Inborn Errors of Metabolism

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KEYWORDS

• Metabolic • Acidosis • Hypoglycemia • Hyperammonemia • Fatty acid oxidation • Urea cycle • Organic acidemia

KEY POINTS

- Inborn errors of metabolism (IEMs) are not uncommon; their overall incidence is more than 1:1000.
- Neonates with IEMs usually present with nonspecific signs; therefore, maintaining a high index of suspicion is extremely important for early diagnosis of IEMs.
- Metabolic acidosis with hyperammonemia is suggestive of organic acidemias.
- Hypoglycemia without ketosis is suggestive of fatty acid oxidation defects.
- Hyperammonemia with respiratory alkalosis is suggestive of urea cycle defects.
- Liver failure can be caused by galactosemia and tyrosinemia type I.
- Cardiomyopathy can be caused by glycogen storage disease type II and fatty acid oxidation defects.
- Adequate caloric intake and early introduction of the appropriate enteral feeding are important in managing acute metabolic decompensation in neonates with IEMs.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a group of disorders each of which results from deficient activity of a single enzyme in a metabolic pathway. Although IEMs are individually rare, they are collectively common, with an overall incidence of more than 1:1000.[1] More than 500 IEMs have been recognized, with approximately 25% of them having manifestations in the neonatal period.[2,3] Neonates with IEMs are usually healthy at birth with signs typically developing in hours to days after birth. The signs are usually nonspecific, and may include decreased activity, poor feeding, respiratory distress, lethargy, or seizures. These signs are common to several other neonatal conditions, such as sepsis and cardiopulmonary dysfunction. Therefore, maintaining a high index of suspicion is

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important for early diagnosis and the institution of appropriate therapy, which are mandatory to prevent death and ameliorate complications from many IEMs.[3]

The vast majority of IEMs are inherited in an autosomal recessive manner. Therefore, a history of parental consanguinity or a previously affected sibling should raise the suspicion of IEMs. Some IEMs, such as ornithine transcarbamylase (OTC) deficiency, are X-linked. In X-linked disorder, typically male patients have severe disease, whereas female patients are either asymptomatic or have milder disease.

Pathophysiologically, IEMs can be divided into three groups. The first includes IEMs causing intoxication because of defects in the intermediary metabolic pathway, resulting in the accumulation of toxic compounds proximal to the metabolic block; examples are urea cycle defects and maple syrup urine disease (MSUD). The second group includes IEMs resulting in energy deficiency and includes mitochondrial respiratory chain defects. The third group is IEMs resulting in defects in the synthesis or the catabolism of complex molecules in certain cellular organelles, such as lysosomal storage disorders.[3]

CLINICAL MANIFESTATIONS

After an initial symptom-free period, neonates with IEMs can start deteriorating for no apparent reasons and do not respond to symptomatic therapies. The interval between birth and clinical symptoms may range from hours to weeks, depending on the enzyme deficiency. Neonates with IEMs can present with 1 or more of the following clinical groups.[4,5]

Neurologic Manifestations

Deterioration of consciousness is one of the common neonatal manifestations of IEMs that can occur due to metabolic derangements, including acidosis, hypoglycemia, and hyperammonemia. Neonates with these metabolic derangements typically exhibit poor feeding and decreased activity that progress to lethargy and coma. Other common neurologic manifestations of IEMs in the neonatal period are seizures, hypotonia, and apnea (**Box 1**).

Hepatic Manifestations

Neonates with IEMs can present with hepatomegaly and hypoglycemia, cholestatic jaundice, or liver failure presenting with jaundice, coagulopathy, elevated transaminases, hypoglycemia, and ascites (**Box 2**).

Cardiac Manifestations

Some IEMs can present predominantly with cardiac diseases, including cardiomyopathy, heart failure, and arrhythmias (**Box 3**).

Abnormal Urine Odor

An abnormal urine odor is present in IEMs in which volatile metabolites accumulate (**Box 4**).

Distinctive Facial Features

Several IEMs can present with distinctive facial features (**Box 5**).

Hydrops Fetalis

Several lysosomal storage diseases can present with hydrops fetalis (**Box 6**).

Box 1
IEMs associated with neurologic manifestations in neonates

- Deterioration in consciousness
  - Metabolic acidosis
    - Organic acidemias
    - Maple syrup urine disease (MSUD)
    - Disorders of pyruvate metabolism
    - Fatty acid oxidation defects
    - Fructose-1,6-bisphosphatase deficiency
    - Glycogen storage disease type 1
    - Mitochondrial respiratory chain defects
    - Disorders of ketolysis
    - 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) lyase deficiency
  - Hypoglycemia
    - Fatty acid oxidation defects
    - Fructose-1,6-bisphosphatase deficiency
    - Glycogen storage disease type 1
    - Organic acidemias
    - Mitochondrial respiratory chain defects
    - HMG CoA lyase deficiency
  - Hyperammonemia
    - Urea cycle disorders
    - Organic acidemias
    - Disorders of pyruvate metabolism
- Seizures
  - Biotinidase deficiency
  - Pyridoxine-dependent epilepsy
  - Pyridoxal phosphate-responsive epilepsy
  - Glycine encephalopathy
  - Mitochondrial respiratory chain defects
  - Zellweger syndrome
  - Sulfite oxidase/molybdenum cofactor deficiency
  - Disorders of creatine biosynthesis and transport
  - Neurotransmitter defects
  - Congenital disorders of glycosylation
  - Purine metabolism defects
- Hypotonia
  - Mitochondrial respiratory chain defects
  - Zellweger syndrome
  - Glycine encephalopathy

- Sulfite oxidase/molybdenum cofactor deficiency
- Apnea
  - Glycine encephalopathy
  - MSUD
  - Urea cycle disorders
  - Disorders of pyruvate metabolism
  - Fatty acid oxidation defects
  - Mitochondrial respiratory chain defects

Box 2
IEMs associated with neonatal hepatic manifestations

- Liver failure
  - Galactosemia
  - Tyrosinemia type I
  - Hereditary fructose intolerance
  - Mitochondrial respiratory chain defects
- Cholestatic jaundice
  - Citrin deficiency
  - Zellweger syndrome
  - Alpha-1-antitrypsin deficiency
  - Niemann-Pick disease type C
  - Inborn errors of bile acid metabolism
  - Congenital disorders of glycosylation
- Hepatomegaly with hypoglycemia
  - Fructose-1,6-bisphosphatase deficiency
  - Glycogen storage disease type 1

Box 3
IEMs associated with neonatal cardiomyopathy

- Glycogen storage diseases type II (Pompe disease)
- Fatty acid oxidation defects
  - Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency
  - Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency/Trifunctional protein deficiency
  - Carnitine-acylcarnitine translocase (CAT) deficiency
  - Carnitine palmitoyltransferase II (CPT II) deficiency
  - Systemic primary carnitine deficiency
- Mitochondrial respiratory chain defects
- Congenital disorders of glycosylations
- Tricarboxylic acid cycle defects: α-Ketoglutarate dehydrogenase deficiency

Box 4
IEMs associated with abnormal urine odor

- Maple syrup
  - MSUD
- Sweaty feet
  - Isovaleric acidemia
  - Glutaric acidemia type II
- Sulfur
  - Cystinuria
  - Tyrosinemia type I
- Boiled cabbage
  - Tyrosinemia type I
- Old fish
  - Trimethylaminuria
  - Dimethylglycine dehydrogenase deficiency
- Cat's urine
  - Multiple carboxylase deficiency
- Mousy
  - Phenylketonuria

Box 5
IEMs associated with distinctive facial features

- Zellweger syndrome: large fontanelle, prominent forehead, flat nasal bridge, epicanthal folds, hypoplastic supraorbital ridges.
- Pyruvate dehydrogenase deficiency: epicanthal folds, flat nasal bridge, small nose with anteverted flared alae nasi, long philtrum.
- Glutaric aciduria type II: macrocephaly, high forehead, flat nasal bridge, short anteverted nose, ear anomalies, hypospadias, rocker-bottom feet.
- Cholesterol biosynthetic defects (Smith-Lemli-Opitz syndrome): epicanthal folds, flat nasal bridge, toe 2/3 syndactyly, genital abnormalities, cataracts.
- Congenital disorders of glycosylation: inverted nipples, lipodystrophy.

Box 6
IEMs associated with hydrops fetalis

- Lysosomal disorders
  - Mucopolysaccharidosis types I, IVA, and VII
  - Sphingolipidosis (Gaucher disease, Farber disease, Niemann-Pick disease A, GM1 gangliosidosis, multiple sulfatase deficiency)
  - Lipid storage diseases (Wolman and Niemann-Pick disease C)
  - Oligosaccharidosis (galactosialidosis), sialic acid storage disease, mucolipidoses I (sialidosis), mucolipidoses II (I cell disease).
- Zellweger syndrome
- Glycogen storage disease type IV
- Congenital disorders of glycosylation
- Mitochondrial respiratory chain defects

PRINCIPLES OF MANAGEMENT

Early diagnosis and the institution of appropriate therapy are mandatory in IEMs to prevent death and ameliorate complications. Management of suspected IEMs should be started even before birth.[3,5]

Before or During Pregnancy

When a previous sibling has an IEM, the following can be done:

- Prenatal counseling regarding the possibility of having an affected infant.
- Considering intrauterine diagnosis by measurement of abnormal metabolites in the amniotic fluid or by enzyme assay or molecular genetic analysis of amniocytes or chorionic villus cells.
- Planning for delivery in a facility equipped to handle potential metabolic or other complications.

Initial Evaluation

If an IEM is suspected in a neonate, initial laboratory studies should be obtained immediately (**Box 7**). The results of these tests can help to narrow the differential diagnosis and determine which specialized tests are required.

Box 7
Laboratory evaluation for newborns suspected of having IEMs

- Initial laboratory studies
  - Complete blood count
  - Blood gas
  - Blood glucose and electrolytes
  - Plasma ammonia
  - Plasma lactate
  - Liver function tests: transaminases, total and direct bilirubin, albumin, and coagulation profile
  - Urine reducing substances, pH, and ketones
  - Plasma amino acids
  - Urine organic acids
  - Plasma carnitine and acylcarnitine profile
- Additional laboratory studies considered in neonatal seizures
  - Cerebrospinal fluid (CSF) amino acids
  - CSF neurotransmitters
  - Sulfocysteine in urine
  - Very long chain fatty acids

Management of Acute Metabolic Decompensation

Several IEMs can present with acute metabolic decompensation during the neonatal period, such as urea cycle defects and organic acidemias. The principles of managing acute metabolic decompensation are as follows:

- Decrease production of the toxic intermediates by holding enteral intake for 24 to 48 hours and suppressing catabolism. Reversal of catabolism and promotion of anabolism can be achieved by:
  - Providing adequate caloric intake, which is at least 20% greater than the ordinary maintenance. Adequate calories can be achieved parenterally by intravenous (IV) glucose and intralipid and enterally by giving protein-free formula or special formula appropriate for the IEM.
  - Insulin is a potent anabolic hormone and can be administered as a continuous infusion (0.05–0.1 unit/kg/hour) with adjusting the IV glucose to maintain a normal blood glucose.
  - Providing adequate hydration and treating infections aggressively.
  - Introducing enteral feeding as early as possible. The period of enteral feed restriction should not exceed 24 to 48 hours; after that a special formula appropriate for the suspected IEM should be introduced if there are no contraindications for enteral feeding.
- Elimination of toxic metabolites. Toxic metabolites can be eliminated by:
  - IV hydration, which can promote renal excretion of toxins.
  - The use of specific medications that create alternative pathways. For example, carnitine can bind organic acid metabolites and enhance their excretion in urine in organic acidemias. Another example is sodium benzoate, which is used in glycine encephalopathy and urea cycle defects, because it binds to glycine forming hippurate, which is excreted in urine.
  - Hemodialysis is indicated in cases of unresponsive hyperammonemia (>500 mg/dL) in urea cycle defects and hyperleucinemia in MSUD.
- Additional treatments include metabolic acidosis correction with sodium bicarbonate, which can be given as a bolus followed by a continuous infusion, hypoglycemia correction of with IV glucose, and the administration of pharmacologic doses of appropriate cofactors in cases of vitamin-responsive enzyme deficiencies (eg, thiamine in MSUD).

Monitoring

Neonates with IEMs should be monitored closely for any mental status changes, fluid imbalance, evidence of bleeding (if thrombocytopenic), and symptoms of infection (if neutropenic). Biochemical parameters that need to be followed include electrolytes, glucose, ammonia, blood gases, complete blood cell count, and urine ketones.

Long-term Management

Several IEMs require dietary restrictions (eg, leucine-restricted diet in isovaleric acidemia). If hypoglycemia occurs, then frequent feeding and the use of uncooked cornstarch is advised. Cofactors are used in vitamin-responsive IEMs (eg, pyridoxine in pyridoxine-dependent epilepsy). Examples of other oral medications used in chronic management of IEMs are carnitine for organic acidemias, sodium benzoate for urea cycle defects, and nitisinone in tyrosinemia type I.

INBORN ERRORS OF METABOLISM WITH METABOLIC ACIDOSIS

Metabolic acidosis is an important feature of many IEMs (see **Box 1**). The presence or absence of ketosis in metabolic acidosis can help in guiding the diagnostic workup (**Fig. 1**).

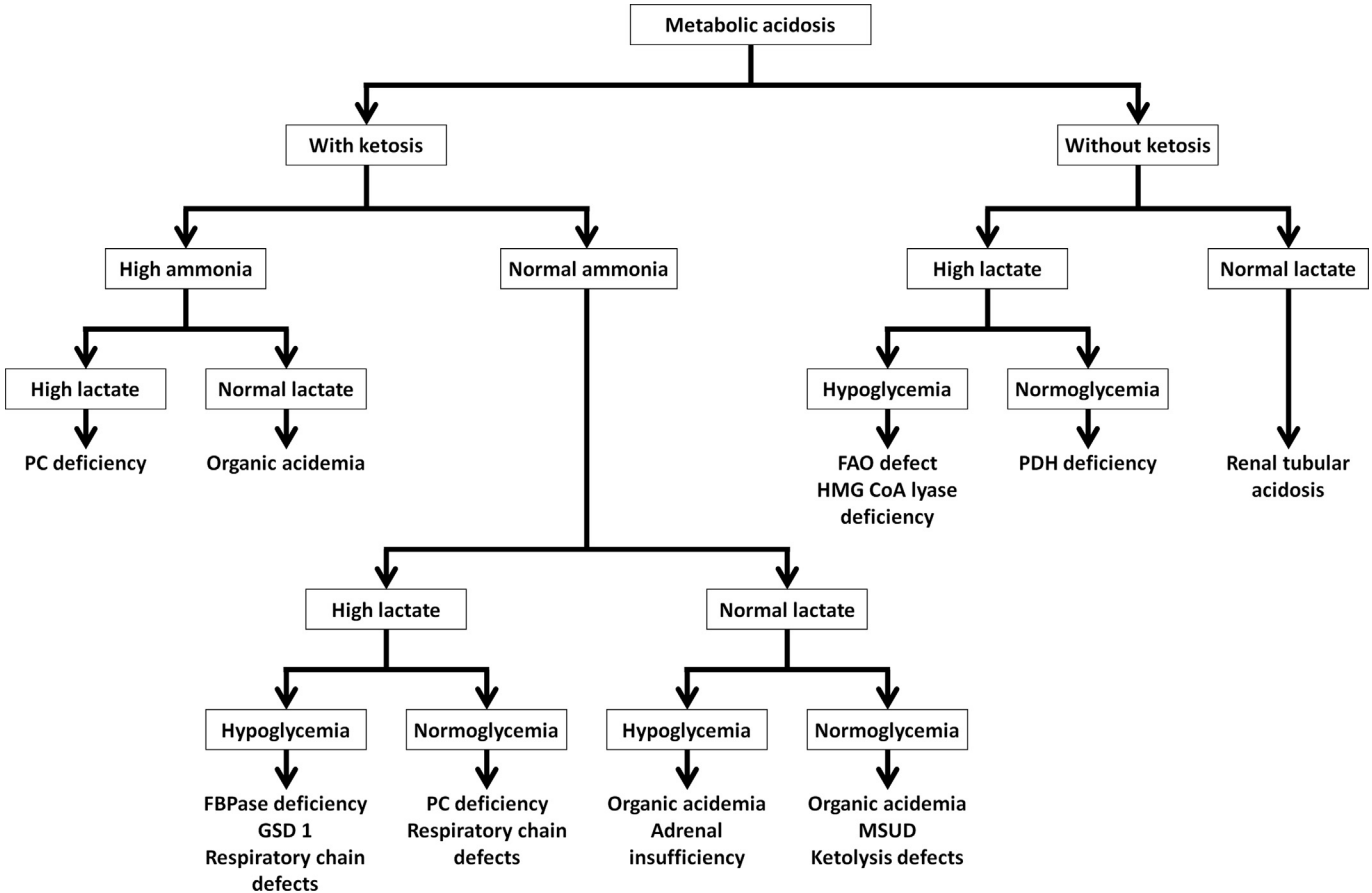

Fig. 1. Approach to neonatal metabolic acidosis. FAO, fatty acid oxidation; FBPase, fructose-1,6-bisphosphatase deficiency; GSD I, glycogen storage disease type 1; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MSUD, maple syrup urine disease; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase. Note that although a significant elevation in lactate is more associated with mitochondrial respiratory chain defects and pyruvate metabolism disorders, milder lactate elevations can be seen in organic acidemias and MSUD.

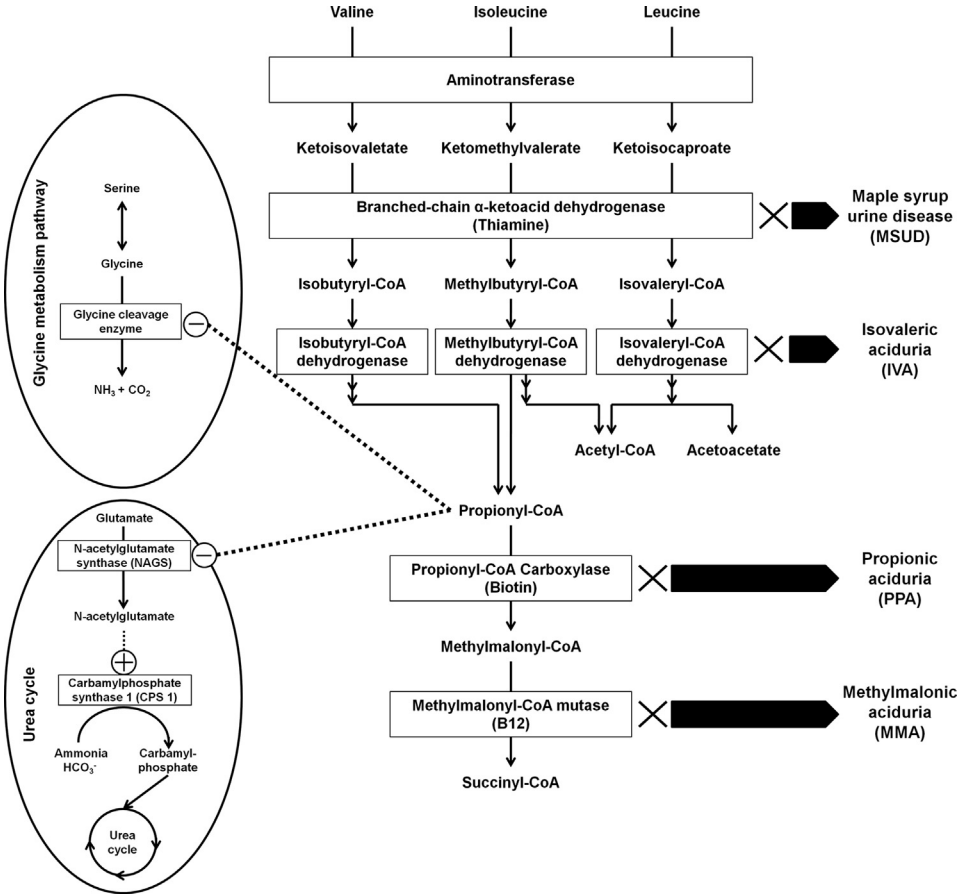

Fig. 2. Branched-chain amino acid metabolic pathways with related IEMs. Note that propionic acid inhibits glycine cleavage enzyme and NAGS resulting in elevated glycine and hyperammonemia, respectively in propionic and methylmalonic acidemias.

Organic Acidemias

Organic acidemias are characterized by the excretion of organic acids in urine. Isovaleric acidemia (IVA), propionic acidemia (PPA), and methylmalonic acidemia (MMA) result from enzymatic defects in the branched-chain amino acids metabolism (**Fig. 2**). The organic acid intermediate metabolites are toxic to brain, liver, kidney, pancreas, retina, and other organs.

Manifestations

Infants with organic acidemias usually present in the neonatal period with poor feeding, vomiting, decreased activity, truncal hypotonia with limb hypertonia, seizures, hypothermia, unusual odor (see **Box 4**), lethargy progressing to coma, and multiorgan failure.

Diagnosis

In addition to metabolic acidosis and ketosis, initial laboratory evaluation can reveal hypoglycemia and elevated transaminases. Hyperammonemia and hyperglycinemia can result from the inhibition of N-acetylglutamate synthase and glycine cleavage enzyme, respectively by propionic acid (see **Fig. 2**). Organic acids also can suppress bone marrow, resulting in neutropenia or pancytopenia. The specific diagnosis can be reached by performing urine organic acid analysis, serum acylcarnitine profile, enzyme assay, and molecular genetic testing (**Table 1**).

Table 1
Enzyme deficiency, genes, and biochemical abnormalities in organic acidemias

Organic acidemias	Enzymes	Genes	Urine Organic Acid Analysis	Plasma Acylcarnitine Profile
Propionic academia (PPA)	Propionyl-CoA carboxylase	*PCCA* and *PCCB*	Elevated hydroxypropionic acid, methylcitric acid, and propionyl glycine	Elevated propionylcarnitine (C3)
Methylmalonic acidemia (MMA)	Methylmalonyl-CoA mutase	*MUT*	Elevated methylmalonic, hydroxypropionic, and methylcitric acids	Elevated propionylcarnitine (C3)
Isovaleric academia (IVA)	Isovaleryl-CoA dehydrogenase	*IVD*	Elevated hydroxyisovaleric acid and isovalerylglycine	Elevated isovalerylcarnitine (C5)

Management

Management of acute decompensation includes holding protein intake, suppressing catabolism with glucose and insulin infusions, correcting acidosis with sodium bicarbonate infusion, and administering carnitine (100–300 mg/kg/d) to enhance the excretion of organic acids in urine. Hemodialysis may be considered if these measures fail. Chronic treatment includes oral carnitine and dietary restrictions. A diet low in amino acids producing propionic acid (isoleucine, valine, methionine, and threonine) is used for PPA and MMA, and a leucine-restricted diet is used for IVA. Biotin is a cofactor for propionyl-CoA carboxylase and can rarely be beneficial in PPA.

Vitamin B12 (adenosylcobalamin) is a cofactor for methylmalonyl-CoA mutase, and hydroxycobalamin injection (1 mg daily) can be given as a trial in MMA. Glycine (150–250 mg/kg/d) enhances the excretion of isovaleric acid in urine and should be used in IVA.[6,7]

Maple Syrup Urine Disease

MSUD is caused by decreased activity of the branched-chain α-ketoacid dehydrogenase (BCKAD), which catalyzes the second step in the metabolic pathway of the branched-chain amino acids (BCAAs) (leucine, isoleucine, and valine) (see **Fig. 2**). Decreased activity of BCKAD results in the accumulation of BCAAs and corresponding ketoacids in tissues and plasma. The pathophysiology in MSUD can be explained by the neurotoxicity of leucine, which interferes with the transport of other large neutral amino acids across the blood-brain barrier leading to cerebral amino acid deficiency that has adverse consequences for brain growth and neurotransmitter synthesis.

Manifestations

Neonates with classic MSUD typically present in the first week of life with poor feeding, irritability, ketosis, maple syrup odor of urine and cerumen (see **Box 4**), lethargy, opisthotonus, stereotyped movements (fencing and bicycling), coma, and apnea.

Diagnosis

MSUD can be diagnosed biochemically by the identification of elevated plasma alloisoleucine and the BCAAs with perturbation of the normal 1:2:3 ratio of isoleucine:leucine:valine. Ketoacids and hydroxyacids can be detected in urine organic acid analysis or the dinitrophenylhydrazine (DNPH) test. Enzyme activity and molecular testing for the genes coding BCKAD subunits (*BCKDHA*, *BCKDHB*, and *DBT*) are available.

Management

Management of acute presentation includes holding protein intake and suppressing catabolism with glucose and insulin infusions. Isoleucine and valine supplementations (20–120 mg/kg/d) and adequate caloric intake also are needed. Hemodialysis can be considered for rapid correction of hyperleucinemia. Thiamine, a cofactor for BCKAD, can be tried for 4 weeks at a dosage of 10 mg/kg/d. Long-term management requires a BCAA-restricted diet.[8]

Disorders of Pyruvate Metabolism

Defects in pyruvate metabolism cause the accumulation of pyruvate in plasma, which is subsequently converted into lactate causing an elevated plasma lactate and metabolic acidosis. Disorders of pyruvate metabolism include pyruvate dehydrogenase (PDH) and pyruvate carboxylase (PC) deficiencies (**Fig. 3**).

Pyruvate dehydrogenase deficiency

PDH catalyzes the conversion of pyruvate to acetyl-CoA and is composed of E1α, E1β, E2, E3, and E3BP subunits (see **Fig. 3**). PDH deficiency occurs mostly due to defects in E1α, which is encoded by the *PDHA1* gene located on chromosome X. Therefore, PDH deficiency is usually X-linked with the most severe illness occurs in male infants.

Manifestations Neonates with PDH deficiency typically present with severe lactic acidosis, hypotonia, seizures, apnea, distinctive facial features (see **Box 5**), lethargy,

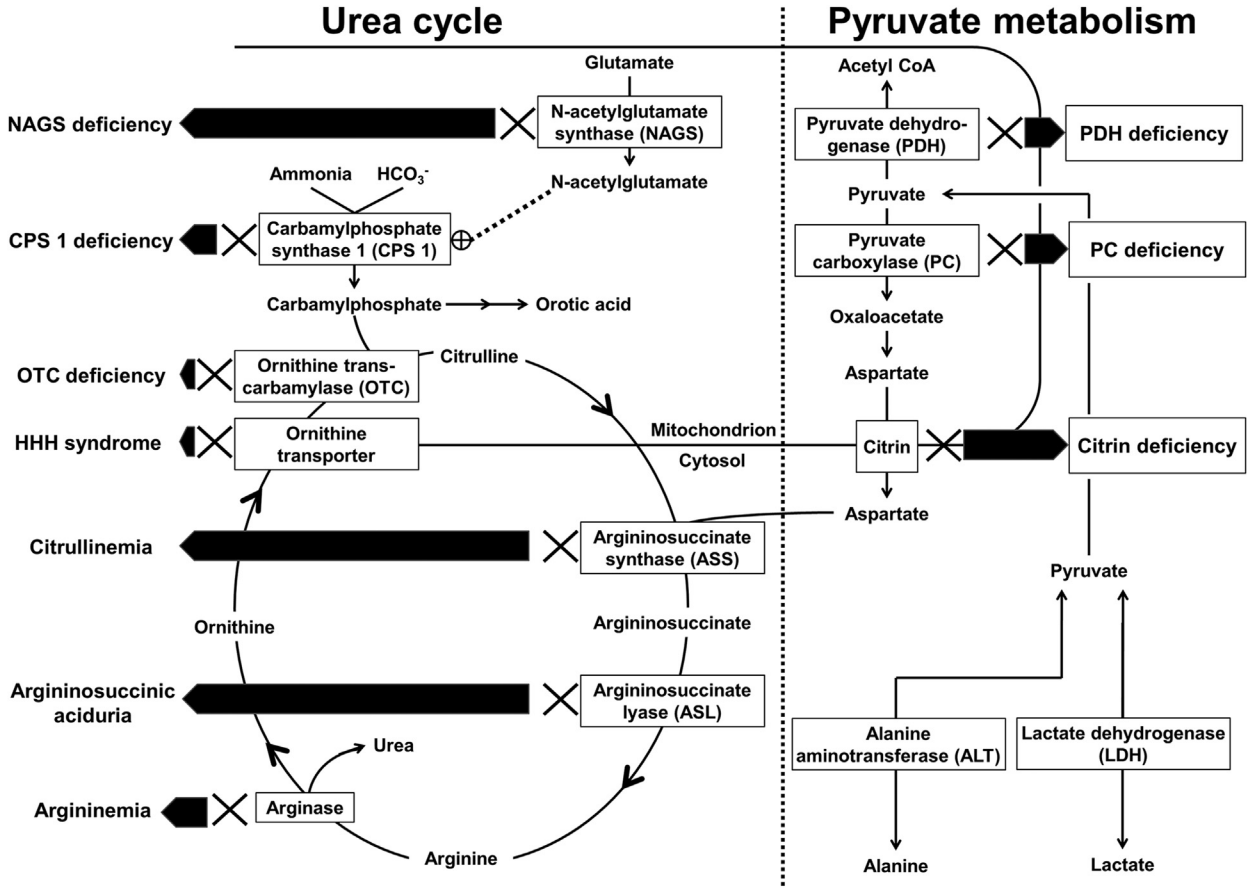

Fig. 3. Metabolic pathways for urea cycle and pyruvate with the related IEMs. HHH, hyperornithinemia-hyperammonemia-homocitrullinemia.

coma, and brain changes, including cerebral atrophy, hydrocephaly, corpus callosum agenesis, cystic lesions, gliosis, and hypomyelination.

Diagnosis Diagnosis is confirmed by enzyme studies and molecular genetic testing.

Management The prognosis is very poor, and treatment is not effective. Acidosis correction with bicarbonate and hydration with glucose infusion are needed during the acute presentation. However, excess administration of glucose may worsen the acidosis, and a ketogenic diet may reduce the lactic acidosis. Thiamin, a cofactor for PDH, can be used (10 mg/kg/d).[9]

Pyruvate carboxylase deficiency

PC catalyzes the conversion of pyruvate to oxaloacetate (see **Fig. 3**).

Manifestations Neonates with severe form of PC deficiency present with severe lactic acidosis, seizures, hypotonia, lethargy, and coma.

Diagnosis Biochemical profile of PC deficiency includes lactate acidosis, ketosis, hyperammonemia, hypercitrullinemia, and low aspartate. Oxaloacetate is the precursor of aspartate. Therefore, impaired oxaloacetate synthesis in PC deficiency results in low aspartate leading to urea cycle inhibition (see **Fig. 3**). Enzyme studies and molecular gene sequencing for *PC* gene are necessary for a definitive diagnosis.

Management The prognosis is poor, and treatment is not effective. Correction of acidosis with bicarbonate and hydration with glucose infusion are needed during the acute presentation. Biotin is a cofactor for PC and can be given (5-20 mg/d).[9,10]

INBORN ERRORS OF METABOLISM WITH HYPOGLYCEMIA

Hypoglycemia is a frequent finding in neonates. The suspicion of an IEM should be raised if the hypoglycemia is severe and persistent without any other obvious etiology (see **Box 1**). The presence or absence of ketosis can help in guiding the diagnostic workup (**Fig. 4**).

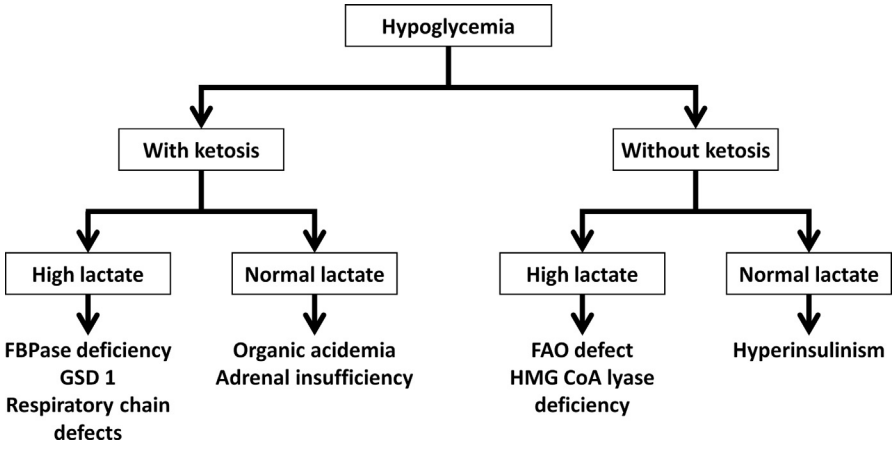

Fig. 4. Approach to neonatal hypoglycemia. FAO, fatty acid oxidation; FBPase: fructose-1,6-bisphosphatase; GSD I: glycogen storage disease type 1; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Fatty Acid Oxidation Defects

Fatty acids are transported into the mitochondria where they are catabolized through β-oxidation to yield acetyl-CoA units. Disorders of fatty acid oxidation result from defects in the mitochondrial transfer or β-oxidation. When fat cannot be used, glucose is consumed, resulting in a hypoketotic hypoglycemia. In addition, the released fat from adipose tissue accumulates in the liver, skeletal muscle, and heart, resulting in hepatopathy and skeletal and cardiac myopathy. Diagnosis is based on abnormalities in acylcarnitine profile, enzyme assay, and molecular testing (**Table 2**).

Very long chain acyl-CoA dehydrogenase deficiency

Very long chain acyl-CoA dehydrogenase (VLCAD) catalyzes the initial step of β-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons.

Manifestations Infants with the severe form of VLCAD deficiency typically present in the first months of life with cardiomyopathy, arrhythmias, hypotonia, hepatomegaly, and hypoglycemia.

Management Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding. Diet restrictions with a low-fat formula and supplemental medium-chain triglycerides should be initiated early. Cardiac dysfunction is reversible with early intensive supportive care and diet modification.[11]

Table 2
Acylcarnitine profiles and genes in fatty acid oxidation defects

Fatty Acid Oxidation Defect	Genes	Acylcarnitine Profile
Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency	*ACADVL*	Elevated C16 (hexadecanoylcarnitine), C14 (tetradecanoylcarnitine), C14:1 (tetradecenoylcarnitine), and C12 (dodecanoylcarnitine).
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	*ACADM*	Elevated C6 (hexanoylcarnitine), C8 (octanoylcarnitine), C10 (decanoylcarnitine), and C10:1 (decenoylcarnitine).
Short chain acyl-CoA dehydrogenase (SCAD) deficiency	*ACADS*	Elevated C4 (butyrylcarnitine).
Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	*HADHA*	Elevated C14OH (hydroxytetradecenoylcarnitine), C16OH (hydroxyhexadecanoylcarnitine), C18OH (hydroxystearoylcarnitine), and C18:1OH (hydroxyoleylcarnitine).
Carnitine palmitoyltransferase I (CPTI) deficiency	*CPT1A*	Elevated total carnitine; and decreased C16 (hexadecanoylcarnitine), C18 (octadecanoylcarnitine), and C18:1 (octadecenoylcarnitine).
Carnitine palmitoyltransferase II (CPTII) deficiency	*CPT2*	Decreased total carnitine; and elevated C16 (hexadecanoylcarnitine) and C18:1 (octadecenoylcarnitine).
Systemic primary carnitine deficiency	*SLC22A5*	Decreased total carnitine

Medium-chain acyl-CoA dehydrogenase deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) is responsible for the initial dehydrogenation of fatty acids with a chain length between 4 and 12 carbons.

Manifestations Infants with MCAD deficiency usually present between ages 3 and 24 months with hypoketotic hypoglycemia, vomiting, hepatomegaly elevated transaminases, lethargy, and seizures. Sudden and unexplained death can be the first manifestation of MCAD deficiency.

Management Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding. Uncooked cornstarch also can be used to prevent the hypoglycemia.[12]

Fructose-1,6-Bisphosphatase Deficiency

Deficiency of fructose-1,6-bisphosphatase (FBPase), a key enzyme in gluconeogenesis, impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose.

Manifestations

Infants with FBPase deficiency can present during the first week of life with lactic acidosis, hypoglycemia, ketosis, hepatomegaly, seizures, irritability, lethargy, hypotonia, apnea, and coma.

Diagnosis

Diagnosis is confirmed by enzyme assay and *FBP1* gene sequencing.

Management

The acute presentation can be treated with glucose infusion and bicarbonate to control hypoglycemia and acidosis. Maintenance therapy aims at avoiding fasting by frequent feeding and uncooked starch use. Restriction of fructose and sucrose is also recommended.[13]

Glycogen Storage Disease Type 1

Glycogen storage disease type 1 (GSD I) is caused by the deficiency of glucose-6-phosphatase (G6Pase) activity. The lack of liver G6Pase activity leads to inadequate conversion of glucose-6-phosphate into glucose through normal glycogenolysis and gluconeogenesis pathways, resulting in severe hypoglycemia and the accumulation of glycogen and fat in the liver and kidneys.

Manifestations

Some neonates with GSD I present with severe hypoglycemia; however, the common age of presentation is 3 to 4 months with hypoglycemia, lactic acidosis, hepatomegaly, hyperuricemia, hyperlipidemia, growth failure, and hypoglycemic seizures. Hypoglycemia and lactic acidosis can develop after a short fast (2–4 hours).

Diagnosis

Diagnosis can be confirmed by enzyme assay and sequencing of the *G6PC* gene.

Management

The acute presentation should be treated with glucose infusion and bicarbonate to control the hypoglycemia and the acidosis. Maintenance therapy aims to maintain normal glucose levels by frequent feeding, the use of uncooked starch, and intragastric continuous feeding if needed. The diet should be low in fat, sucrose, and fructose and high in complex carbohydrate.[14]

INBORN ERRORS OF METABOLISM WITH HYPERAMMONEMIA

It is essential to measure ammonia in every sick neonate whenever septic workup is considered. Hyperammonemia can be caused by IEMs or acquired disorders (Box 8). The presence of respiratory alkalosis or metabolic acidosis can help in guiding

Box 8
Differential diagnosis of hyperammonemia

- IEM
  - Urea cycle enzyme defects
    - N-Acetylglutamate synthase (NAGS) deficiency
    - Carbamoylphosphate synthase 1 (CPS 1) deficiency
    - Ornithine transcarbamoylase (OTC) deficiency
    - Argininosuccinate synthase (ASS) deficiency (citrullinemia)
    - Argininosuccinate lyase (ASL) deficiency (argininosuccinic aciduria)
    - Arginase deficiency
  - Transport defects of urea cycle intermediates
    - Mitochondrial ornithine transporter (HHH syndrome)
    - Aspartate-glutamate shuttle (citrin) deficiency
    - Lysinuric protein intolerance
  - Organic acidemias
    - Propionic acidemia
    - Methylmalonic acidemia
  - Fatty acid oxidation disorders
    - Medium-chain acyl-CoA dehydrogenase deficiency
    - Systemic primary carnitine deficiency
    - Long-chain fatty acid oxidation defects
  - Pyruvate carboxylase deficiency
  - Tyrosinemia type 1
  - Galactosemia
  - Ornithine aminotransferase deficiency
  - Hyperinsulinism-hyperammonemia syndrome
  - Mitochondrial respirator chain defects
- Acquired disorders
  - Transient hyperammonemia of the newborn
  - Diseases of the liver and biliary tract
    - Herpes simplex virus infection
    - Biliary atresia
    - Liver failure
  - Severe systemic neonatal illness

- Neonates sepsis
- Infection with urease-positive bacteria (with urinary tract stasis)
- Reye syndrome

- Medications
  - Valproic acid
  - Cyclophosphamide
  - 5-pentanoic acid
  - Asparaginase

- Anatomic variants
  - Vascular bypass of the liver (porto-systemic shunt)
- Technical
  - Inappropriate sample (eg, capillary blood)
  - Sample not immediately analyzed

the evaluation (Fig. 5). Ammonia can cause brain damage through several mechanisms. The major one is causing cerebral edema by affecting the aquaporin system and water and potassium homeostasis in brain. Hyperammonemia also can disrupt ion gradients, neurotransmitters, transport of metabolites, and mitochondrial function in brain.

Urea Cycle Disorders

Urea cycle is the principal mechanism for the clearance of waste nitrogen resulting from breakdown of protein and other nitrogen-containing molecules through the conversion of ammonia to urea. Urea cycle disorders (UCDs) result from defects in urea cycle enzymes leading to the accumulation of ammonia and other precursor metabolites (see Fig. 3). UCDs are among the most common IEMs. They are inherited as autosomal recessive conditions, with the exception of OTC deficiency, which is an X-linked disorder.

Manifestations

Infants with severe forms of UCDs typically present during the first few days of life with poor feeding, vomiting, hyperventilation, hypothermia, seizures, apnea, hypotonia, lethargy, and coma.

Diagnosis

In neonatal-onset UCDs, ammonia levels are usually higher than 300 μmol/L and are often in the range of 500–1500 μmol/L. Other laboratory abnormalities include respiratory alkalosis secondary to hyperventilation, low urea, mild elevation of transaminases, and coagulopathy. Plasma amino acid profile and urinary orotic acid can help in reaching the diagnosis (see Fig. 5). The diagnosis is confirmed by enzyme assay and molecular genetic testing (Table 3).

Acute management

Treatment of acute presentation includes the following:

1. Decreasing the production of ammonia from protein intake and breakdown. Suppression of catabolism can be achieved through the use of glucose infusion, insulin infusion, and intralipid administration. Protein intake can be completely

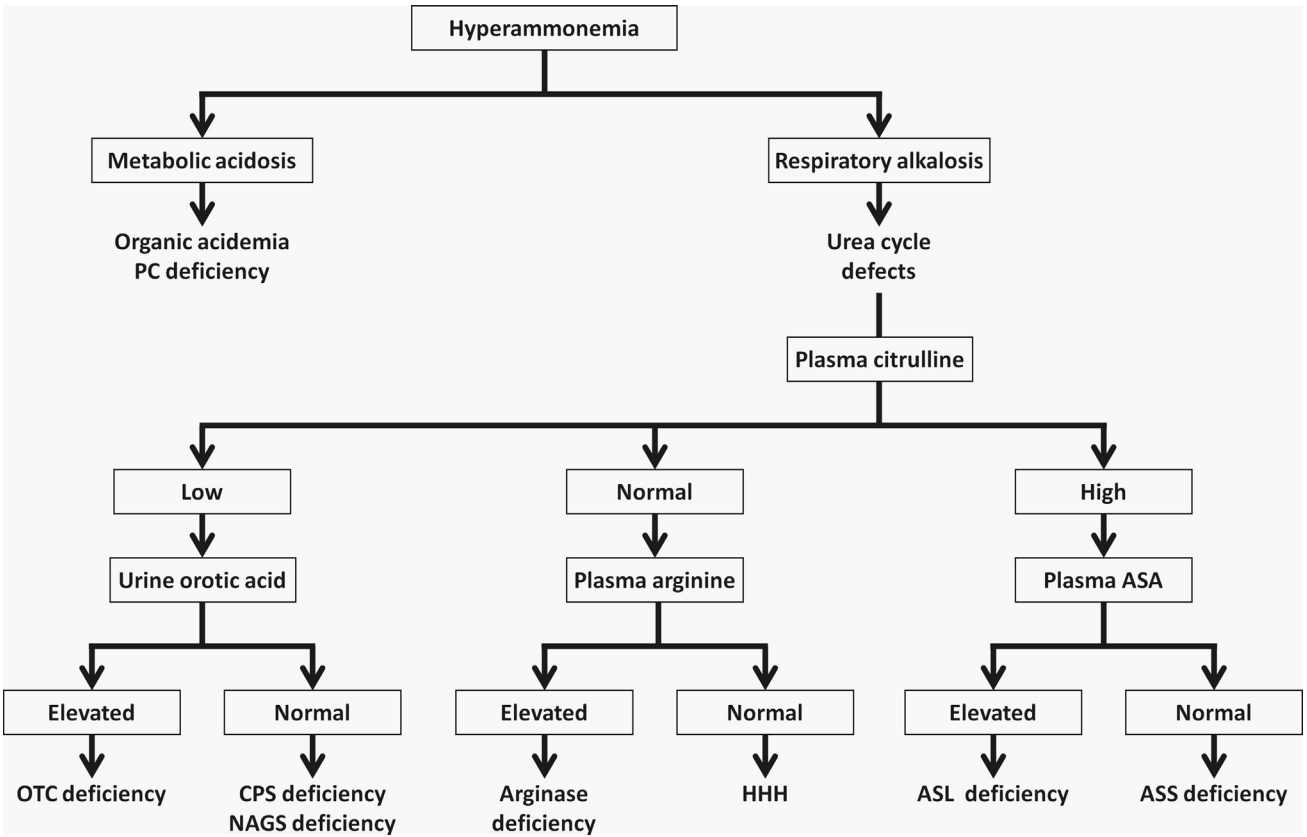

Fig. 5. Approach to neonatal hyperammonemia. ASA, argininosuccinic acid; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; CPS, carbamylphosphate synthase; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; NAGS, N-acetyl glutamate synthase; OTC, ornithine transcarbamylase; PC, pyruvate carboxylase.

Table 3
Enzymatic and molecular genetic diagnosis of urea cycle defects

Urea Cycle Disorder	Gene	Tissue for Enzyme Assay
N-acetylglutamate synthase (NAGS) deficiency	*NAGS*	Liver biopsy
Carbamoylphosphate synthetase I (CPS 1) deficiency	*CPS1*	Liver biopsy
Ornithine transcarbamylase (OTC) deficiency	*OTC*	Liver biopsy
Argininosuccinate synthase (ASS) deficiency (citrullinemia)	*ASS1*	Fibroblasts
Argininosuccinate lyase (ASL) deficiency (argininosuccinicaciduria)	*ASL*	Fibroblasts
Arginase deficiency	*ARG1*	Red blood cells

restricted for 24 to 48 hours, followed by introducing an essential amino acid formula to maintain the appropriate levels of essential amino acids, which is necessary to reverse the catabolic state.

2. Removing ammonia. Ammonia elimination can be enhanced by the use of the intravenous ammonia-scavenging drug (Ammonul), which contains both sodium benzoate and sodium phenylacetate and is given as a loading dose of 250 mg/kg over 60-120 minutes followed by the same dose over 24 hours as a maintenance infusion. L-arginine hydrochloride is used with Ammonul as loading and maintenance as well. The L-arginine doses are 200 mg/kg for loading and similar dose for maintenance in carbamoylphosphate synthase (CPS) deficiency and OTC deficiency; and 600 mg/kg in argininosuccinate synthase (ASS) deficiency and argininosuccinate lyase (ASL) deficiency. L-arginine hydrochloride is not used in arginase deficiency. Hemodialysis is the only method for rapid removal of ammonia from blood and should be considered if ammonia is very high (>500 μmol/L). However, while preparing for dialysis, the glucose, insulin, and ammonia scavenger therapy should be maintained.
3. Reduce the risk for neurologic damage by avoiding fluid overload and treating seizures that can be subclinical.

Long-term management

Maintenance therapy includes the following:

1. Protein-restricted diet. In general, infants require 1.2 to 2.0 g protein/kg with half of the required protein provided from essential amino acids formula and half from regular infant formula.
2. Oral ammonia scavenger medications include sodium benzoate (250–400 mg/kg/d) and sodium phenylbutyrate (250–500 mg/kg/d).
3. Replacement of arginine (200-600 mg/kg/d for ASS and ASL deficiencies) and citrulline (100–200 mg/kg/d for OTC and CPS deficiencies).
4. Carbamyl glutamate (Carbaglu) is a synthetic analogue for N-acetylglutamate, which is the natural activator of CPS1. Therefore, Carbaglu is very effective in N-acetyl glutamate synthase (NAGS) deficiency and can be tried in individuals with CPS1 deficiency.
5. In children with severe types of UCDs, liver transplantation can be considered.[15,16]

INBORN ERRORS OF METABOLISM WITH NEONATAL SEIZURE

The possibility of IEMs should always be considered in neonates with unexplained and refractory seizures (see **Box 1**).[17]

Biotinidase Deficiency

Biotinidase is essential for the recycling of the vitamin biotin, which is a cofactor for several essential carboxylase enzymes.

Manifestations

Untreated children with profound biotinidase deficiency usually present between ages 1 week and 10 years with seizures, hypotonia, metabolic acidosis, elevated lactate, hyperammonemia, and cutaneous symptoms, including skin rash, alopecia, and recurrent viral or fungal infections.

Diagnosis

The diagnosis is established by assessing the biotinidase enzyme activity in blood. Sequencing of *BTD,* the gene coding biotinidase enzyme, can also be performed.

Management

Acute metabolic decompensation can be treated by glucose and sodium bicarbonate infusions. Symptoms typically improve with biotin (5–10 mg oral daily) treatment. Children with biotinidase deficiency who are diagnosed before developing symptoms (eg, by newborn screening) and who are treated with biotin do not develop any manifestations.[18]

Pyridoxine-Dependent Epilepsy

Pyridoxine-dependent epilepsy occurs due to the deficiency of antiquitin enzyme in the lysine metabolism pathway. Antiquitin functions as a piperideine-6-carboxylate (P6C)/α-aminoadipic semialdehyde (AASA) dehydrogenase, therefore its deficiency results in the accumulation of AASA and P6C. The latter binds and inactivates pyridoxal phosphate, which is a cofactor in neurotransmitters metabolism.

Manifestations

Newborns with pyridoxine-dependent epilepsy present soon after birth with irritability, lethargy, hypotonia, poor feeding, and seizures that are typically prolonged with recurrent episodes of status epilepticus.

Diagnosis

The diagnosis is established clinically by showing a response to pyridoxine. Administering 100 mg of pyridoxine IV while monitoring the electroencephalogram (EEG) can result in cessation of the clinical seizures with corresponding EEG changes generally over a period of several minutes. If a clinical response is not demonstrated, the dose can be repeated up to 500 mg. Oral pyridoxine (30 mg/kg/d) can result in cessation of the seizures within 3 to 5 days. The diagnosis can be confirmed biochemically by demonstrating high levels of pipecolic acid, ASAA, and P6C, and molecularly by detecting mutations in *ALDH7A1*, the gene coding antiquitin.

Management

In general, seizures are controlled with 50 to 100 mg of pyridoxine daily.[19]

Pyridoxal Phosphate-Responsive Epilepsy

Pyridoxal phosphate-responsive epilepsy results from deficiency of pyridox(am)ine phosphate oxidase (PNPO), an enzyme that interconverts the phosphorylated forms of pyridoxine and pyridoxamine to the biologically active pyridoxal phosphate.

Manifestations

Infants with pyridoxal phosphate–responsive epilepsy typically present during the first day of life with lethargy, hypotonia, and refractory seizures that are not responsive to pyridoxine.

Diagnosis

Diagnosis is established by the demonstration of cessation of seizure with pyridoxal phosphate administration (50 mg orally) with corresponding EEG changes usually within an hour. Glycine and threonine are elevated in plasma and cerebrospinal fluid (CSF), whereas monoamine metabolites and pyridoxal phosphate are low in CSF. Mutational analysis for *PNPO* gene is available.

Management

Seizures can usually be controlled with pyridoxal phosphate 30-50 mg/kg/d divided in four doses.[20]

Glycine Encephalopathy (Nonketotic Hyperglycinemia)

Glycine encephalopathy occurs due to the deficiency of glycine cleavage enzyme resulting in glycine accumulation in all tissues including the brain. Glycine increases neuronal excitability by activating the N-methyl D-aspartate (NMDA) receptors.

Manifestations

Neonates with glycine encephalopathy typically present in the first hours to days of life with progressive lethargy, poor feeding, hypotonia, seizures, myoclonic jerks, and apnea.

Diagnosis

Biochemical diagnosis is based on the demonstration of elevated plasma glycine level and the CSF-to–plasma glycine ratio (samples of plasma and CSF should be obtained at approximately the same time for accurate calculation of the ratio). Molecular genetic testing is available for *GLDC*, *AMT*, and *GCSH*, the 3 genes coding the glycine cleavage enzyme subunits. Enzymatic activity in liver tissue also can be measured.

Management

No effective treatment is available. Sodium benzoate (250–750 mg/kg/d) can be used to reduce glycine levels. The NMDA receptor antagonists dextromethorphan, ketamine, and felbamate can result in improvement in seizure control. However, these treatments have been of limited benefit to the ultimate neurodevelopmental outcome.[21]

INBORN ERRORS OF METABOLISM WITH HYPOTONIA

Hypotonia is a common symptom in sick neonates. Some IEMs can present predominantly as hypotonia in the neonatal period (see **Box 1**).

Mitochondrial Disorders

Mitochondria are found in all nucleated human cells and generate most of the cellular energy in the form of ATP through the respiratory chain complexes. Mitochondria contain extrachromosomal DNA (mitochondrial DNA [mtDNA]). However, most mitochondrial proteins are encoded by the nuclear DNA (nDNA). Mutations in mtDNA or mitochondria-related nDNA genes can result in mitochondrial diseases that arise as a result of inadequate energy production required to meet the energy needs of various organs, particularly those with high energy demand, including the central nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine systems. Defects in nDNA genes are inherited in autosomal recessive, autosomal dominant, or X-linked manners, whereas mtDNA is maternally inherited.

Manifestations

Manifestations of mitochondrial diseases can start at any age. Neonates with mitochondrial diseases can present with apnea, lethargy, coma, seizures, hypotonia, spasticity, muscle weakness and atrophy, cardiomyopathy, renal tubulopathy, hepatomegaly, liver dysfunction or failure, lactic acidosis, hypoglycemia, anemia, neutropenia, and pancytopenia. Some infants with mitochondrial diseases display a cluster of clinical features that fall into a discrete clinical syndrome (**Box 9**). However, there is often considerable clinical variability, and many affected individuals do not fit into one particular syndrome.

Diagnosis

Biochemical abnormalities in mitochondrial diseases include lactic acidosis, ketosis, and elevated tricarboxylic acid cycle intermediates in urine organic acid analysis. The histology of affected muscles typically shows ragged red fibers that represent peripheral and intermyofibrillar accumulation of abnormal mitochondria. The enzymatic activity of respiratory chain complexes can be assessed on skeletal muscle, skin fibroblast, or liver tissue. Molecular testing for mtDNA content and sequencing for mtDNA and known mitochondrial-related nDNA genes also can be performed.

Management

Currently, there are no satisfactory therapies available for the vast majority of mitochondrial disorders. Treatment remains largely symptomatic and does not significantly alter the course of the disease.[22,23]

Box 9
Mitochondrial syndromes associated with neonatal presentation

- Pearson syndrome:
  - Sideroblastic anemia
  - Neutropenia
  - Thrombocytopenia
  - Exocrine pancreatic dysfunction
  - Renal tubular defects
- Barth syndrome:
  - Concentric hypertrophic cardiomyopathy
  - Skeletal myopathy
  - Neutropenia
  - Affects male individuals (X-linked)
- Hepatocerebral mitochondrial DNA depletion syndromes
  - Hepatic dysfunction or failure
  - Hypotonia
  - Seizures
  - Lactic acidosis
  - Hypoglycemia

Zellweger Syndrome

Zellweger syndrome is a disorder of peroxisomal biogenesis. Peroxisomes are cell organelles that possess anabolic and catabolic functions, including synthesizing plasmalogens, which are important constituents of cell membranes and myelin, β-oxidation of very long chain fatty acids (VLCFA), oxidation of phytanic acid, and formation of bile acids.

Manifestations

Neonates with Zellweger syndrome typically present with distinctive facial features (see **Box 5**), poor feeding, severe weakness and hypotonia, widely split sutures, seizures, hepatomegaly, jaundice, elevated transaminases, short proximal limbs, and stippled epiphyses.

Diagnosis

Biochemical abnormalities include elevated phytanic acid and VLCFA and low plasmalogens. Many proteins are involved in peroxisomal biogenesis. Therefore, complementation analyses allow the determination of which protein is defective and molecular genetic analysis for the responsible gene can be performed for molecular confirmation.

Management

There is no effective treatment and management is largely symptomatic.[24]

INBORN ERRORS OF METABOLISM WITH HEPATIC MANIFESTATIONS

Several IEMs can have hepatic manifestations in the neonatal period (see **Box 2**). Galactosemia is the most common metabolic cause of liver disease in neonates.

Galactosemia

Galactosemia occurs due to deficiency of the galactose-1-phosphate uridyltransferase (GALT) that catalyzes the conversion of galactose-1-phosphate and uridine diphosphate (UDP)-glucose to UDP-galactose and glucose-1-phosphate. When GALT enzyme activity is deficient, galactose-1-phosphate and galactose accumulate. Galactose is converted to galactitol in cells and produces osmotic effects resulting in cell dysfunction.

Manifestations

Symptoms of classic galactosemia occur in neonates within days of ingestion of lactose (glucose-galactose disaccharide) through breast milk or standard lactose-containing formulas. These manifestations include poor feeding, vomiting, diarrhea, failure to thrive, hypoglycemia, jaundice, hepatomegaly, elevated transaminases, coagulopathy, ascites, liver failure, renal tubulopathy, lethargy, irritability, seizures, cataracts, and *Escherichia coli* neonatal sepsis.

Diagnosis

The biochemical profile of galactosemia includes elevated galactose in plasma, galactose-1-phosphate in erythrocytes, and galactitol in urine. Diagnosis is confirmed by measuring GALT enzyme activity in erythrocytes and sequencing the *GALT* gene.

Management

Lactose-free formula should be started during the first 3 to 10 days of life for the signs to resolve and the prognosis to be good.[25,26]

Tyrosinemia Type I

Tyrosinemia type I occurs due to deficiency of fumarylacetoacetate hydrolase (FAH), which functions in the catalytic pathway of tyrosine. FAH deficiency results in the accumulation of fumarylacetoacetate and its derivative succinylacetone, both of which form glutathione adducts thereby rendering cells susceptible to free radical damage. In addition, fumarylacetoacetate is an alkylating agent that has a widespread effect on cellular metabolism resulting in cell death.

Manifestations

Children with tyrosinemia type I can present during early infancy with vomiting, diarrhea, hepatomegaly, hypoglycemia, sepsis, liver failure with coagulopathy, ascites, jaundice, renal tubulopathy, and abnormal odor (see **Box 4**).

Diagnosis

Biochemical abnormalities include elevated urine succinylacetone and tyrosine metabolites (p-hydroxyphenylpyruvate, p-hydroxyphenyllactate, and p-hydroxyphenylacetate) and elevated tyrosine and methionine in plasma. Serum α-fetoprotein is markedly elevated. Diagnosis can be confirmed by enzyme assay and molecular genetic testing for the *FAH* gene.

Management

Nitisinone (NTBC) (1–2 mg/kg/d divided in 2 doses) blocks hydroxyphenylpyruvate dioxygenase, the second step in the tyrosine degradation pathway, and prevents the accumulation of fumarylacetoacetate and its derivative succinylacetone. Low tyrosine diet is also needed.[27]

Hereditary Fructose Intolerance

Hereditary fructose intolerance occurs due deficiency of fructose 1,6-biphosphate aldolase (aldolase B), which is part of the catabolic pathway of fructose. Fructose intake results in accumulation of fructose-1-phosphate and trapping of phosphate, leading to diminished ATP regeneration.

Manifestations

Clinical manifestations develop after the exposure to fructose from sucrose (glucose–fructose disaccharide) in soy-based formulas or later at weaning from fruits and vegetables. These manifestations include vomiting, hypoglycemia, jaundice, lethargy, irritability, seizures, coma, hepatomegaly, jaundice, elevated transaminases, coagulopathy, edema, ascites, liver failure, and renal tubulopathy.

Diagnosis

The diagnosis can be established enzymatically by measuring the aldolase B activity in liver tissue and molecularly by sequencing the *ALDOB* gene.

Management

Management is based on eliminating sucrose, fructose, and sorbitol from diet.[28]

Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency

Citrin is a mitochondrial aspartate-glutamate carrier that transports aspartate from mitochondria to cytosol (see **Fig. 3**). One of the clinical manifestations of citrin deficiency is neonatal intrahepatic cholestasis.

Manifestations
Newborn infants with citrin deficiency can present with transient intrahepatic cholestasis, prolonged jaundice, hepatomegaly, fatty liver, elevated transaminases, hypoproteinemia, coagulopathy, growth failure, hemolytic anemia, and hypoglycemia. Neonatal intrahepatic cholestasis caused by citrin deficiency is generally not severe, and symptoms disappear by the age of 1 year with appropriate treatment.

Diagnosis
Biochemical abnormalities include elevated plasma citrulline, arginine, threonine, methionine, and tyrosine. Sequencing the *SLC25A13* gene that codes citrin is available.

Management
Management includes the supplementation of fat-soluble vitamins and the use of lactose-free formula and high medium-chain triglycerides. Subsequently, a diet rich in lipids and protein and low in carbohydrates is recommended.[29]

INBORN ERRORS OF METABOLISM WITH CARDIOMYOPATHY

Some metabolic disorders can present predominantly with cardiomyopathy (see **Box 3**).

Glycogen Storage Disease Type II (Pompe Disease)

Glycogen storage disease type II (GSD II) is caused by the deficiency of the lysosomal enzyme acid α-glucosidase (GAA, acid maltase). The enzyme defect results in the accumulation of glycogen within the lysosomes in different organs.

Manifestations
Infants with the classic infantile-onset GSD II typically present in the first 2 months of life with hypotonia, muscle weakness, hepatomegaly, hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, macroglossia, respiratory distress, and hearing loss.

Diagnosis
Nonspecific tests supporting the diagnosis include elevated serum creatinine kinase level and urinary oligosaccharides. The diagnosis is confirmed enzymatically by assessing GAA enzyme activity and molecularly by sequencing the *GAA* gene.

Management
Enzyme replacement therapy using alglucosidase alfa (Myozyme) should be initiated as soon as the diagnosis is established. The response to enzyme replacement therapy is better for those in whom the therapy is initiated before age 6 months and before the need for ventilatory assistance.[30]

Best Practices

- IEMs are not uncommon, neonates with IEMs usually present with nonspecific signs, and early diagnosis and institution of therapy are mandatory to prevent death and ameliorate complications from many IEMs. Therefore, a high index of suspicion for IEMs should be maintained. Consider metabolic evaluation in sick neonates and those with hypotonia, seizures, cardiomyopathy, and hepatopathy.
- After performing the initial metabolic workup, you can narrow the differential diagnosis by the following categorizations:
  - In metabolic acidosis with hyperammonemia, consider organic acidemia (or PC deficiency if lactate is also very high).

- In hypoglycemia without ketosis, consider fatty acid oxidation defects or HMG CoA lyase deficiency.
- In hypoglycemia with ketosis and elevated lactate, consider fructose-1,6-bisphosphatase deficiency and glycogen storage disease type 1.
- In hyperammonemia with respiratory alkalosis, consider urea cycle defects.
- In liver failure, galactosemia and tyrosinemia type I should be evaluated.
- In cardiomyopathy, consider glycogen storage disease type II and fatty acid oxidation defects.

- When managing acute metabolic decompensation, make sure about the following:
  - Provide adequate calories, at least 20% above what is normally needed.
  - Use insulin infusion to reverse catabolism.
  - Limit the enteral feeding restriction to 24 to 48 hours and introduce enteral feeding with the appropriate formula early (after 24–48 hours).

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