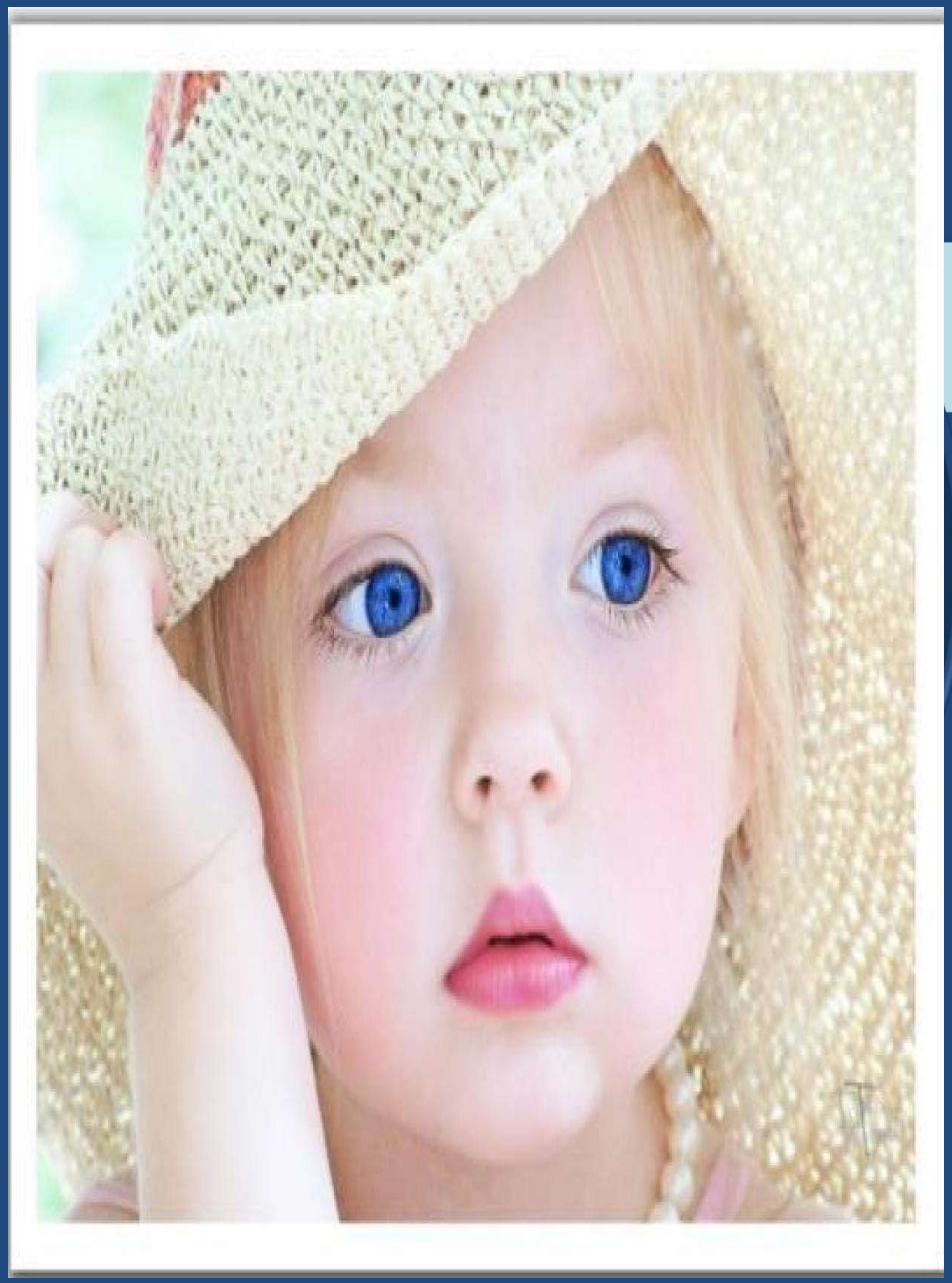

Metabolic diseease in children

Dr Neda Mostofizadeh

Pediatric Endocrinologist

Isfahan Medical University

Definition:

- ***Metabolic disorders result from the absence or abnormality of an enzyme or its cofactor.***

- ***It leads to either accumulation or deficiency of a specific metabolite.***

What is a Metabolic Disease?

- Garrod's Hypothesis

Perinatal history :

- ***Perinatal history for many common IEM, is usually normal .***
- ***Impaired metabolism in the fetus is generally well-compensated for by the mother.***

Perinatal history:cont

But:

Low maternal serum estriol :

Smith-Lemli-Opitz syndrome .

Isolated steroid sulfatase deficiency .

Multiple sulfatase deficiency.

Decreased fetal movement :

Smith-Lemli-Opitz syndrome.

GSD type IV .

Lysosomal storage diseases.

Peroxisomal disorders (Zellweger syndrome).

Perinatal history:cont

HELLP syndrome ,fatty liver of pregnancy :

- ***long-chain ٣-hydroxyacly-CoA dehydrogenase deficiency***

Prolonged labor:

- ***Steroid sulfatase deficiency .***

Non-immune hydrops:

- ***Numerous IEM.***

Past medical history:

- ***Recurrent vomiting.***
- ***Hospitalization for lethargy or dehydration.***
- ***Recurrent hypoglycemia.***
- ***Metabolic decompensation out of proportion to duration or severity of acute illness.***
- ***Personal or family history of thrombotic events (homocystinuria).***

Physical Examination

History & Physical exam:

- ***May be:***

  Normal.

  Nonspecific findings.

  Clues to specific disorders

History &Ph.exam:

Episodic abdominal pain :

- ***Fabry disease .***
- ***hepatic porphyrias .***

Photophobia ,corneal scarring:

- ***cystinosis .***
- ***tyrosinemia type II .***

Muscle cramping :

- ***Fatty acid oxidation defects.***
- ***Muscle glycogenoses.***
- ***GSD.***
- ***Myoadenylate deaminase deficiency .***

Developmental delay.

Lethargy in the morning.

History & Ph.exam:

- ***Poor feeding.***
- ***Frequent vomiting.***
- ***Poor growth/failure to thrive.***
- ***Protein or carbohydrate aversion.***
- ***Diarrhea: (carbohydrate intolerance or mitochondrial disorders).***

Familial History

Family history:

- ***Consanguinity .***
- ***Similarly affected individuals .***
- ***Early childhood deaths due to:***

- ✓ ***Neurologic***
- ✓ ***cardiac, and/or hepatic dysfunction.***
- ✓ ***sepsis***
- ✓ ***unexplained deaths in siblings or maternal male relatives.***

Age at presentation :

- ***The first metabolic decompensation can occur every time from ١ to ٦٠ years of age even in neonatal period.***

Triggers:

Certain sugars :

Disorders of carbohydrate intolerance (galactosemia, hereditary fructose intolerance).

Protein :

urea cycle defects

organic acidemias

amino acid disorders

hyperinsulinism with hyperammonemia.

Triggers:

Carbohydrate :

Pyruvate dehydrogenase deficiency.

Mitochondrial respiratory chain disorders.

Hyperinsulinism.

Complementary foods (infant cereals, fruit juice, and pureed fruits, vegetables, or meats) :

Disorders of carbohydrate metabolism.

Urea cycle defects.

Organic acidemias.

Triggers:

Infection, fever, fasting, or catabolism :

Amino acid disorders.
Organic acidemias.
Fatty acid oxidation disorders.
Urea cycle defects.
Disorders of gluconeogenesis and glycogenolysis.

Anesthesia or surgery :

Thromboembolic events (homocystinuria).
Disorders triggered by fasting.

Certain drugs :

Porphyria .
G6PD deficiency.


Laboratory Evaluation

Laboratory evaluation:

Testing should be performed:

- ***At the time of presentation.***
- ***Before treatment.***

- ***Laboratory values may be normal when the patient is well.***

- ***Consider other conditions in the differential diagnosis (sepsis, cardiac disease) .***

Diagnosis:

Detection of abnormal metabolites in:

- ***plasma***
- ***Urine***
- ***CSF***

Assay of enzyme activity in :

- ***Skin .***
- ***RBC.***
- ***WBC.***
- ***skeletal muscle.***
- ***Liver***
- ***and/or chromosome or DNA analysis .***

Initial evaluation :

- ***CBC/diff***
- ***Bs***
- ***Amoniac***
- ***Electrolytes***
- ***BUN/Cr***
- ***uric acid***
- ***LFT***
- ***Bilirubin***
- ***PT***
- ***Urine(color, odor, dipstick, ketones)***
- ***LDH, aldolase, CPK, and urine myoglobin (in case of myopathy).***

Further evaluations:

- ***Quantitative plasma amino acids***
- ***Acylcarnitine profile***
- ***Lactate***
- ***Qualitative urine organic acids***

- ✓ ***These tests should only be performed as indicated by the clinical presentation and initial laboratory evaluation.***

Approch in patients with suspected metabolic disorder:

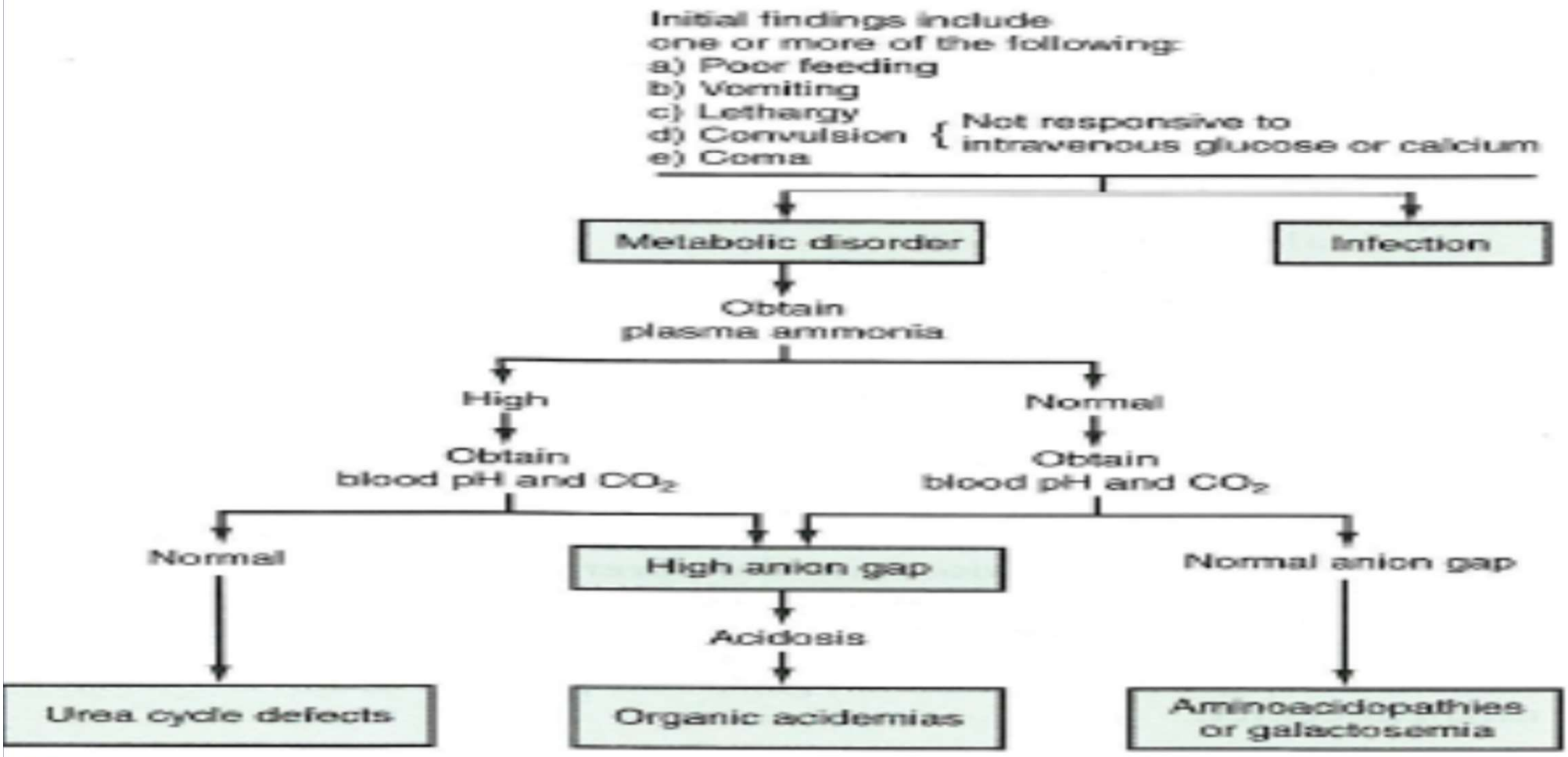

Figure 78–1 Clinical approach to a newborn infant with a suspected genetic metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

Approch in patients with organic acidemia:

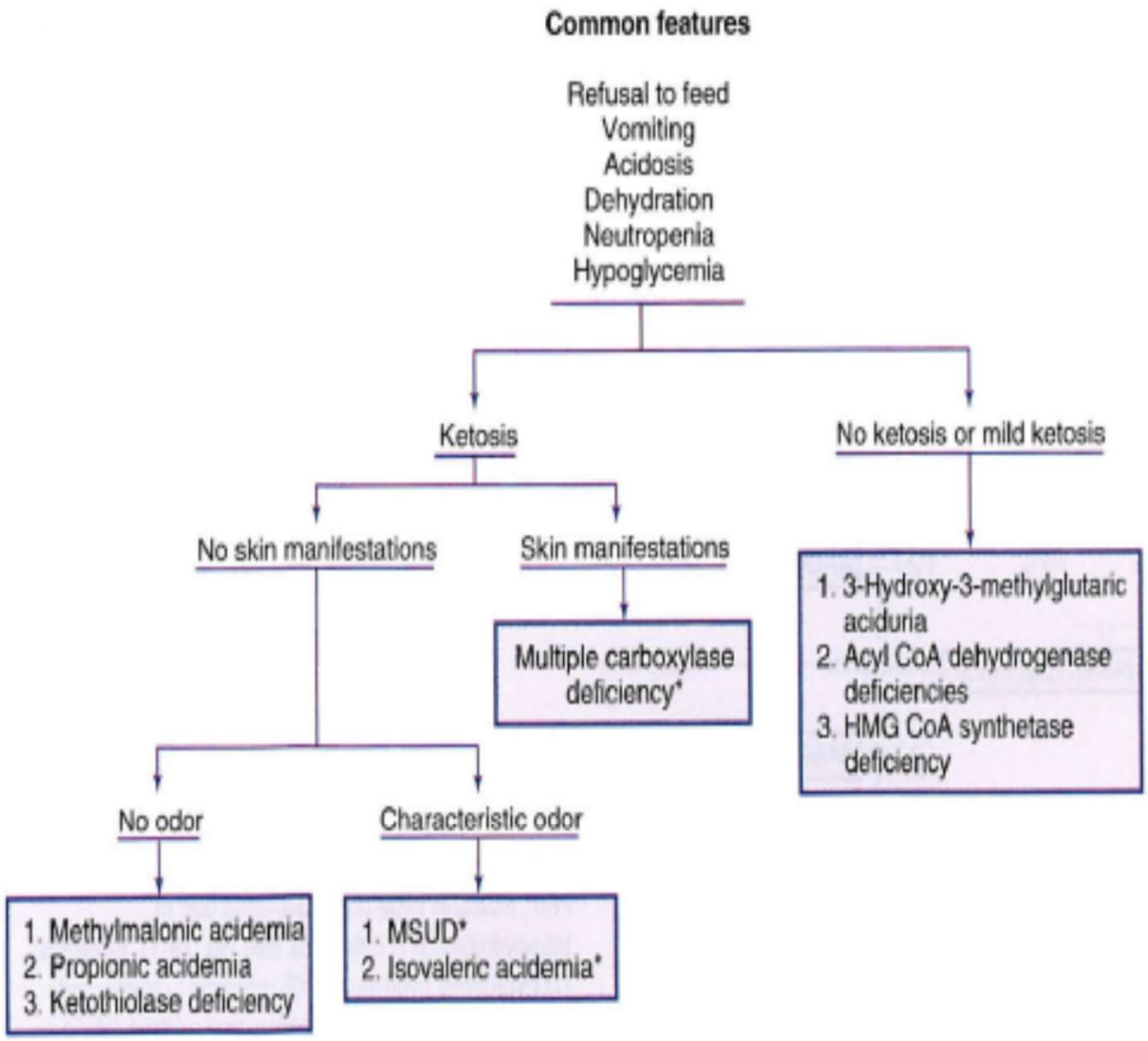

Figure 79-6 Clinical approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 79-2). MSUD, maple syrup urine disease.

Approch in suspected LSD patients:

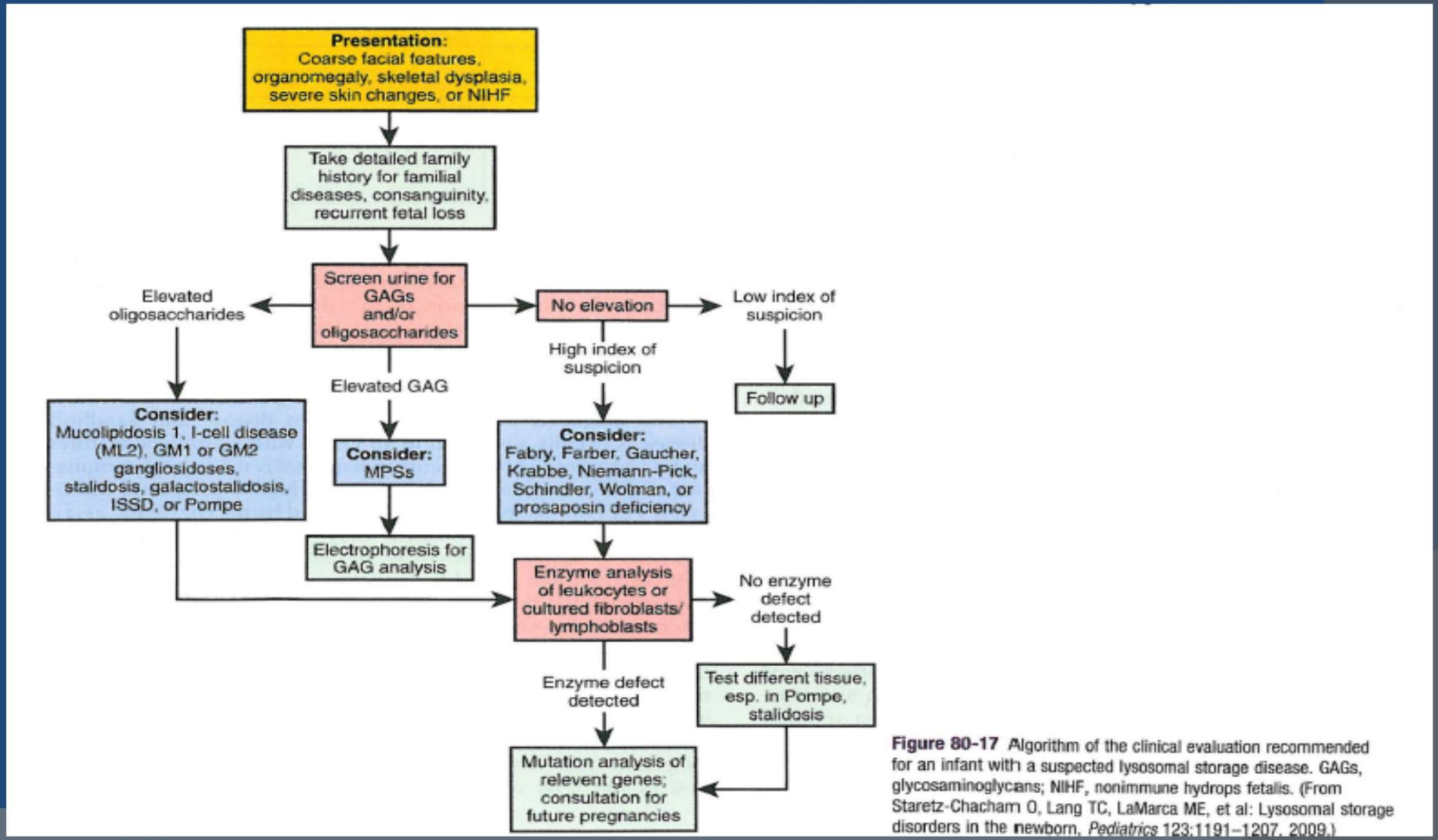

Figure 80-17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. GAGs, glycosaminoglycans; NIHF, nonimmune hydrops fetalis. (From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, *Pediatrics* 123:1191–1207, 2009.)

Approch in patients with hyperammonemia:

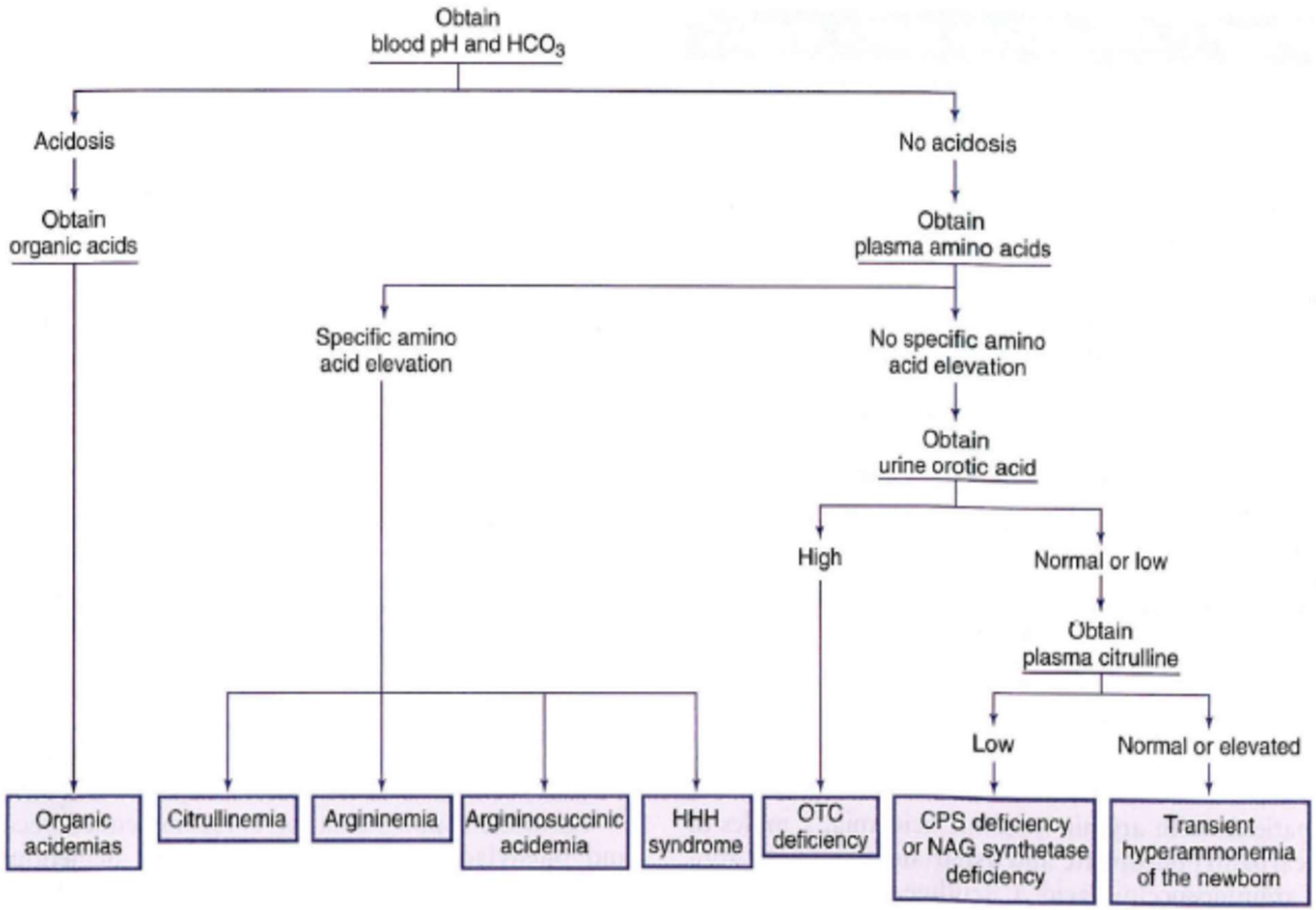

Figure 79-13 Clinical approach to a newborn infant with symptomatic hyperammonemia. CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, *N*-acetylglutamate; OTC, ornithine transcarbamylase.

Important aspects in Lab data:

CBC:

- ***IEM may involve any or all of the cell lines.***
- ***Provide a clue to sepsis .***

ABG:

- ***Organic acidemias (Metabolic acidosis with increased AG).***
- ***Respiratory alkalosis(UCD as a result of hyperammonemia).***

Important aspects in Lab data:

Ammonia :

- ***Blood sample should be obtained from an artery or vein without using a tourniquet, placed on ice for transport to the laboratory, and analyzed immediately.***

- ***Ammonia (≥١٢٠ micromol/L [٢٠٠microgram/mL] in the newborn, and ≥ ٨٠ micromol/L [١٤٠ microgram/mL] in older infants and children) is neurotoxic.***

Important aspects in Lab data:

Electrolytes:

- ***Necessary to calculate the anion gap.***
- ***Detect hyponatremia and hyperkalemia.***

Uric acid :

- ***low (defects of purine metabolism or molybdenum cofactor deficiency)***
- ***Increased (Lesch-Nyhan disease or GSD).***

Urine :

- ***Presence or absence of ketones (etiology of hypoglycemia)***
- ***Urine pH (determining the cause of metabolic acidosis)***

Important aspects in Lab data:

Urine:

- ***Decreased urine SG (vomiting)***
- ***glucosuria***
- ***proteinuria.***
- ***Leukocyte esterase or nitrites (UTI as a trigger factor)***
- ***Reducing substances and negative glucose in dipstick (a clue to galactosemia,carbohydrate intolarence disorder).***

- ✓ ***Absence of reducing substances in the urine does not exclude these disorders.***
- ✓ ***Renal tubular dysfunction occurs in a number of IEM.***

Important aspects in Lab data:

- ***False-positive tests for urine reducing substances :***

- ***Penicillins***
- ***Salicylates***
- ***Ascorbic acid***
- ***Drugs excreted as glucuronides.***

Specialized tests :

Plasma amino acids:

Is used to confirm the diagnosis of:

- ***Urea cycle disorders.***
- ***Disorders of amino acid metabolism .***

- ✓ ***Is typically performed by HPLC, although MS(MS/MS) can be used.***
- ✓ ***Mild elevations of ٥ to ١٠ percent above normal usually are not significant.***

Specialized tests :

Urine organic acids :

Is performed by (GC/MS).
Qualitative assay is adequate

Lactate and pyruvate :

- **Should be measured in arterial blood .**
- **Tourniquet pressure and/or hemolysis may increase lactate level erroneously .**
- **Transported on ice .**

✓ **For accurate measurement of pyruvate, the sample must be collected in perchlorate (or a similar media) to inactivate enzymes that degrade pyruvate.**

Specialized tests :

Lactic acidosis:

- Mitochondrial disorders.
- Glycogen storage diseases.
- Disorders of gluconeogenesis.
- Disorders of pyruvate metabolism.

✓ The ratio of **lactate to pyruvate** :normal value **١٠:١ to ٢٠:١ .**

High lactate-to-pyruvate ratio:

- Mitochondrial disorders .
- Pyruvate carboxylase deficiency.

Specialized tests :

Normal or low lactate-to-pyruvate ratio :

- ***GSD***
- ***pyruvate dehydrogenase deficiency.***

Elevated lactic acid may be present in:

- ***Disorders of amino acid metabolism.***
- ***Organic acidemias.***
- ***Fatty acid oxidation disorders.***

- ✓ ***Lactate-to-pyruvate ratio sometimes is normal in mitochondrial disorders.***

Specialized tests :

Acylcarnitine profile :

- ***Is performed by MS/MS.***
- ***Is measured in a plasma sample or a filter-paper bloodspot.***
- ***Diagnosis of fatty acid oxidation disorders.***
- ***May detect organic acidemias.***

Other specialized tests:

- ***Eye examination (by ophthalmolist).***
- ***Echo(presence of cardiomyopathy).***
- ***Skin, skeletal muscle, or liver biopsy .***
- ***LP (glucose, protein, lactate, pyruvate, glycine, serine, alanine, organic acids, pterins neurotransmitters) .***
- ***Serum ketones and/or free fatty acids (hypoglycemia.)***

Other specialized tests:

Quantitative plasma carnitine levels :

Fatty acid oxidation disorders .

Urine sulfocysteine :

sulfite oxidase and molybdenum cofactor deficiencies.

Urine purine analysis :

Disorders of purine metabolism.

Other specialized tests:

Urine polyol analysis :

- ***Disorders of polyol metabolism.***

Plasma and urine creatine and guanidinoacetate :

- ***Abnormalities of creatine metabolism (guanidinoacetate methyltransferase deficiency).***

Urinary glycosaminoglycans, oligosaccharides:

- ***Lysosomal storage disorders***


Classification

Acute or progressive intoxication or encephalopathy :

- ***Accumulation of toxic compounds proximal to the metabolic block.***
- ***Symptom free-interval .***
- ***Clinical signs of acute or chronic intoxication .***
- ***Progressive or recurrent metabolic disturbances.***

- ✓ ***Amino acid disorders.***
- ✓ ***organic acidemias.***
- ✓ ***urea cycle disorders.***
- ✓ ***Disorders of carbohydrate intolerance (eg, galactosemia, hereditary fructose intolerance).***

Disorders with energy deficiency :

- ***Deficiency in energy production or utilization in the liver, myocardium, skeletal muscle, or brain.***
- ***Signs or symptoms due to accumulation of toxic compounds.***

- ***Disorders of glycogenolysis /gluconeogenesis.***
- ***Fatty acid oxidation defects.***
- ***Disorders of ketogenesis.***
- ***Mitochondrial disorders.***

Critical illness

Critical illness :

- ***IEM may present with acute metabolic decompensation in individuals of any age.***

- ***Most episodes are associated with one or more of the followings:***

  Hypoglycemia+-ketosis

  Hyperammonemia

  Acid-base disorder

  Lactic acidosis

  seizure

Hypoglycemia :

- ***Fatty acid oxidation disorders.***
- ***GSD .***
- ***Gluconeogenic disorders.***
- ***Fructose intolerance.***
- ***Amino acid disorders.***
- ***organic acidemias.***
- ***Mitochondrial disorders .***

ketosis:

ketosis presents in:

- ***GSD.***
- ***Organic acidemia.***
- ***MSUD.***

Ketosis absent or inappropriately low in:

- ***Fatty acid oxidation disorders.***
- ***Disorders of ketogenesis (HMG-CoA lyase and ٣-ketothiolase deficiency) .***

Hyperammonemia:

- ***Urea cycle defects.***
- ***Organic acidemias.***
- ***Fatty acid oxidation defects.***
- ***Liver dysfunction.***
- ***Mitochondrial disorders*** .

Metabolic acidosis:

- ***Organic acidemias***
- ***MSUD***
- ***GSD***
- ***Disorders of gluconeogenesis***
- ***Fatty acid oxidation disorders***
- ***Disorders of pyruvate metabolism***
- ***Disorders of fructose metabolism***
- ***Mitochondrial disorders***

Lactic acidosis :

- ***Abnormal oxidative metabolism.***
- ***Disorders of oxidative phosphorylation.***
- ***GSD.***
- ***Disorders of gluconeogenesis.***
- ***Disorders of pyruvate metabolism***.

Lactate to pyruvate ratio: (normal value ١٠:١ to ٢٠:١)

Lactic acidosis :

lactate to pyruvate ratio:

High:

Mitochondrial disorders.

Pyruvate carboxylase deficiency.

Normal or low :

GSD and pyruvate dehydrogenase deficiency.

- ✓ ***Lactate-to-pyruvate ratio sometimes is normal in mitochondrial disorders.***
- ✓ ***Elevated lactic acid may be present in disorders of amino acid metabolism, organic acidemias, and fatty acid oxidation disorders .***

Seizure:

- ***Metabolic disorders are rare causes of seizures in children.***

BUT

- ***Many IEM are associated with seizure.***


Other presentations?

Developmental Delay:

Is seen in:

Disorders of urea cycle and amino acid metabolism
Organic acidemias
Disorders of creatine metabolism
Peroxisomal disorders
Lysosomal storage disorders
Mitochondrial disorders
Disorders of oxidative phosphorylation.

- ***IEM account for only ١ to ٥ percent of cases of developmental delay.***

Hepatomegaly:

Hepatomegaly :(with or without splenomegaly):

GSD.
Lysosomal storage diseases (Gaucher, Niemann-Pick).
Galactosemia.
Peroxisomal disorders.
Tyrosinemia.
Bile acid disorders.
Congenital disorders of protein glycosylation .

Specific presentations in metabolic disorders:

Isolated hepatosplenomegaly :

- *Lactate, TG, uric acid, and creatine kinase(GSD).*
- *urine mucopolysaccharides and oligosaccharides (lysosomal storage disorders.)*
  Galactose-1-phosphate (galactosemia).

- *urine galactitol (galactosemia) .*
- *Serum very long-chain fatty(peroxisomal disorders).*
- *Quantitative plasma amino acid (tyrosinemia) .*
- *Liver biopsy.*

Specific presentations in metabolic disorders:

Isolated hepatosplenomegaly :

If the diagnosis is not established after the primary evaluation:

- ***Enzyme assays (eg, Gaucher, Niemann-Pick, or sialidosis).***
- ***urine bile acid analysis (disorders of bile acid metabolism).***
- ***Transferrin isoelectric focusing(CDG).***

Specific presentations in metabolic disorders:

Hypertrophic cardiomyopathy :

- *GSD type II .*
- *Mucopolysaccharidoses.*

Specific presentations in metabolic disorders:

Dilated cardiomyopathy:

- *Fatty acid oxidation disorders.*
- *Organic acidemias.*
- *Mitochondrial disorders (eg, disorders of oxidative phosphorylation).*

Specific presentations in metabolic disorders:

The initial evaluation in cardiomyopathy includes:

- *Plasma acylcarnitine profile.*
- *Quantitative plasma carnitine levels.*
- *Qualitative urine organic acid analysis.*
- *Serum lactate and pyruvate levels.*
- *Skeletal muscle biopsy (mitochondrial enzyme stains).*

Skeletal Myopathy:

Is seen in:

- *Lysosomal storage disease.*
- *Nonlysosomal glycogen storage diseases.*
- *Disorders of fatty acid oxidation.*
- *Mitochondrial disorders.*

Post-mortem evaluations:

- *Collect relevant blood, urine, and tissue specimens before or shortly after death (within one to two hours) .*
- *Plasma amino acids, lactate, pyruvate , and total and free carnitine are not accurate when post-mortem specimens are analyzed .*
- *Several blood spots (٤ to ٦) on a newborn screening card or filter paper for acylcarnitine analysis or other studies.*
- *Plasma (٣ to ٥ mL) in lithium heparin tube, separated and frozen at -٧٠ºC.*

Post-mortem evaluations:

- ***Whole blood*** *٥ to ١٠ mL in EDTA tube for DNA analysis; the sample should be refrigerated, not frozen.*
- ***Urine*** *(٥ to ١٠ mL, or more if possible) frozen in ١ to ٢ mL aliquots in plain sterile containers.*
- ***CSF*** *(٣ to ٥ mL, in one mL aliquots) frozen and stored at -٧٠ºC.*
- ***Organic acid analysis*** *may be performed on vitreous humor if urine is not available (collected by intraocular puncture at autopsy, frozen at -٢٠ºC or -٧٠ºC) .*

Post mortom evaluation:

- ***Postmortem needle biopsy of the liver.***
- ***Photographs of dysmorphic features.***
- ***Radiographic studies (neurologic, cardiac, or skeletal abnormalities).***
- ***Skin biopsy .***
- ***Samples of muscle .***


Thanks for your attention