Neonatal Presentations of Metabolic Disorders

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Practice Gaps

1. Metabolic acidosis or primary respiratory alkalosis can be an early sign of neonatal hyperammonemia.
2. Metabolic disorders in a neonate can involve any organ system and can be challenging to diagnose.
3. Early detection of treatable metabolic conditions is important for prognosis.
4. A normal newborn screening result does not exclude a metabolic disorder.

Abstract

Metabolic disorders in a neonate can present with involvement of any organ system and can be challenging to diagnose. A newborn can present with an acute metabolic crisis such as hyperammonemia or seizures needing immediate management, with a more chronic clinical picture such as cholestatic liver disease, or with structural abnormalities such as skeletal manifestations. Early detection of treatable metabolic conditions is important to improve outcomes. Newborn screening has facilitated early detection and initiation of therapy for many metabolic disorders. However, normal testing does not rule out a metabolic disorder and a high index of suspicion should remain when caring for any critically ill neonate without a diagnosis. Whole exome sequencing (WES) or whole genome sequencing (WGS) can be powerful tools in rapid diagnosis of a potentially treatable metabolic condition in a critically ill neonate. This review presents classic clinical presentations of neonatal metabolic disorders and also highlights some uncommon neonatal manifestations of metabolic disorders to improve the recognition and diagnosis of these conditions.

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ABBREVIATIONS

FAOD	fatty acid oxidation defect
FTT	failure to thrive
HFI	hereditary fructose intolerance
HIE	hypoxic-ischemic encephalopathy
IUGR	intrauterine growth restriction
LPI	lysinuric protein intolerance
MMA	methylmalonic acidemia
MRI	magnetic resonance imaging
NBS	newborn screening
PA	propionic acidemia
RUSP	Recommended Uniform Screening Panel
WES	whole exome sequencing
WGS	whole genome sequencing

Objectives

After completing this article, readers should be able to:

1. Recognize the need to order a serum ammonia evaluation in a neonate with an unexplained metabolic acidosis or respiratory alkalosis.
2. Recognize that a variety of symptoms such as a history of fetal hydrops, hypoxic-ischemic encephalopathy, cardiomyopathy, liver failure, cholestatic liver disease, skeletal dysplasia, or *Escherichia coli* sepsis can be a clue to a metabolic disorder.
3. Describe treatable metabolic disorders that present during the neonatal period.

INTRODUCTION

Inborn errors of metabolism, also known as biochemical genetic disorders or metabolic disorders (referred to as such in this article), are a group of thousands of rare genetic conditions that can present at any age from the fetal period to adulthood and can involve multiple organ systems. (1)(2)(3) Neonatologists may only see a handful of newborns with metabolic disorders during their career. Although there is no effective treatment for some metabolic disorders and the prognosis can be poor, some conditions can be effectively managed with dietary modifications, medications, supplements, or organ transplantation. Early detection of these treatable conditions is important to improve outcomes. Therefore, neonatologists should have a high index of suspicion for a metabolic disorder in any critically ill neonate with an unusual or unexplained presentation. Newborn screening (NBS) has facilitated early detection and initiation of therapy for many metabolic disorders. However, a normal test result does not rule out a metabolic disorder, and a high index of suspicion should remain when caring for any critically ill neonate without a diagnosis.

The purpose of this review is to summarize the classic clinical presentations of neonatal metabolic disorders as well as to highlight some uncommon neonatal manifestations of metabolic disorders to improve recognition of these conditions. In this review, we focus on manifestations of these disorders during the neonatal period; clinical presentations after this period are beyond the scope of this review. We will discuss symptoms that can indicate a metabolic disorder rather than listing metabolic disorders and their clinical presentations. We present several examples of metabolic disorders related to each clinical finding. For a comprehensive list of metabolic disorders associated with each clinical sign, the reader is encouraged to refer to more comprehensive publications, many of which are referenced here.

NEONATAL HYPERAMMONEMIA AND METABOLIC ACIDOSIS

In neonates, classic scenarios in which a metabolic disorder is more likely include those in which a neonate has severe metabolic acidosis with an anion gap, lactic acidosis, or hyperammonemia, which can also occur together. Severe metabolic acidosis with an anion gap occurs when a nonvolatile acid accumulates as a result of a block in a metabolic pathway. An anion gap metabolic acidosis is typical in neonates with organic acidemias such as methylmalonic acidemia (MMA) and propionic acidemia (PA) as well as mitochondrial disorders in which lactic acid accumulates.

Neonatal hyperammonemia results from either a primary or secondary defect in the urea cycle, which is responsible for converting ammonia that is produced during protein metabolism into blood urea nitrogen, which is then excreted by the kidneys. Neonates with primary defects in the urea cycle such as ornithine transcarbamylase deficiency typically do not present with metabolic acidosis but rather, have primary respiratory alkalosis resulting from tachypnea. This tachypnea is thought to be caused by stimulation of the central nervous system respiratory center by the ammonium ion. (4)(5) In a neonate with hyperammonemia and a primary respiratory alkalosis (pH >7.45, low partial pressure of carbon dioxide [P_{CO_2}]), urea cycle defects are highest on the differential. Neonatal hyperammonemia with severe metabolic acidosis is a typical presentation of organic acidemias such as MMA, PA, and isovaleric acidemia. (6)(7) Neonates with fatty acid oxidation defects (FAOD) may also present with neonatal hyperammonemia and often have a history of low/undetectable serum glucose. If the later is true, lipid administration should be avoided pending diagnosis. Mitochondrial disorders are a less common but possible cause of neonatal hyperammonemia and should be considered if there is a

TABLE 1. **Metabolic Etiologies and Laboratory Evaluation of Neonatal Hyperammonemia**

	ACIDOSIS VS ALKALOSIS	ETIOLOGY[a]	COMMENTS	DIAGNOSTIC/HELPFUL BIOCHEMICAL LABORATORY STUDIES
Neonatal hyperammonemia[a]	Metabolic acidosis (increased anion gap)	Organic acidemias	• Anion gap acidosis is severe	• Urine organic acids (diagnostic)
		• MMA	• MMA: often lactic acidosis	• Plasma acylcarnitines
		• PA	• PA: at risk for cardiomyopathy	• Plasma total and free carnitine (secondary carnitine deficiency)
		• Isovaleric acidemia		• Plasma amino acids
		• Multiple carboxylase deficiency		• Serum/plasma MMA level
		• Multiple acyl-CoA dehydrogenase deficiency		• Serum lactic acid
		• 3-Hydroxymethylglutaryl-CoA dehydrogenase deficiency		• High BUN
		• 3-Methylcrotonyl-CoA carboxylase deficiency		• Gene sequencing[b]
		Mitochondrial disorders	See "Other" for features and diagnostic studies for mitochondrial disorders	
	Respiratory alkalosis (primary)	Urea cycle defects	• Typically very low BUN	• Plasma amino acids
		• NAGS deficiency	• Hyperammonemia typically severe in NAGS, CPS, OTC and ASS deficiency	• Urine orotic acid
		• CPS deficiency	• Hyperammonemia not very common in arginase deficiency	• Urine organic acids (orotic)
		• OTC deficiency		
		• Argininosuccinate synthetase deficiency (citrullinemia)		
		• Argininosuccinate lyase deficiency		
		• Arginase deficiency		
		Amino acid transporter deficiencies	• Only a minority of patients with HHH or LPI do not present during neonatal period	• HHH and LPI: plasma amino acids, urine amino acids
		• HHH syndrome		
		• LPI		
		• Transient hyperammonemia of the newborn	• Typically <36 weeks' gestational age, birthweight <2.5 kg, respiratory distress, presents <24 hours after birth	• Typical diagnostic metabolites of urea cycle or other disorders are not present
			• May be severe and require ammonia scavengers and/or dialysis	

Continued

TABLE 1. (Continued)

ACIDOSIS VS ALKALOSIS	ETIOLOGY[a]	COMMENTS	DIAGNOSTIC/HELPFUL BIOCHEMICAL LABORATORY STUDIES
Other[c]	Fatty acid oxidation defects	• Often severe hypoglycemia on initial presentation	• Plasma acylcarnitine profile
	• Carnitine transporter deficiency	• Risk of cardiomyopathy and cardiac arrhythmias	• Plasma total and free carnitine
	• Carnitine palmitoyl transferase 2 deficiency		• Urine organic acids
	• Carnitine acylcarnitine translocase deficiency		• Gene sequencing[b]
	• Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency		• Enzyme assay from fibroblasts[d]
	• Very-long-chain acyl-CoA dehydrogenase deficiency		
	Mitochondrial disorders	• Severe lactic acidosis, multisystem involvement	• There are currently no diagnostic biochemical markers for mitochondrial disorders
	• Mitochondrial DNA defects		• Genetic testing or enzyme analysis may lead to diagnosis
	• A defect in one of the multiple nuclear mitochondrial genes		
	Pyruvate carboxylase deficiency	• Lactic acidosis, ketosis, hypoglycemia, FTT, seizures	• Plasma amino acids
			• Gene sequencing
	HIHA	• Fasting or protein (leucine) sensitive hypoglycemia	• High insulin
			• Gene sequencing

ASS= argininosuccinate synthetase; BUN=blood urea nitrogen; CoA=coenzyme A; CPS= carbamyl phosphate synthetase; FTT=failure to thrive; HHH= Hyperornithinemia-hyperammonemia-homocitrullinemia; HIHA=hyperinsulinism/hyperammonemia syndrome; LPI= lysinuric protein intolerance; MMA=methylmalonic acidemia; NAGS=N-acetylglutamate synthetase; OTC=ornithine transcarbamylase; PA=propionic acidemia.

[a]*This is not a comprehensive list of all possible causes of neonatal hyperammonemia. For example, liver failure, portocaval shunt, and bacterial colonization with urease-positive organisms may also lead to hyperammonemia. This table lists the most common metabolic causes of neonatal hyperammonemia.*

[b]*Gene sequencing is typically done after a diagnosis has already been made via biochemical testing for confirmation and genetic counseling.*

[c]*These conditions can present with either metabolic acidosis or respiratory alkalosis depending on other contributing factors such as sepsis or dehydration, but often neither metabolic acidosis nor respiratory alkalosis have the same degree of severity as do organic acidemias or urea cycle defects, respectively.*

[d]*Skin biopsy for fibroblast culture and subsequent enzyme assay from fibroblasts may be necessary in cases in which biochemical and genetic testing do not provide a definitive diagnosis.*

concurrent severe lactic acidosis. Neonates with organic acidemias, especially MMA, can also have lactic acidosis because of secondary mitochondrial dysfunction (8)(9)(10); however, typically this acidosis is not as significant as that seen in patients with a primary mitochondrial disorder. Table 1 provides a list of conditions that may present with neonatal hyperammonemia and diagnostic or helpful biochemical laboratory studies that should be performed while initiating therapy.

Treatment of neonatal hyperammonemia is beyond the scope of this review; however, keys to management, briefly, are as follows:

- Provision of energy in the form of carbohydrate and lipids to promote anabolism. Unless FAOD is suspected in which case lipids should be avoided.
- Insulin administration if hyperglycemia develops
- Correction of dehydration
- Central catheter for high dextrose (>12.5%) concentration intravenous fluids and frequent blood sampling
- Administration of an intravenous ammonia scavenger (eg, sodium benzoate/sodium phenylacetate)
- Hemodialysis or continuous renal replacement therapy, in some cases, to rapidly decrease ammonia levels

For further review of the management of hyperammonemia, we refer the reader to publications focused on the management of neonatal hyperammonemia. (6)(11)(12)(13)(14) Hyperammonemia is one of the most common neonatal presentations of metabolic disorders that will go undetected unless the ammonia level is checked. A timely diagnosis and initiation of therapy to lower ammonia levels are vital for prognosis.

FETAL MANIFESTATIONS OF NEONATAL METABOLIC DISORDERS

Nonimmune Fetal Hydrops

Because of early diagnosis and treatment of rhesus (Rh) isoimmunization, nonimmune causes now account for the majority of fetal hydrops cases. (15)(16) Metabolic disorders account for about 1% to 15% of nonimmune fetal hydrops. (15)(16)(17) In particular, patients with storage disorders such as mucopolysaccharidosis type VII (Sly syndrome), Gaucher disease, infantile galactosialidosis, and transaldolase deficiency can present with fetal hydrops. In a fetus with hydrops or a neonate with a history of fetal hydrops, a metabolic cause should be sought if more common conditions such as fetal anemia, an infection, a chromosomal disorder, and cardiac abnormalities have been ruled out. A metabolic disorder should also be considered if nonimmune hydrops is also associated with other features of storage disorders such as a large placenta, hepatosplenomegaly, or coarse features.

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) has multiple etiologic factors, ranging from placental insufficiency to chromosomal/genetic and infectious causes. Metabolic disorders that can lead to IUGR include mitochondrial disorders (energy deficiency), peroxisomal disorders, disorders of cobalamin metabolism, and cholesterol biosynthesis defects. Typically, however, IUGR is not the only clinical manifestation of these conditions.

In the following sections, several clinical findings are presented based on organ systems; if the reason for these findings is unknown, the clinician should consider a metabolic disorder. Some of the clinical findings presented often have a fetal origin and may be detected prenatally, especially those that involve structural changes.

NEUROLOGIC

Encephalopathy

Neonatal encephalopathy is defined as abnormal brain function in a newborn manifested by decreased level of consciousness and responsiveness, such as a poor suck. Hypoxic-ischemic encephalopathy (HIE) is among the most common causes of neonatal encephalopathy. Metabolic disorders can manifest similarly to, and mimic, HIE. (18) In general, neonates with HIE are symptomatic since birth whereas newborns with metabolic disorders typically become symptomatic after an initial normal period. However, some metabolic disorders, such as mitochondrial disorders, may potentially cause a lower tolerance of stress during labor and the affected neonate may present with a clinical picture similar to HIE.

Neonatal seizures, as a result of metabolic disorders, may also cause neonatal encephalopathy and manifest immediately at birth (see next section). Brain magnetic resonance imaging (MRI) may help distinguish between HIE and metabolic causes of encephalopathy because HIE causes typical radiographic patterns of brain injury. (19)(20)(21) A metabolic cause should be considered in cases of neonatal encephalopathy if an acute perinatal event is absent (making HIE less likely), symptoms started after an initial normal period, or seizures persist without an intracranial abnormality. Neonatal hyperammonemia and related conditions (Table 1), maple syrup urine disease, and conditions that cause neonatal seizures (Table 2) should be considered when metabolic causes of neonatal encephalopathy are being considered.

Seizures

Most neonatal seizures are caused by acute brain injury, and brain MRIs can often determine the cause (eg, structural brain abnormality, intracranial bleeding, HIE). (22)(23) However, brain MRI findings in some metabolic disorders, such as molybdenum cofactor deficiency, can mimic that of HIE. (24)(25) Table 2 lists metabolic causes of neonatal seizures with treatable or potentially treatable conditions marked with an asterisk. Most of the time, however, therapy should be initiated before the onset of symptoms or very early in the course of symptoms (preferably before brain MRI findings are apparent) such as in molybdenum cofactor deficiency and serine biosynthesis defects. (26)(27)(28) Treatment before the onset of symptoms can be possible for disorders detected on NBS or if a diagnosis has been made prenatally (eg, because of a history of metabolic disorder in a previous child). Metabolic disorders should be strongly considered if the brain MRI in a neonate with

TABLE 2. **Metabolic Causes of Neonatal Seizures**

Neonatal seizures	Typically present with isolated neonatal seizures	Cerebral folate deficiency (cerebral folate receptor gene *FOLR1*)*
		Creatine metabolism disorders (various genes)*
		Folinic acid responsive seizures*
		Glycine Encephalopathy (also known as non-ketotic hyperglycinemia)[a,]*
		Glucose Transporter (GLUT1) deficiency*
		Molybdenum cofactor deficiency (3 genes)[b,]*
		Pyridoxal (activated B6) responsive seizures (pyridoxal phosphate-binding protein gene *PLBP*, pyridoxamine 5-prime-phosphate oxidase gene *PNPO*)*
		Pyridoxine (B6) responsive seizures (*ALDH7A1* gene)*
		Serine biosynthesis defect[c,]*
		Sulfite oxidase deficiency
	Typically present with other systemic symptoms (such as metabolic acidosis, lactic acidosis, hyperammonemia)	Biotinidase deficiency (though does not typically present in neonatal period)*
		Fatty acid oxidation defects (if severe hypoglycemia)*
		Maple syrup urine disease*
		Mitochondrial disorders (severe lactic acidosis, often multisystem involvement)
		Organic acidemias (eg, methylmalonic acidemia, propionic acidemia, multiple carboxylase deficiency)[d,]*
		Peroxisomal disorders (eg, Zellweger syndrome)
		Urea cycle defects (if severe hyperammonemia)*

Conditions for which a treatment may be available are marked with an asterisk.
[a]No effective therapy available but glycine reduction may relieve symptoms in some cases.
[b]Treatment available only for 1 type of molybdenum cofactor deficiency and should be started before the onset, or early (within days of onset of symptoms).
[c]No effective therapy available but serine supplementation may relieve symptoms if started early.
[d]Treatment is available for some organic acidemias. Seizures, if they do occur, mostly occur during an acute metabolic crisis (eg, hyperammonemia). Therefore, the most important approach to treatment and prevention of seizures is management and prevention of an acute metabolic crisis.

seizures does not demonstrate a structural anomaly or acute injury, if the perinatal history is normal, and especially if electroencephalography shows burst suppression. Identifying treatable conditions early is important for prognosis. Diagnosis often requires sampling of cerebrospinal fluid for neurotransmitters or amino acids and/or genetic testing (gene panels for neonatal seizures, whole exome sequencing [WES], whole genome sequencing [WGS]).

Microcephaly

Although many metabolic disorders cause microcephaly postnatally, microcephaly at birth can be found in neonates with mitochondrial disorders, pyruvate metabolism disorders, cobalamin synthesis defects, serine synthesis defects (also a cause of neonatal seizures), and sterol synthesis defects. (29) For additional information, refer to the section on maternal conditions affecting a neonate.

Hypotonia

Neonatal hypotonia is a nonspecific symptom that can arise from an abnormality in the central nervous system, peripheral nervous system, neuromuscular junction, muscle itself, or a metabolic or electrolyte abnormality. If the cause is metabolic, possible disorders include mitochondrial disorders, peroxisomal disorders, and Pompe disease.

Hydrocephalus

Hydrocephalus is not a common presentation of a metabolic disorder in a neonate but has been described in patients with cobalamin C and cobalamin D disorders. (30)(31)(32)

OPHTHALMOLOGIC

Patients with metabolic diseases often need to be followed for ophthalmologic manifestations. Furthermore, the ophthalmologic evaluation in a sick neonate may lead to a diagnosis of a metabolic disorder. Neonates with metabolic disease can have eye abnormalities because of an accumulation of an abnormal metabolic product (eg, galactosemia, mucopolysaccharidoses) or a deficient energy metabolism (mitochondrial diseases). Ocular manifestations of metabolic disorders include corneal clouding (mucopolysaccharidoses, mucolipidoses), congenital cataract (see next section), and cherry red spot (Niemann-Pick A and B, galactosialidoses, gangliosidoses). (2)(33)

Cataract

Although many metabolic manifestations in the eye present later in infancy or childhood, in the neonatal period, the finding of a cataract in a neonate with multisystem disease can be an indication of galactosemia, a peroxisomal disorder, Lowe syndrome, or multiple acyl-coenzyme A (CoA) dehydrogenase deficiency. (33)

CARDIAC

Cardiomyopathies

A cardiomyopathy diagnosis can reveal an undetected metabolic disorder or a diagnosis of a metabolic disorder can reveal an undetected cardiomyopathy or risk for it in future years. Metabolic disorders can cause a dilated, hypertrophic or left ventricular noncompaction type of cardiomyopathy. (34)(35) Metabolic disorders in which cardiomyopathy can be the presenting symptom include primary carnitine deficiency (typically associated with a dilated cardiomyopathy, though cardiac presentation is more common later in childhood), very-long-chain acyl-CoA-dehydrogenase deficiency and other long-chain FAODs (typically dilated cardiomyopathy), Pompe disease (hypertrophic cardiomyopathy), mitochondrial disorders (fatal infantile hypertrophic obstructive cardiomyopathy, also dilated cardiomyopathy), or Barth syndrome (X-linked, more common in males, associated with left ventricular noncompaction type). Neonates with PA are at risk for either dilated or hypertrophic cardiomyopathy. Furthermore, although a neonate with cardiomyopathy often has lactic acidosis because of poor perfusion secondary to cardiac dysfunction, severe intractable lactic acidosis in a neonate should prompt an evaluation for a mitochondrial disorder.

Arrhythmias

Accumulation of storage material in cardiomyocytes leading to cardiac conduction defects and arrhythmias may occur in storage disorders. Though this typically does not occur in neonates, newborns with Pompe disease can exhibit a shortened PR interval on electrocardiography. (36) Arrhythmias may also be caused by the accumulation of toxic metabolites as occurs during a metabolic crisis in patients with an FAOD. (37)(38)

RESPIRATORY

Tachypnea

Tachypnea is a common nonspecific symptom in both term and preterm infants that can have multiple causes, including central nervous system disorders, primary pulmonary processes, or physiologic disturbances such as hypoxemia or hypercapnia. A metabolic cause for neonatal tachypnea should be sought in cases of anion gap metabolic acidosis, because the tachypnea could be the result of accumulating organic acid (organic acidemias) or lactic acid (mitochondrial diseases). These infants typically have a secondary respiratory alkalosis in an attempt to compensate for their metabolic acidosis. Tachypnea associated with a primary respiratory alkalosis (pH >7.45, no anion gap) should prompt a clinician to consider hyperammonemia as a result of a urea cycle defect, especially if there is any level of encephalopathy.

Pulmonary alveolar proteinosis can occur in patients with lysinuric protein intolerance (LPI), (39) and pulmonary arterial hypertension can be seen in some neonates with glycogen storage disorders, such as type I glycogen storage disease (von Gierke), (40) but these typically do not manifest during the neonatal period.

GASTROINTESTINAL/NUTRITIONAL

Liver Failure

Metabolic disorders account for 13% to 54% of cases of neonatal liver failure. (41)(42) Galactosemia, tyrosinemia, mitochondrial disorders (especially mitochondrial DNA depletion syndromes), and congenital disorders of glycosylation are common metabolic causes of liver failure in neonates, though tyrosinemia typically presents after the neonatal period. Galactosemia can present within days of consuming galactose-containing milk (breast milk or lactose-containing formula) with signs of hepatocellular damage such as jaundice, hepatomegaly, elevated transaminases, and coagulopathy. *Escherichia coli* sepsis is relatively common in symptomatic neonates with galactosemia. Positive urine-reducing substances without the presence of glucose in the urine can be a sign of galactosemia. All galactose (lactose)–containing products must be immediately stopped if galactosemia is being considered, and soy-based formula used until a diagnosis is either confirmed or ruled out. (43) Neonatal acute liver failure with elevated transaminases, coagulopathy, and severe lactic acidosis can be seen in neonates with mitochondrial DNA depletion syndromes (typically, multiple genes involved). (44)(45) The diagnosis of hereditary fructose intolerance (HFI) should be considered in a neonate who presents with recurrent episodes of liver dysfunction (elevated transaminases, even coagulopathy) with hypoglycemia, lactic acidosis, and hyperuricemia that rapidly corrects with stopping formula and provision of

a dextrose infusion. Although an infant with HFI typically presents with the classic clinical symptoms when the child starts consuming vegetables and fruit (important sources of fructose), some infant formulas may contain fructose, sucrose, or sorbitol (the latter 2 can be metabolized to fructose) and symptoms can occur earlier. (46)

Cholestatic Liver Disease

Cholestatic liver disease is common in sick neonates, and parenteral nutrition–induced cholestasis is common in patients in the NICU. Peroxisomal disorders, mevalonic aciduria, and congenital disorders of glycosylation are also possible causes of neonatal cholestatic liver disease, especially in a neonate with multisystem involvement. Bile acid synthesis defects typically present with isolated cholestatic liver disease. (47)(48) In adults, citrin deficiency typically manifests with recurrent hyperammonemia, but neonates often present with intrahepatic cholestasis. (49)

Pancreatitis

Neonates with PA, MMA, isovaleric acidemia, and other organic acidemias are at risk for pancreatitis, especially during a metabolic crisis. Therefore, amylase and lipase should be checked in these patients with symptoms of pancreatitis such as vomiting. (6)(7)(50)

Hepatosplenomegaly

Neonates with various storage disorders (eg, GM1 gangliosidosis, I-cell disease, mucopolysaccharidosis type VII (Sly), or Niemann-Pick type A and C) can present with hepatosplenomegaly or splenomegaly. A storage disorder is more likely if there are additional findings such as fetal hydrops, ascites, coarse facial features, and skeletal abnormalities such as dysostosis multiplex. (2)

Failure to Thrive

Failure to thrive (FTT) is a nonspecific finding that can be present in multiple metabolic diseases as a result of different causes such as malabsorption (associated with exocrine pancreatic insufficiency, intestinal disaccharidase deficiencies), aminoaciduria (associated with renal Fanconi syndrome), or energy failure (found in mitochondrial diseases). Metabolic causes of FTT should be sought, especially if the patient has already been evaluated for more common causes or if there are other signs of a metabolic disorder (eg, acidosis, dysmorphic features, multisystem involvement).

Diarrhea

Diarrhea resulting from metabolic disorders can be related to deficient absorption such as rare intestinal disaccharidase deficiencies (congenital lactase deficiency or sucrase isomaltase deficiency). (51)(52) Protein-losing enteropathy in an infant with multisystem involvement (eg, cardiac, liver) can be a clue to congenital disorders of glycosylation. (53)(54)

RENAL

Hemolytic Uremic Syndrome

A metabolic etiology is not typically considered in cases of hemolytic uremic syndrome, which is well-described in patients with cobalamin synthesis pathway defects especially in cobalamin C defect. (55)(56)

Renal Fanconi Syndrome

Generalized aminoaciduria, glucosuria, and renal tubular acidosis can be seen in neonates with galactosemia, hereditary cystinosis, hereditary fructose intolerance, mitochondrial disorders, and Fanconi-Bickel syndrome (hepatorenal glycogenosis, glycogen storage disease type XI). (2)(57)

Renal Cysts

Multiple renal cysts or polycystic kidneys can be seen, even prenatally, in patients with peroxisomal disorders (eg, Zellweger syndrome), congenital disorders of glycosylation, carnitine palmitoyl transferase II deficiency, and some congenital disorders of glycosylation. (2)(58)(59)

SKELETAL

Stippled Epiphyses

Peroxisomal disorders are classic metabolic disorders associated with stippled epiphyses (chondrodysplasia punctata). These include peroxisomal biogenesis defects such as Zellweger syndrome as well as defects in peroxisomal enzymes such as rhizomelic chondrodysplasia punctata. (58)(60)(61) Of note, warfarin embryopathy can mimic some features of peroxisomal disorders, particularly structural defects such as stippled epiphyses. (62)

Orthopedic/Skeletal

Rhizomelic (proximal) shortening of limbs is typical of peroxisomal disorders. Multiple skeletal abnormalities (ie, dysostosis multiplex) such as thoracic deformity, kyphosis, hip dislocation, clubfeet, and deformed long bones can be

seen at birth in neonates with mucolipidosis type II (I-cell disease), GM1 gangliosidosis, or multiple sulfatase deficiency. (63)(64) A storage disorder should be considered in an infant with skeletal involvement, coarse features, and/or multisystem disease. Arthrogryposis multiplex congenita (ie, multiple congenital contractures) have been described in neonates with mitochondrial disorders (65) and storage disorders such as perinatal-lethal Gaucher disease. (66)

DERMATOLOGIC

Jaundice

Cholestatic liver disease can lead to jaundice (see gastrointestinal section).

Ichthyosis

Ichthyosiform or collodion skin changes are typical of the perinatal lethal form of Gaucher disease. A history of fetal hydrops, ascites, and hepatosplenomegaly in a critically ill newborn further supports this diagnosis. Congenital ichthyosis (often with congenital erythroderma) can also be seen in neonates with peroxisomal disorders, X-linked chondrodysplasia punctata, serine synthesis defects, steroid sulfatase deficiency, and multiple sulfatase deficiency. Of note, low maternal serum unconjugated estriol in prenatal screening can be an indication of X-linked ichthyosis in a male fetus. (67)(68)

DYSMORPHIC FEATURES

Dysmorphic facial features are common in many chromosomal and genetic syndromes. Neonates with metabolic disease can have coarse facial features, especially in severe forms of storage disorders such as multiple sulfatase deficiency, mucolipidosis type II (I-cell disease), infantile galactosialidosis, infantile sialidosis, GM1 gangliosidosis, and peroxisomal disorders (especially Zellweger syndrome). (2) Multisystem involvement is, again, typical of these conditions.

HEMATOLOGIC

Cytopenias

Anemia, thrombocytopenia, and neutropenia, in isolation or in combination (including pancytopenia), can occur in neonates with metabolic disorders. Cytopenia can be caused by a deficiency of a metabolite essential for cytopoiesis, bone marrow infiltration by storage material, hypersplenism, or bone marrow suppression during a metabolic crisis. Macrocytic anemia can be seen in inborn errors of cobalamin (B_{12}) or folate (folic acid) metabolism. Bone marrow infiltration and hypersplenism leading to anemia and often pancytopenia can occur in storage disorders such as Gaucher disease. Pancytopenia (often relatively mild and transient lasting a few weeks) can be found, especially in neonates with organic acidemias during and after an acute metabolic crisis and is well described in patients with MMA and PA. (6)(69)

Vacuolated Lymphocytes

Patients with diseases such as Pompe disease, mucolipidosis type II, mucopolysaccharidoses, and Niemann-Pick disease type I often have vacuolated lymphocytes that are seen on a blood smear. (2)

Coagulopathy

Any metabolic disorder that presents with liver failure typically also has an associated coagulopathy and can be caused by galactosemia and mitochondrial DNA depletion defects.

Hemophagocytic Lymphohistiocytosis

Several metabolic disorders have been described to cause a hemophagocytic lymphohistiocytosis/macrophage activation syndrome; these include LPI, multiple sulfatase deficiency, Gaucher disease, and galactosialidosis as well as some organic acidemias. (70)

ODORS

Some metabolic disorders have a classic distinctive odor in sweat, urine, or other body secretions because of the accumulating metabolite. The odor is typically stronger during a metabolic crisis or when a metabolic disorder is poorly controlled. Table 3 includes examples of typical odors that have been typically associated with metabolic disorders.

NEWBORN SCREENING

NBS, especially expanded NBS with tandem mass spectrometry, has made it possible to analyze multiple analytes simultaneously and detect several inborn errors of metabolism. Most organic acidemias, FAODs, and amino acidemias can be detected via NBS. To promote uniform and comprehensive NBS, the Department of Health and Human Services has a list of ~40 conditions called the Recommended Uniform Screening Panel (RUSP), which is periodically updated with new disorders. (3)(71)(72) It is recommended that all states screen for the conditions listed in the RUSP. However, although this list offers guidance, it is not enforced by law. Some states adopt new

TABLE 3. **Typical or Distinctive Odors Described in Metabolic Disorders**

ODOR	METABOLIC DISEASE
Maple syrup	Maple syrup urine disease
Boiled cabbage	Tyrosinemia Hypermethioninemia
Mousy, musty	Phenylketonuria
Sweaty feet	Isovaleric acidemia Glutaric acidemia type II
Rotting fish	Trimethylaminuria (odor only manifestation)
Cat urine	3-hydroxy-3-methylglutaric aciduria
Tomcat urine	Multiple carboxylase deficiency

recommendations early whereas others are still in the process of adopting them. Some states also screen for additional disorders not listed in the RUSP. This leads to slight heterogeneity of disorders screened for by each state. (73) The most recent additions to the RUSP (and adopted by many states) include Pompe disease, mucopolysaccharidosis type I (ie, Hurler syndrome), and X-linked adrenoleukodystrophy. Disorders are typically detected with either an elevated (upstream from the metabolic defect) or low (downstream from the metabolic defect) amount of analyte, or via enzyme activity. It is important to recognize that a normal NBS does not rule out a metabolic disorder because an infant's metabolite may have been above or below a cutoff value at the time the NBS was performed. Also, most metabolic disorders are not detected on NBS. Examples of disorders not detected via NBS include mitochondrial disorders, disorders of pyruvate metabolism, congenital disorders of glycosylation, and most storage diseases, as well as most conditions that cause neonatal seizures (Table 2), with some exceptions. Therefore, maintaining a high index of suspicion of an inborn error of metabolism is vital in any critically ill neonate.

MATERNAL METABOLIC DISORDERS AFFECTING THE FETUS OR NEONATE

Maternal metabolic disorders can affect the neonate because the maternal metabolite can be toxic and thus, teratogenic. Alternatively, high maternal amounts of the metabolite can be transferred across the placenta to the fetus and postnatally lead to a false-positive NBS.

Teratogenic Effect

Maternal uncontrolled phenylketonuria is a well-known cause of a metabolic disorder with adverse fetal effects. High maternal phenylalanine levels during pregnancy can lead to microcephaly, intellectual disability, congenital heart defects, esophageal atresia, and IUGR. The specific effects and extent of the impact depend on the magnitude and timing of high phenylalanine levels with the period of organogenesis (ie, first trimester) being the most sensitive for structural anomalies.

False-positive NBS Result

Two well-described maternal conditions that can cause a false-positive NBS result in a neonate are primary carnitine deficiency (carnitine transporter deficiency, low C0 on NBS) and 3-methylcrotonyl-coA-carboxylase deficiency (high C5-OH). If an infant has a positive NBS result for these conditions, it could be the result of a maternal condition.

WHOLE EXOME/GENOME SEQUENCING

A comprehensive review of WES and WGS is beyond the scope of this review; however, these diagnostic modalities have proven to be powerful tools in the rapid diagnosis of genetic and metabolic disorders in critically ill neonates and can provide a diagnosis in up to 30% to 50% of critically ill infants in the NICU. (74)(75)(76)(77)(78)(79)(80) Early diagnosis can guide clinical management and improve prognosis in cases for which a therapy is available or help direct care toward palliative care in cases with a poor prognosis.

SUMMARY

Metabolic disorders can present in various ways in a neonate, ranging from a subtle symptom or finding in 1 organ system to a severe multisystem presentation requiring immediate management. Early recognition of treatable conditions can improve mortality and morbidity in neonates affected by these conditions. Furthermore, a definitive diagnosis allows for genetic counseling about recurrence risk, which is important for early recognition of these conditions in future pregnancies or early in the neonatal period. Prenatal diagnosis can help plan for a delivery at a tertiary care center with expertise in metabolic disorders. Expanded NBS with more conditions added periodically, as well as WES and WGS, will continue to lead to earlier diagnoses of metabolic disorders in a neonate. A high index of suspicion and continuous medical education about the advancing knowledge of these conditions will help neonatologists detect

metabolic conditions early and initiate treatment in those conditions for which an effective therapy is available.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology, clinical manifestations, laboratory features, and management of infants with lysosomal, peroxisomal, and mitochondrial disorders.
- Know the causes and differential diagnosis of metabolic encephalopathy.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of carbohydrates.
- Know the clinical manifestations, laboratory features, and treatment of disorders of cholesterol synthesis.
- Know the clinical manifestations, laboratory features, and treatment of organic acid disorders.

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1. A 2-day-old male term infant presents with lethargy, poor feeding, and tachypnea. Laboratory evaluation reveals hyperammonemia and a respiratory alkalosis. Which of the following is most likely to be a potential diagnosis for this patient?

   A. Methylmalonic acidemia.
   B. Propionic acidemia.
   C. Ornithine transcarbamylase deficiency.
   D. Lactic acid dehydrogenase deficiency.
   E. X-linked hypophosphatemia.

2. A 3-day-old term male infant presents with seizures, vomiting, poor feedings, and hyperammonemia. He is diagnosed with methylmalonic acidemia. He is admitted to the NICU. Which of the following would be an appropriate part of initial therapy?

   A. Increase protein administration via both enteral and intravenous routes.
   B. Vitamin C loading and subsequently in 4-hour intervals given intravenously.
   C. Limit fluids to half maintenance to prevent renal overloading.
   D. Insulin administration if hyperglycemia develops.
   E. Therapeutic hypothermia for 24 hours during medical coma.

3. A 1-day-old female term neonate is noted to have seizures both clinically and then confirmed on electroencephalography. Which of the following characteristics would be most consistent with the cause of seizures being a metabolic disorder?

   A. History of a perinatal event such as acute maternal hemorrhage or cord entanglement.
   B. Persistent seizures without an intracranial abnormality.
   C. Seizures that started soon after delivery, with abnormal neurologic examination findings including hypotonia and lethargy at birth that gradually improved.
   D. No other organ involvement other than neurologic symptoms.
   E. Normal laboratory evaluation including blood gas, electrolytes, and ammonia level.

4. A 2-day-old female neonate presents with jaundice, emesis, and lethargy. Newborn screening result is positive for galactosemia. Which of the following ophthalmologic findings is seen in this condition?

   A. Cataracts.
   B. Glaucoma.
   C. Optic atrophy.
   D. Microphthalmia.
   E. Iris atrophy.

5. A neonate presents with jaundice, hepatomegaly, and *Escherichia coli* sepsis at 1 week of age. Which of the following metabolic disorders is most likely to present with *E coli* sepsis?

   A. Mitochondrial depletion syndrome.
   B. Pyruvate kinase deficiency.
   C. DNA-induced encephalopathy.
   D. Methylmalonic acidemia.
   E. Galactosemia.

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