714	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	0.548	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.071	<0.17	>0.38	Normal
C4	Butyrylcarnitine	1.702	<0.49	>0.78	*
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.124	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.195	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.157	<0.08	>0.33	*
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.288	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.053	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	0.262	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.054	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.104	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.076	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.078	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.026	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.072	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.035	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.098	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.041	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.014	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.004	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.671	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.005	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.027	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.030	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.390	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.532	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.185	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.008	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.006	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.003	<0/022	>0/063	Normal

بیمارستان مرکز طبی کودکان - دکتر حسن اهری

Children's Medical Center

END OF KESHAVARZ BLVD.-DR.GHARIB ST. ٦٦٩٢٠٩٨١-٣ بیمارستان دکتر حسن اهری انتهای بلوار کشاورز خیابان دکتر قریب

شماره آزمایشگاه : L011102405	نام : محمدعلی تکین فر	جنس : مرد	OPD	تاریخ پذیرش	۱۴۰۱/۱۱/۰۴ ۱۲:۵۸		
کد برگه : ۲۵۸۵۰۰۲	نام پدر :	سن : ۲۹ روز		تاریخ جواب :	۱۴۰۱/۱۱/۱۲ ۰۹:۰۱		
کد پذیرش : ۵۹۳۷۵٦٤	پزشک معالج: دکتر طالع - علی	نوع بیمه: آزاد		تاریخ چاپ :	۱۴۰۲/۰٦/۰٦ ۱٤:۳۹		

HPLC(plasma)

Test	Result	Unit	Reference Value
Aspartic Acid	7.3	uMol/L	0-20
Glutamic Acid	75.3	uMol/L	10-120
Asparagine	42.4	uMol/L	24-60
Serine	145.1	uMol/L	60-200
Glutamine	653.0	uMol/L	396-746
Histidine	79.5	uMol/L	50-130
Glycine	179.8	uMol/L	140-490
Threonine	196.1	uMol/L	40-240
Citrulline	31.0	uMol/L	8-47
Arginine	69.0	uMol/L	40-160
Taurine	49.0	uMol/L	19-216
Alanine	226.7	uMol/L	240-600
Tyrosine	654.7	uMol/L	30-120
a-Aminobutric Acid	11.9	uMol/L	6-38
Tryptophane	54.9	uMol/L	15-73
Methionine	20.0	uMol/L	6-49
Valin	152.6	uMol/L	140-350
Phenylalanine	44.9	uMol/L	30-80
Isolucine	73.5	uMol/L	30-130
leucine	110.6	uMol/L	60-230
Ornitine	81.0	uMol/L	20-135
Lysine	126.8	uMol/L	80-250

Comment : پلاسما ایکتر

* *Rechaked*

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-01-110516

date:01/11/08

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Mohamadali Neginfar	Lab number:2405	Patient's ID:012011105000018014040516
Sample type: urine	Gender: male	age:18d
Physician/referred by: CMC	Reception Date:01/11/05	Reporting date: 01/11/08

Result:

Abnormal Compound	Cut off	measure
Homovanillic acid	42.35%	104.58%
Vanilmandelic acid	156.72%	210.30%
Adipic acid	13.00%	21.48%
Lactic acid	6.70%	16.62%
4-Hydroxyphenyllactic acid	12.51%	2749.88%
Ethylmalonic acid	7.45%	182.81%
Pyruvic acid-oxime	32.61%	179.46%
Phenyllactic acid	5.79%	13.15%
Methylsuccinic acid	8.62%	56.36%
4-Hydroxyphenylacetic acid	139.99%	771.84%
Phenylpyruvic acid-oxime	0.50%	2.26%
4-Hydroxyphenylpyruvic acid	1.90%	785.61%

Comment:

- TFP
- LCHAD

→ ↑ C_{16OH}- C_{18OH}

C_{16OH}: (3-hydroxyhexadecanoyl carnition)
C_{18OH}: (3-hydroxyoctadecanoyl carnitine)

- **CPT_2**
- **CACT**

→ ↑ C_{16}- $C_{18:1}$

C_{16}: Hexadecanoyl carnitine
$C_{18:1}$: octadecenoyl carnitine

Elevated C0

- Diagn.: CPT1 deficiency: ↑ C0/(C16 + C18)
- Confirm.: Acylcarnitines (plasma), carnitine status
- Secondary to rhabdomyolysis

Very low C0

- DD: Carnitine transporter deficiency ,organic acidurias, prematurity; if FTR normal: test mother for carnitine deficiency
- Confirm.: OA urine, carnitine status, fractional tubular re-absorption (FTR) of carnitine
- **Plasma acylcarnitine analysis - low C0 (usually <10**
- **µM); low acylcarnitine signals generally**
- **Urine organic acids analysis - non-specific findings;**
- **absence of dicarboxylic acids.**

Carnitine Uptake/Transport Deficiency (CUD)

- **Low C0 (free carnitine)**
- **C3 (propionyl carnitine) + C16 (palmitoyl carnitine) < 2**
- ***Maternal CUD*** - In some newborns, the low free carnitine is reflective of maternal CUD.
- **C0+C2+C3+C16+C18:1/Cit informative marker**
- **Low C0 :**medications including valproate, other…
- Secondary carnitine deficiencies,
- insufficient dietary intake,
- Renal tubulopathy,

Pro	Proline	130.09	<374	>404	Normal
Tyr	Tyrosine	127.58	<292.74	>336.58	Normal
Val	Valine	94.10	<131	>143	Normal
C0	Free Carnitine	3.334	7.14-43.34	<5.6, 48	*
C2	Acetylcarnitine	0.825	5.92-40.68	<3.95, >45.29	*
C3	Propionylcarnitine	0.090	0.37-4.30	<0.31 , >5	*
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.026	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.025	<0.49	>0.67	Normal
C4DC & C5OH	ethylmalonylcarnitine & Hydroxyisovalerylcarnit	0.027	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.039	<0.39	>0.47	Normal
C5:1	Tiglylcarnitine	0.007	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.050	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.016	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.216	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.013	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.038	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.020	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.008	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.009	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.009	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.004	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.009	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.007	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.003	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.000	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	0.042	0.41-6.09	<0.33 , >7.13	*
C16OH	Hydroxyhexadecanoylcarnitine	0.002	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.004	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.001	<0.11	>0.134	Normal
C18	Octadecanoylcarnitine	0.031	0.19-1.71	<0.16 , >1.89	*
C18:1	Octadecenoylcarnitine	0.080	0.32-2.33	<0.27 , >2.55	*
C18:2	Octadecadienylcarnitine	0.012	0.059-0.56	<0.05 , >0.66	*
C18:1OH	Hydroxyoctadecenoylcarnitine	0.002	<0.07	>0.14	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.002	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.001	<0/022	>0/11	Normal

Pro	Proline	130.09	<374	>404	Normal
Tyr	Tyrosine	127.58	<292.74	>336.58	Normal
Val	Valine	94.10	<131	>143	Normal
C0	Free Carnitine	3.334	7.14-43.34	<5.6, 48	*
C2	Acetylcarnitine	0.825	5.92-40.68	<3.95, >45.29	*
C3	Propionylcarnitine	0.090	0.37-4.30	<0.31 , >5	*
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.026	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.025	<0.49	>0.67	Normal
C4DC & C5OH	ethylmalonylcarnitine & Hydroxyisovalerylcarnit	0.027	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.039	<0.39	>0.47	Normal
C5:1	Tiglylcarnitine	0.007	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.050	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.016	<0.11	>0.14	Normal
C6DC	Methylglutarylcarnitine	0.216	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.013	<0.10	>0.3	Normal
C8:1	Octenoylcarnitine	0.038	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.020	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.008	<0.11	>0.21	Normal
C10:2	Decadienylcarnitine	0.009	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.009	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.004	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.009	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.007	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.003	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.000	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	0.042	0.41-6.09	<0.33 , >7.13	*
C16OH	Hydroxyhexadecanoylcarnitine	0.002	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.004	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.001	<0.11	>0.134	Normal
C18	Octadecanoylcarnitine	0.031	0.19-1.71	<0.16 , >1.89	*
C18:1	Octadecenoylcarnitine	0.080	0.32-2.33	<0.27 , >2.55	*
C18:2	Octadecadienylcarnitine	0.012	0.059-0.56	<0.05 , >0.66	*
C18:1OH	Hydroxyoctadecenoylcarnitine	0.002	<0.07	>0.14	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.002	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.001	<0/022	>0/11	Normal

C 2
(Acetylcarnitine)

- Elevate in:Carnitine supplementation or ketosis (deficiency if low)
- HMG CoA synthase deficiency(3-hydroxy-3 methyl glutary CoA synthase deficiency)
- Conf:plasma AC,in organic acid crotonylglysine/4 hydroxy- 6 methyl-2-pyrone
- Low C2 in CUD/Ethylmalonic Enchephalopathy
- ,CPT2,MCAD

Carnitine Palmitoyl Transferase Type I Deficiency (CPT IA)

- Primary High Markers
- Elevated C0
- **Elevated C0 (Free Carnitine)/C16 (palmitoyl carnitine) + C18 (octadecanoyl carnitine) ratio**
- Primary Low Markers
- **Low C16 (palmitoyl carnitine)**
- **Low C18 (octadecanoyl carnitine)**
- Low C18:1
- Low C18:2
- OA: **unremarkable. No specific diagnostic metabolites.**

Carnitine Palmitoyl Transferase Type II Deficiency (CPT II)

- Primary Markers
- Elevated C16 (palmitoyl carnitine)
- Elevated C18
- Informative Markers
- Elevated C12
- Elevated C16OH
- Elevated C18:1 (oleyl carnitine)
- OA: **either normal, or showing dicarboxylic aciduria and 3-hydroxydicarboxylic aciduria with reduced ketones when fasting. No specific diagnostic metabolites.**

Carnitine/Acylcarnitine Translocase Deficiency (CACT)

- Primary Markers
- Elevated C16 (palmitoyl carnitine)
- **Elevated C18 (octadecanoyl carnitine)**
- Informative Markers
- Elevated C12
- Elevated C16OH
- Elevated C18:1 (oleyl carnitine)

Elevated long-chain acylcarnitines

- DD: ↑ C16, C18; low C0: carnitine translocase or CPT2 deficiency
- ↑ C14:1, C14, C14:1/C4, C14:1/C12:1, etc.: VLCAD deficiency
- ↑ C16OH, C18:1OH LCHAD/MTP deficiency
- C12-OH 3-Hydroxy dodecanoyl- LCHAD/TFP deficiency/C14-OH
- Confirm: Acylcarnitines (plasma), OA (urine), carnitine status

Very Long Chain Acyl Co-A Dehydrogenase Deficiency (VLCAD)

- Primary Markers
- Elevated C14:1 (tetradecenoyl carnitine)
- **Elevated C14:1/C2 ratio**
- **High Secondary Markers**
- **Elevated C12 (dodecanoyl carnitine)**
- **Elevated C12:1 (dodecenoyl carnitine)**
- Elevated C14 (tetradecanoyl carnitine)
- **Elevated C14:2 (tetradecadienoyl carnitine)**
- **Elevated C16 (palmitoyl carnitine)**
- **Urine organic acids analysis - either normal, or showing**
- **dicarboxylic aciduria with reduced ketones when fasting**

Long Chain 3-OH Acyl Co-A Dehydrogenase Deficiency (LCHAD) and Trifunctional Protein Deficiency (TFP)

- Abnormal Screen Result:
- Primary Marker
- Elevated C16-OH (3-OH palmitoyl carnitine)
- Secondary Markers
- Elevated C14:1 (tetradecenoyl carnitine)
- Elevated C14 (tetradecanoyl carnitine)
- Elevated C18 (octadecanoyl carnitine)
- Elevated C18:1-OH (3-OH oleyl carnitine)
- C14-OH/C12-0H
- OA: either normal, or showing dicarboxylic aciduria and 3-hydroxydicarboxylic aciduria with reduced ketones when fasting. No specific diagnostic
- metabolites for LCHAD; 3-OH-monocarboxylic acids might accumulate in TFP deficiency

Malonic aciduria /Medium/Short Chain 3-OH acyl CoA Dehydrogenase Deficiency (M/SCHAD

- Metab.: ↑ C3DC, C4OH
- **Elevated C3DC (malonyl carnitine) + C4OH (3-OH butyryl carnitine)**
- **Elevated C3DC (malonyl carnitine) + C4OH (3-OH butyryl carnitine)/C10 (decanoyl carnitine) ratio**
- **C10-OH**
- **OA:Malonic acid**
- C4OH In 1: SCHAD OA:3 Hydroxy Glutaric acid
- 2:3 hydroxyisobutyryl coa hydrolase deficiency

Gly	Glycine	88.10	<307	>417	Normal
Leu+Ile	Leucine+Isoleucine	82.06	<201	>252	Normal
Met	Methionine	9.08	6.97-22	<4.90, >31	Normal
Orn	Ornithine	66.67	<177	>193	Normal
Phe	Phenylalanine	34.33	<64	>111	Normal
Pro	Proline	58.87	<351	>371	Normal
Tyr	Tyrosine	47.46	<120	>140	Normal
Val	Valine	95.68	<131	>171	Normal
C0	Free Carnitine	37.553	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	9.407	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	2.515	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	1.147	<0.17	>0.38	*
C4	Butyrylcarnitine	0.235	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.197	<0.19	>0.78	*
C5	Isovalerylcarnitine	0.166	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.049	<0.08	>0.33	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.196	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.051	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	0.215	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.046	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.061	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.055	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.044	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.022	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.027	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.020	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.067	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.032	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.012	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.004	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.560	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.007	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.034	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.031	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.523	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.783	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.254	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.015	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.010	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.006	<0/022	>0/063	Normal

Gly	Glycine	88.13	<307	>417	Normal
Leu+Ile	Leucine+Isoleucine	80.14	<201	>252	Normal
Met	Methionine	9.27	6.97-22	<4.90, >31	Normal
Orn	Ornithine	60.58	<177	>193	Normal
Phe	Phenylalanine	29.07	<64	>111	Normal
Pro	Proline	63.32	<351	>371	Normal
Tyr	Tyrosine	41.49	<120	>140	Normal
Val	Valine	99.22	<131	>171	Normal
C0	Free Carnitine	39.927	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	14.314	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	2.280	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	1.188	<0.17	>0.38	*
C4	Butyrylcarnitine	0.250	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.183	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.152	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.032	<0.08	>0.33	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.203	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.047	<0.11	>0.18	Normal
C6DC	Methylglutarylcarnitine	0.208	<0.52	>0.56	Normal
C8	Octanoylcarnitine	0.050	<0.10	>0.37	Normal
C8:1	Octenoylcarnitine	0.062	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.067	<0.132	>0.190	Normal
C10:1	Decenoylcarnitine	0.051	<0.10	>0.18	Normal
C10:2	Decadienylcarnitine	0.018	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.030	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.015	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.076	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.037	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.014	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.003	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.690	0.48-6.09	<0.28 , >8.16	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.004	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.038	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.054	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.756	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	1.334	0.32-2.17	<0.24 , >2.61	Normal
C18:2	Octadecadienylcarnitine	0.397	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.016	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.014	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.003	<0/022	>0/063	Normal

Gly	Glycine	153.00	<417	>632	Normal
Leu+Ile	Leucine+Isoleucine	59.60	<170	>224	Normal
Met	Methionine	12.70	9.0-32	<6.39 , >45	Normal
Orn	Ornithine	53.00	<133	>148	Normal
Phe	Phenylalanine	29.20	<69	>129	Normal
Pro	Proline	61.90	<292	>314	Normal
Tyr	Tyrosine	38.20	<264	>140	Normal
Val	Valine	80.90	<156	>199	Normal
C0	Free Carnitine	25.90	8/0-40	<4.68 , >57	Normal
C2	Acetylcarnitine	13.90	7-38	<5, >40	Normal
C3	Propionylcarnitine	1.09	0.3-4/6	<0.21 , >6	Normal
C3DC & C8OH	Malonylcarnitine & 3-Hydroxyoctanoylcarnitine	0.00	<0/05	>0/15	Normal
C4	Butyrylcarnitine	0.22	<0.55	>0/862	Normal
C4OH	Hydroxybutyrylcarnitine	1.13	<0.3	>0.64	*
C4DC	Methylmalonylcarnitine	0.06	<0/25	>0.5	Normal
C5	Isovalerylcarnitine	0.08	<0.36	>0.54	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.10	<0/15	>0.16	Normal
C5:1	Tiglylcarnitine	0.01	<0.03	>0.143	Normal
C5OH	Hydroxyisovalerylcarnitine	0.10	<0/27	>0.6	Normal
C6	Hexanoylcarnitine	0.09	<0.09	>0.16	Normal
C6DC	Adipoylcarnitine	0.03	<0.05	>0.087	Normal
C8	Octanoylcarnitine	0.06	<0.08	>0.34	Normal
C8:1	Octenoylcarnitine	0.06	<0/18	>0.19	Normal
C10	Decanoylcarnitine	0.04	<0.14	>0.18	Normal
C10:2	Decadienoylcarnitine	0.02	<0.03	>0.07	Normal
C10:1	Decenoylcarnitine	0.01	<0.12	>0.22	Normal
C12	Dodecanoylcarnitine	0.07	<0.3	>0.75	Normal
C12:1	Dodecenoylcarnitine	0.05	<0.2	>0.39	Normal
C14	Tetradecanoylcarnitine	0.05	<0/35	>0.64	Normal
C14:2	Tetradecadienoylcarnitine	0.00	<0.05	>0.11	Normal
C14:1	Tetradecenoylcarnitine	0.06	<0.17	>0.36	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.00	<0/03	>0/04	Normal
C16	Hexadecanoylcarnitine	0.56	0/55-7/08	<0/324 ,>10	Normal
C16:1	Hexadecenoylcarnitine	0.03	<0/47	>0.51	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.03	<0/14	>0.19	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.00	<0.05	>0.2	Normal
C18	Octadecanoylcarnitine	0.48	0.22-1/67	<0.142 , >2.18	Normal
C18:2	Octadecadienoylcarnitine	0.24	0/07-0/68	<0.046 , >1.08	Normal
C18:1	Octadecenoylcarnitine	0.73	0/35-2/5	<0.156 , >3.09	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.0216	<0/09	>0/1	Normal
C18:1OH	Hydroxyoleoylcarnitine	0.00704	<0/04	>0.07	Normal
C18OH	Hydroxystearoylcarnitine	0.00704	<0/03	>0.08	Normal

Pre-analytical aspects C8
Factors affecting the screening results

- C8 concentrations decrease slightly with increasing birth weight and in general, males have slightly higher C8 concentrations than females;
- **Potential for false negatives :**
- Transfusions could result in a false negative result, At least 72 hours is recommended

Dextrose administration in a sick neonate with MCADD prior to blood collection may reduce octanoylcarnitine levels.

It is known that C8 falls in older infants (after approximately 1 month of age)

False positive C8

- ***Premature/sick infants*** - Some special formulas and breast milk fortifiers fed to premature/sick infants contain medium chain triglycerides (MCT) as the primary fat source. These feedings may cause false elevations of some acyl carnitines analyzed in MCAD screening, particularly C8, C10:1 and C8/C10.
- Hypoxia/stress induced lipolysis/riboflavin deficiency or deficient mother/valproate therapy/mithocondrial myopathy/ Physiological stress / Early sampling , contamination
- MAD DEFICIENCY:C4,C5,C6,C8,C10,C12,C14,C14:1

Elevated medium-chain acylcarnitines

- Diagn.: MCAD deficiency: ↑ C8, C8/C2, C8/C12
- **Abnormal Screen Result: Primary Markers**
- **Elevated C8 (octanoyl carnitine)**
- Elevated C10 (decanoyl carnitine)
- Elevated C10:1 (decenoyl carnitine)
- Secondary Markers
- **Elevated C6 (hexanoyl carnitine)**
- Elevated C8/C10
- Confirm.: Acylcarnitines (plasma), OA
- (urine- **elevated hexanoylglycine and suberylglycine, often with 5-OH-hexanoic acid, also with dicarboxylic acids when fasting. Variants can be normal**

Orn	Ornithine	88.17	<177	>195	Normal
Phe	Phenylalanine	33.31	<64	>111	Normal
Pro	Proline	160.03	<351	>371	Normal
Tyr	Tyrosine	51.21	<120	>140	Normal
Val	Valine	57.62	<131	>171	Normal
C0	Free Carnitine	23.499	7.77-42	<4.38, >58	Normal
C2	Acetylcarnitine	6.296	6.2-40.5	<4.3, >44.8	Normal
C3	Propionylcarnitine	0.519	0.38-4.24	<0.27 , >5.82	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.062	<0.17	>0.38	Normal
C4	Butyrylcarnitine	0.128	<0.49	>0.78	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.154	<0.19	>0.78	Normal
C5	Isovalerylcarnitine	0.078	<0.39	>0.57	Normal
C5:1	Tiglylcarnitine	0.004	<0.08	>0.33	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.118	<0.41	>0.45	Normal
C6	Hexanoylcarnitine	0.864	<0.11	>0.18	*
C6DC	Methylglutarylcarnitine	0.923	<0.52	>0.56	*
C8	Octanoylcarnitine	2.557	<0.10	>0.37	*
C8:1	Octenoylcarnitine	0.171	<0.18	>0.21	Normal
C10	Decanoylcarnitine	0.169	<0.132	>0.190	*
C10:1	Decenoylcarnitine	0.820	<0.10	>0.18	*
C10:2	Decadienylcarnitine	0.039	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.019	<0.16	>0.37	Normal
C12:1	Dodecenoylcarnitine	0.012	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.040	<0/39	>0.7	Normal
C14:1	Tetradecenoylcarnitine	0.014	<0.12	>0.25	Normal
C14:2	Tetradecadienoylcarnitine	0.009	<0/02	>0.11	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.003	<0/01	>0/02	Normal
C16	Hexadecanoylcarnitine	0.400	0.48-6.09	<0.28 , >8.16	*
C16OH	Hydroxyhexadecanoylcarnitine	0.004	<0.04	>0.14	Normal
C16:1	Hexadecenoylcarnitine	0.015	<0.31	>0.32	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.018	<0/11	>0/178	Normal
C18	Octadecanoylcarnitine	0.284	0.21-1.71	<0.14 , >2.17	Normal
C18:1	Octadecenoylcarnitine	0.287	0.32-2.17	<0.24 , >2.61	*
C18:2	Octadecadienylcarnitine	0.136	0.06-0.6	<0.057 , >0.65	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.004	<0.07	>0.17	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.004	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.003	<0/022	>0/063	Normal

Val	Valine	58.78	<131	>143	Normal
C0	Free Carnitine	21.936	7.14-43.34	<5.6, 48	Normal
C2	Acetylcarnitine	6.391	5.92-40.68	<3.95, >45.29	normal
C3	Propionylcarnitine	0.759	0.37-4.30	<0.31 , >5	Normal
C3DC&C4OH	Malonylcarnitine & Hydroxybutyrylcarnitine	0.032	<0.2	>0.31	Normal
C4	Butyrylcarnitine	0.115	<0.49	>0.67	Normal
C4DC & C5OH	Methylmalonylcarnitine & Hydroxyisovalerylcarnitine	0.125	<0.27	>0.78	Normal
C5	Isovalerylcarnitine	0.112	<0.39	>0.47	Normal
C5:1	Tiglylcarnitine	0.012	<0.08	>0.204	Normal
C5DC & C6OH	Glutarylcarnitine & Hydroxyhexanoyl carnitine	0.108	<0.49	>0.58	Normal
C6	Hexanoylcarnitine	0.572	<0.11	>0.14	*
C6DC	Methylglutarylcarnitine	0.641	<0.52	>0.56	*
C8	Octanoylcarnitine	1.520	<0.10	>0.3	*
C8:1	Octenoylcarnitine	0.073	<0.19	>0.22	Normal
C10	Decanoylcarnitine	0.099	<0.139	>0.16	Normal
C10:1	Decenoylcarnitine	0.398	<0.11	>0.21	*
C10:2	Decadienylcarnitine	0.021	<0.08	>0.12	Normal
C12	Dodecanoylcarnitine	0.021	<0.16	>0.32	Normal
C12:1	Dodecenoylcarnitine	0.010	<0.27	>0.5	Normal
C14	Tetradecanoylcarnitine	0.038	<0/389	>0.592	Normal
C14:1	Tetradecenoylcarnitine	0.013	<0.13	>0.24	Normal
C14:2	Tetradecadienoylcarnitine	0.009	<0.026	>0.041	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.002	<0/016	>0/02	Normal
C16	Hexadecanoylcarnitine	0.404	0.41-6.09	<0.33 , >7.13	*
C16OH	Hydroxyhexadecanoylcarnitine	0.003	<0.04	>0.1	Normal
C16:1	Hexadecenoylcarnitine	0.012	<0/31	>0/34	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.020	<0.11	>0.134	Normal
C18	Octadecanoylcarnitine	0.222	0.19-1.71	<0.16 , >1.89	Normal
C18:1	Octadecenoylcarnitine	0.280	0.32-2.33	<0.27 , >2.55	*
C18:2	Octadecadienylcarnitine	0.160	0.059-0.56	<0.05 , >0.66	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0.004	<0.07	>0.14	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.006	<0.022	>0.024	Normal
C18OH	Hydroxystearoylcarnitine	0.002	<0/022	>0/11	Normal

Urine Organic Acid Analysis

Growth And Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-01-021626

date:01/02/17

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Karnia Maleki	Lab number:7794	Patient's ID:01201021700021001404162 6
Sample type: urine	Gender: male	age:2m, 10d
Physician/referred by: CMC	Reception Date:01/02/17	Reporting date: 01/02/17

Result:

Abnormal Compound	Cut off	measure
Suberic acid	11.51%	32.51%
Octenedioic acid	8.37%	12.06%

Comment:
The urine organic acid analysis shows increased level of dicarboxylic acids that based on previous result of patient, suspected diagnosis is Medium-chain Acyl-CoA dehydrogenase (MCAD) deficiency. Confirmation of disease with genetic testing is recommended.

Medium Chain Ketoacyl CoA Thiolase Deficiency (MCAT)

- Abnormal Screen Result: Elevated C8 (octanoyl carnitine
- C8-OH
- C6
- Dienoyl Co-A Reductase Deficiency (DE RED)
- Elevated C10:2 (decadienoyl carnitine)
- C10:2/C10

C8:1(L-Octenoyl carnitine)

- C8:1(Octanoylcarnitine)is detected in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. MCAD is characterized by an intolerance to prolonged fasting, recurrent episodes of hypoglycemic coma with medium-chain dicarboxylic aciduria, impaired ketogenesis, and low plasma and tissue carnitine levels .L-Octanoylcarnitine is also found to be associated with celiac disease and glutaric aciduria II

Glutaric Aciduria Type II (GA II) (C4– C18)

- multiple acyl Co-A dehydrogenase deficiency (MADD)
- Primary Markers
- Elevated C4 (butyryl carnitine)
- Elevated C5 (isovaleryl carnitine)
- Secondary Markers
- Elevated C6 (hexanoyl carnitine)
- Elevated C8 (octanoyl carnitine)
- Elevated C10 (decanoyl carnitine)
- Elevated C10:1
- Elevated C12
- Elevated C12:1
- Elevated C14
- **Elevated C14:1 (tetradecenoyl carnitine)**
- Elevated C16OH
- Elevated C5DC

3/C) Mitochondrial disorders:

- There is not any specific finding in acyl carnitine profile
- High blood level of:
  - Lactate
  - L/P ratio
- Metabolic acidosis

- U.GCMS: increased level of:
  - Lactate
  - 3-hydroxybutyrate
  - Acetoacetate
  - Fumarate
  - Succinate
  - Malate
  - 2- ketoglutarate

Galactose (Gal) and galactose metabolites

- Findings: – Galactose (plasma, dried blood spots); pathological if > 10 mg/dl (0.55 mM)
- – Galactose-1-phosphate (erythrocytes); pathological if > 0.5 mg/dl (19 µM)
- – Galactitol (urine); pathological if > 10 mmol/mol creatinine
- – Enzyme studies (erythrocytes): GALT, galactokinase, epimerase
- – Mutation studies (EDTA whole blood)

Pre-analytical aspects

- Galactosemia
- *Measurement of blood spot galactose-1-phosphate-uridyl-transferase (GAL-1-PUT)*
- *Thin-layer chromatography of sugars (galactose) using dried blood spots*
- *Measurement of blood spot galactose-1-phosphate (GALP)*

Galactosaemia

- Method: Gal-1-P uridyltransferase (GALT) activity; quantitation of galactose (Gal) and Gal-1-P (either in parallel or as second tier tests; in GALT and UDP-Gal epimerase [GALE]deficiencies almost all galactose [> 90%] is Gal-1-P).
- DD: ↓ GALT activity: classical galactosaemia (GALT deficiency)
- ↑ Gal: inborn errors of Gal metabolism : GALT/GALE/GALK deficiencies);
- liver failure (various causes); open ductus venosus arantii

- GALT activity may be false normal after erythrocyte (exchange) transfusion. Exposure of test card to humid heat may cause denaturation of enzymes and consecutively a

false positive result for GALT activity

- **Abnormal Screen Result: Elevated total galactose with low GALT: at risk for classical galactosemia.**
- **Normal total galactose with very low GALT: at risk for Duarte galactosemia, or at risk for classical galactosemia, if infant on non-lactose feeding at time of screening.**
- **Elevated total galactose with normal GALT: at risk for GALK or GALE deficiency.**
- Repeat screening for galactosemia should be done 120 days after the last transfusion.

- **If GALT is normal in the initial specimen, repeat galactosemia screening as soon as possible. NO NEED TO STOP BREAST FEEDING OR CHANGE FORMULA TYPE at this time.**
- Neonatal Presentation: GALT - hypoglycemia, jaundice, sepsis, failure to thrive
- Duarte variant galactosemia - None
- GALK - None
- GALE - Usually none


Thanks