Eighth Edition

Enhanced DIGITAL VERSION Included

Fenichel's Clinical Pediatric Neurology

A Signs and Symptoms Approach

J. Eric Piña-Garza
Kaitlin C. James

ELSEVIER

Expert CONSULT Built with inkling | E books

Any screen. Any time. Anywhere.

Activate the eBook version of this title at no additional charge.

Expert Consult eBooks give you the power to browse and find content, view enhanced images, share notes and highlights—both online and offline.

Unlock your eBook today.

1. Visit **expertconsult.inkling.com/redeem**
2. Scratch off your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign up
6. Go to "My Library"

It's that easy!

Scan this QR code to redeem your eBook through your mobile device:

Place Peel Off Sticker Here

For technical assistance:
email expertconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8200 (outside the US)

ELSEVIER

Fenichel's Clinical Pediatric Neurology

This page intentionally left blank

Eighth Edition

Fenichel's Clinical Pediatric Neurology

A Signs and Symptoms Approach

AUTHORS

J. Eric Piña-Garza, MD
Director, Pediatric Epilepsy
The Children's Hospital at TriStar Centennial
Nashville, TN, United States

Kaitlin C. James, MD
Assistant Professor, Pediatric Neurology
Director, Pediatric Epilepsy Monitoring Unit
Departments of Pediatrics and Neurology
Monroe Carell, Jr. Children's Hospital at Vanderbilt
Nashville, TN, United States

ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

FENICHEL'S CLINICAL PEDIATRIC NEUROLOGY, A SIGNS AND SYMPTOMS APPROACH, EIGHTH EDITION ISBN: 978-0-323-48528-9

Library of Congress Control Number: 2019940504

Content Strategist: Melanie Tucker
Content Development Specialist: Angie Breckon
Publishing Services Manager: Shereen Jameel
Project Manager: Rukmani Krishnan
Design Direction: Ryan Cook

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

For our children.

This page intentionally left blank

This page intentionally left blank

1

Paroxysmal Disorders

OUTLINE

Paroxysmal neurological disorders are characterized by the sudden onset of neurological dysfunction and stereotyped recurrence. In children, such events often clear completely. Examples of paroxysmal disorders include epilepsy, migraine, periodic paralysis, and paroxysmal movement disorders.

APPROACH TO PAROXYSMAL DISORDERS

The diagnosing physician rarely witnesses the paroxysmal event. It is important to obtain the description of the event from the observer or a video recording and not second hand. The information easily becomes distorted if transferred from the observer to the parent and then to you. Most "spells" are not seizures, and epilepsy is not a diagnosis of exclusion. Physicians often misdiagnose syncope as a seizure, as many people stiffen and tremble at the end of a faint. The critical distinction is that syncope is associated with pallor and preceded by dimming of vision, and a feeling of lightheadedness or clamminess, whereas seizures are rarely preceded by these things. Also, the patient with syncope has a fast recovery of consciousness and coherence if allowed to remain supine postictal.

Spells seldom remain unexplained when viewed. Because observation of the spell is critical to diagnosis, ask the family to record the spell. Most families either own or can borrow a camera or a cell phone with video capability. Even when a purchase is required, a video is often more cost effective than brain imaging, and the family has something useful to show for the expenditure. Always ask the following two

questions: Has this happened before? Does anyone else in the family have similar episodes? Often, no one offers this important information until requested. Episodic symptoms that last only seconds and cause no abnormal signs usually remain unexplained and do not warrant laboratory investigation. The differential diagnosis of paroxysmal disorders is somewhat different in the neonate, infant, child, and adolescent, and is therefore presented best by age groups.

PAROXYSMAL NEUROLOGICAL DISORDERS OF NEWBORNS

Seizures are the main paroxysmal disorder of the newborn, occurring in 1.8%–3.5% of live births in the United States, and an important feature of neurological disease.[1] Uncontrolled seizures may contribute to further brain damage. Brain glucose decreases during prolonged seizures and excitatory amino acid release interferes with DNA synthesis. Therefore, seizures identified by electroencephalography (EEG) that occur without movement in newborns are important to identify and treat. The challenge for the clinician is to differentiate seizure activity from normal neonatal movements and from pathological movements caused by other mechanisms (Box 1.1).

The long-term prognosis in children with neonatal seizures is better in term newborns than in premature newborns.[2] However, the etiology of the seizures is the primary determinant of prognosis.

Seizure Patterns

Seizures in newborns, especially in the premature, are poorly organized and difficult to distinguish from normal activity. Newborns with hydranencephaly or atelencephaly are capable of generating the full variety of neonatal seizure patterns, which supports the notion that seizures may arise from the brainstem in such cases. The absence of myelinated pathways for seizure propagation may confine seizures originating in one hemisphere and make them less likely to spread beyond the contiguous cortex or to produce secondary bilateral synchrony.

BOX 1.1 Movements That Resemble Neonatal Seizures

- Benign nocturnal myoclonus[a]
- Jitteriness[a]
- Nonconvulsive apnea
- Normal movement
- Opisthotonos
- Pathological myoclonus

[a]Denotes the most common conditions and the ones with disease-modifying treatments

BOX 1.2 Seizure Patterns in Newborns

- Apnea with tonic stiffening of body
- Focal clonic movements of one limb or both limbs on one side[a]
- Multifocal clonic limb movements[a]
- Myoclonic jerking
- Paroxysmal laughing
- Tonic deviation of the eyes upward or to one side[a]
- Tonic stiffening of the body

[a]Denotes the most common conditions and the ones with disease-modifying treatments

Box 1.2 lists clinical patterns that have been associated with epileptiform discharges in newborns. This classification is useful but does not do justice to the rich variety of patterns actually observed, nor does the classification account for the 50% of prolonged epileptiform discharges on the EEG without visible clinical changes. Generalized tonic-clonic seizures rarely occur. Many newborns suspected of having generalized tonic-clonic seizures are actually *jittery* (see Jitteriness, discussed later in this chapter). Newborns paralyzed to assist mechanical ventilation pose an additional problem in seizure identification. In this circumstance, the presence of rhythmic increases in systolic arterial blood pressure, heart rate, and oxygenation desaturation should alert physicians to the possibility of seizures.

The term *subtle seizures* encompasses several different patterns in which tonic or clonic movements of the limbs are lacking, for example tonic deviation of the eyes. One of the most common manifestations of seizures in the young infant is behavioral arrest and unresponsiveness. Behavioral arrest is only obvious when the child is very active, which is not common in a sick neonate and therefore often goes unnoticed.

The definitive diagnosis of neonatal seizures often requires EEG monitoring. A split-screen 16-channel video EEG is the ideal means for monitoring. An aEEG (amplitude integrated EEG) is also a useful monitoring technique. Seizures in the newborn may be widespread and electrographically detectable even when the newborn is not convulsing clinically.

Focal Clonic Seizures

Clinical features. Repeated, irregular slow clonic movements (1–3 jerks/second) affecting one limb or both limbs on one side are characteristic of focal clonic seizures. Rarely do such movements sustain for long periods, and

they do not "march" as though spreading along the motor cortex. In an otherwise alert and responsive full-term newborn, unifocal clonic seizures always indicate a cerebral infarction or hemorrhage, or focal brain dysgenesis. In newborns with states of decreased consciousness, focal clonic seizures may indicate a focal infarction superimposed on a generalized encephalopathy.

Diagnosis. During the seizure, the EEG may show a unilateral focus of high-amplitude sharp waves adjacent to the central fissure. The discharge can spread to involve contiguous areas in the same hemisphere and can be associated with unilateral seizures of the limbs and adverse movements of the head and eyes. The interictal EEG may show focal slowing, sharp waves, or amplitude attenuation.

Newborns with focal clonic seizures should be immediately evaluated using magnetic resonance imaging (MRI) with diffusion-weighted images. Computed tomography (CT) or ultrasound is acceptable for less stable neonates unable to make the trip to the MRI suite or tolerate the time needed for this procedure.

Multifocal Clonic Seizures

Clinical features. In multifocal clonic seizures, migratory jerking movements are noted in first one limb and then another. Facial muscles may be involved as well. The migration appears random and does not follow expected patterns of epileptic spread. Sometimes prolonged movements occur in one limb suggesting a focal rather than a multifocal seizure. Detection of the multifocal nature comes later, when nursing notes appear contradictory concerning the side or the limb affected. Multifocal clonic seizures are ordinarily associated with severe, generalized cerebral disturbances such as hypoxic-ischemic encephalopathy, but may also represent benign neonatal convulsions when noted in an otherwise healthy neonate.

Diagnosis. Standard EEG usually detects multifocal epileptiform activity. Twenty-four hour video-EEG monitoring is the best diagnostic test to confirm diagnosis.

Myoclonic Seizures

Clinical features. Brief, nonrhythmic extension and flexion movements of the arms, the legs, or all limbs characterize myoclonic seizures. They constitute an uncommon seizure pattern in the newborn, but their presence suggests severe, diffuse brain damage.

Diagnosis. No specific EEG pattern is associated with myoclonic seizures in the newborn. Myoclonic jerks often occur in babies born to drug-addicted mothers. Whether these movements are seizures, jitteriness, or myoclonus (discussed later) is uncertain. Myoclonus noticed in an otherwise normal newborn may be a normal involuntary motion (benign myoclonus of drowsiness).

Tonic Seizures

Clinical features. The characteristic features of tonic seizures are extension and stiffening of the body, usually associated with apnea and upward deviation of the eyes. Tonic posturing without the other features is rarely a seizure manifestation.

Diagnosis. Tonic seizures in premature newborns are often a symptom of intraventricular hemorrhage and an indication for ultrasound study. Tonic posturing also occurs in newborns with forebrain damage, not as a seizure manifestation, but as a disinhibition of brainstem reflexes. Prolonged disinhibition results in *decerebrate posturing,* an extension of the body and limbs associated with internal rotation of the arms, dilation of the pupils, and downward deviation of the eyes. Decerebrate posturing is often a terminal sign in premature infants with intraventricular hemorrhage caused by pressure on the upper brainstem (see Chapter 4).

Tonic seizures and decerebrate posturing look similar to *opisthotonos,* a prolonged arching of the back not necessarily associated with eye movements. The cause of opisthotonos is probably meningeal irritation. It occurs in kernicterus, infantile Gaucher disease, and some aminoacidurias.

Seizure-Like Events

Apnea

Clinical features. An irregular respiratory pattern with intermittent pauses of 3–6 seconds, often followed by 10–15 seconds of hyperpnea, is a common occurrence in premature infants. The pauses are not associated with significant alterations in heart rate, blood pressure, body temperature, or skin color. Immaturity of the brainstem respiratory centers causes this respiratory pattern, termed *periodic breathing*. The incidence of periodic breathing correlates directly with the degree of prematurity. Apneic spells are more common during active than quiet sleep.

Apneic spells of 10–15 seconds are detectable at some time in almost all premature and some full-term newborns. Apneic spells of 10–20 seconds are usually associated with a 20% reduction in heart rate. Longer episodes of apnea are almost invariably associated with a 40% or greater reduction in heart rate. The frequency of these apneic spells correlates with brainstem myelination. Even at 40 weeks conceptional age, premature newborns continue to have a higher incidence of apnea than do full-term newborns. The incidence of apnea sharply decreases in all infants at 52 weeks conceptional age. Apnea with bradycardia is unlikely to be a seizure. Apnea with tachycardia raises the possibility of seizure and should be evaluated with simultaneous video EEG recording.

Diagnosis. Apneic spells in an otherwise normal-appearing newborn is typically a sign of brainstem immaturity and not a pathological condition. The sudden onset of apnea and states of decreased consciousness, especially in premature newborns, suggests an intracranial hemorrhage with brainstem compression. Immediate ultrasound examination is in order.

Apneic spells are almost never a seizure manifestation unless associated with tonic deviation of the eyes, tonic stiffening of the body, or characteristic limb movements. However, prolonged apnea without bradycardia, and especially with tachycardia, is a seizure until proven otherwise.

Management. Short episodes of apnea do not require intervention. The rare epileptic apnea requires the use of anticonvulsant agents.

Benign Nocturnal Myoclonus

Clinical features. Sudden jerking movements of the limbs during sleep occur in normal people of all ages (see Chapter 14). They appear primarily during the early stages of sleep as repeated flexion movements of the fingers, wrists, and elbows. The jerks do not localize consistently, stop with gentle restraint, and end abruptly with arousal. When prolonged, the usual misdiagnosis is focal clonic or myoclonic seizures.

Diagnosis. The distinction between nocturnal myoclonus and seizures or jitteriness is that benign nocturnal myoclonus occurs solely during sleep, is not activated by a stimulus, and the EEG is normal.

Management. Treatment is unnecessary, and education and reassurance are usually sufficient. Rarely, a child with violent myoclonus experiences frequent arousals disruptive to sleep, and a small dose of clonazepam may be considered. Videos of children with this benign condition are very reassuring for the family to see and are available on the internet.

Jitteriness

Clinical features. Jitteriness or tremulousness is an excessive response to stimulation. Touch, noise, or motion provokes a low-amplitude, high-frequency shaking of the limbs and jaw. Jitteriness is commonly associated with a low threshold for the Moro reflex, but it can occur in the absence of any apparent stimulation and be confused with myoclonic seizures.

Diagnosis. Jitteriness usually occurs in newborns with perinatal asphyxia, along with the occurrence of seizures. EEG monitoring, the absence of eye movements or alteration in respiratory pattern, and the presence of stimulus activation distinguishes jitteriness from seizures. Newborns of addicted mothers and newborns with metabolic disorders are often jittery.

Management. Reduced stimulation decreases jitteriness. However, newborns of addicted mothers require sedation to facilitate feeding and to decrease energy expenditure.

Hyperekplexia

Clinical features. Hyperekplexia is a potentially treatable condition characterized by exaggerated startle to tactile or auditory stimulation. It is often associated with frequent falls when ambulatory, and hypertonia more than normal or low muscle tone. Seven to 12% of these newborns may have seizures. Apnea and developmental problems are frequent comorbidities. Three genes have been identified with this phenotype and all three affect the glycinergic neurotransmission.[3]

Diagnosis. The diagnosis is made based on the phenotype. Gene positive cases present at birth, but about 50% of the cases without known genetic etiology present after the first month of life.

Management. Clonazepam is effective in most cases.

Differential Diagnosis of Seizures

Seizures are a feature of almost all brain disorders in the newborn. The time of onset of the first seizure indicates the probable cause (Box 1.3). Seizures occurring during the first 24 hours, and especially in the first 12 hours, are usually due to hypoxic-ischemic encephalopathy. Sepsis, meningitis, and subarachnoid hemorrhage (SAH) are next in frequency, followed by intrauterine infection, and trauma. Direct drug effects, intraventricular hemorrhage at term, and pyridoxine and folinic acid dependency are relatively rare causes of seizures, but important to consider as they are treatable conditions.

The more common causes of seizures during the period from 24–72 hours after birth are intraventricular hemorrhage in premature newborns, SAH, cerebral contusion in large full-term newborns, and sepsis and meningitis at all gestational ages. The cause of unifocal clonic seizures in full-term newborns is often cerebral infarction or intracerebral hemorrhage. MRI with diffusion weighted images is diagnostic. Cerebral dysgenesis may cause seizures in neonates and remains an important cause of seizures throughout infancy and childhood. All other conditions are relatively rare. Newborns with metabolic disorders are usually lethargic and feed poorly before the onset of seizures. Seizures are rarely the first clinical feature. After 72 hours, the initiation of protein and glucose feedings makes inborn errors of metabolism, especially aminoaciduria, a more important consideration. Box 1.4 outlines a battery of screening tests for metabolic disorders. Transmission of herpes simplex infection occurs during delivery and symptoms begin during the second half of the first

BOX 1.3 Differential Diagnosis of Neonatal Seizures by Peak Time of Onset

24 Hours
- Bacterial meningitis and sepsis[a] (see Chapter 4)
- Direct drug effect
- Hypoxic-ischemic encephalopathy[a]
- Intrauterine infection (see Chapter 5)
- Intraventricular hemorrhage at term[a] (see Chapter 4)
- Laceration of tentorium or falx
- Pyridoxine dependency[a]
- Subarachnoid hemorrhage[a]

24 to 72 Hours
- Bacterial meningitis and sepsis[a] (see Chapter 4)
- Cerebral contusion with subdural hemorrhage
- Cerebral dysgenesis[a] (see Chapter 18)
- Cerebral infarction[a] (see Chapter 11)
- Drug withdrawal
- Glycine encephalopathy
- Glycogen synthase deficiency
- Hypoparathyroidism-hypocalcemia
- Idiopathic cerebral venous thrombosis
- Incontinentia pigmenti
- Intracerebral hemorrhage (see Chapter 11)
- Intraventricular hemorrhage in premature newborns[a] (see Chapter 4)
- Pyridoxine dependency[a]
- Subarachnoid hemorrhage
- Tuberous sclerosis
- Urea cycle disturbances

72 Hours to 1 Week
- Cerebral dysgenesis (see Chapter 18)
- Cerebral infarction[a] (see Chapter 11)
- Familial neonatal seizures
- Hypoparathyroidism
- Idiopathic cerebral venous thrombosis[a]
- Intracerebral hemorrhage (see Chapter 11)
- Kernicterus
- Methylmalonic acidemia
- Nutritional hypocalcemia[a]
- Propionic acidemia
- Tuberous sclerosis
- Urea cycle disturbances

1 to 4 Weeks
- Adrenoleukodystrophy, neonatal (see Chapter 6)
- Cerebral dysgenesis (see Chapter 18)
- Fructose dysmetabolism
- Gaucher disease type 2 (see Chapter 5)
- GM_1 gangliosidosis type 1 (see Chapter 5)
- Herpes simplex encephalitis[a]
- Idiopathic cerebral venous thrombosis[a]
- Ketotic hyperglycinemias
- Maple syrup urine disease, neonatal[a]
- Tuberous sclerosis
- Urea cycle disturbances

[a]Denotes the most common conditions and the ones with disease-modifying treatments

BOX 1.4 Screening for Inborn Errors of Metabolism That Cause Neonatal Seizures

Blood Glucose Low
- Fructose 1,6-diphosphatase deficiency
- Glycogen storage disease type 1
- Maple syrup urine disease

Blood Calcium Low
- Hypoparathyroidism
- Maternal hyperparathyroidism

Blood Ammonia High
- Argininosuccinic acidemia
- Carbamyl phosphate synthetase deficiency
- Citrullinemia
- Methylmalonic acidemia (may be normal)
- Multiple carboxylase deficiency
- Ornithine transcarbamylase deficiency
- Propionic acidemia (may be normal)

Blood Lactate High
- Fructose 1,6-diphosphatase deficiency
- Glycogen storage disease type 1
- Mitochondrial disorders
- Multiple carboxylase deficiency

Metabolic Acidosis
- Fructose 1,6-diphosphatase deficiency
- Glycogen storage disease type 1
- Maple syrup urine disease
- Methylmalonic acidemia
- Multiple carboxylase deficiency
- Propionic acidemia

week. Conditions that cause early and late seizures include cerebral dysgenesis, cerebral infarction, intracerebral hemorrhage, and familial/genetic neonatal seizures.

Aminoacidopathy

Maple syrup urine disease. An almost complete absence (less than 2% of normal) of branched-chain keto-acid dehydrogenase (BCKD) causes the neonatal form of maple syrup urine disease (MSUD). BCKD is composed of six subunits, but the main abnormality in MSUD is deficiency of the E1 subunit on chromosome 19q13.1–q13.2. Leucine, isoleucine, and valine cannot be decarboxylated, and accumulate in blood, urine, and tissues (Fig. 1.1). See Chapters 5 and 10 for descriptions of later-onset forms. Transmission of the defect is by autosomal recessive inheritance.[4]

Clinical features. Affected newborns appear healthy at birth but lethargy, feeding difficulty, and hypotonia develop after ingestion of protein. A progressive encephalopathy develops by 2–3 days postpartum. The encephalopathy includes lethargy, intermittent apnea, opisthotonos, and stereotyped movements such as "fencing" and "bicycling." Coma and central respiratory failure may occur by 7–10 days of age. Seizures begin in the second week and are associated with the development of cerebral edema. Once seizures begin, they continue with increasing frequency and severity. Without therapy, cerebral edema becomes progressively worse and results in coma and death within 1 month.

Diagnosis. Plasma amino acid concentrations show increased plasma concentrations of the three branch-chained amino acids. Measures of enzyme in lymphocytes or cultured fibroblasts serve as a confirmatory test. Heterozygotes have diminished levels of enzyme activity.

Management. Hemodialysis may be necessary to correct the life-threatening metabolic acidosis. A trial of thiamine (10–20 mg/kg/day) improves the condition in a *thiamine-responsive MSUD variant*. Stop the intake of all-natural protein, and correct dehydration, electrolyte imbalance, and metabolic acidosis. A special diet, low in branched-chain amino acids, may prevent further encephalopathy if started immediately by nasogastric tube. Newborns diagnosed in the first 2 weeks and treated rigorously have the best prognosis.

Glycine encephalopathy. A defect in the glycine cleaving system causes glycine encephalopathy (nonketotic hyperglycinemia). Inheritance is autosomal recessive.[5]

Clinical features. Affected newborns are normal at birth but become irritable and refuse feeding anytime from 6 hours to 8 days after delivery. The onset of symptoms is usually within 48 hours, but delays by a few weeks occur in milder allelic forms. *Hiccupping* is an early and continuous feature; some mothers relate that the child hiccupped in utero as a prominent symptom. Progressive lethargy, hypotonia, respiratory disturbances, and myoclonic seizures follow. Some newborns survive the acute illness, but cognitive impairment, epilepsy, and spasticity characterize the subsequent course.

In milder forms, the onset of seizures occurs after the neonatal period. The developmental outcome is better, but does not exceed moderate cognitive impairment.

Diagnosis. During the acute encephalopathy, the EEG demonstrates a burst-suppression pattern, which evolves into hypsarrhythmia during infancy. The MRI may be normal or may show agenesis or thinning of the corpus callosum. Delayed myelination and atrophy are later findings. Hyperglycinemia and especially elevated concentrations of glycine in the cerebrospinal fluid (CSF) in the absence

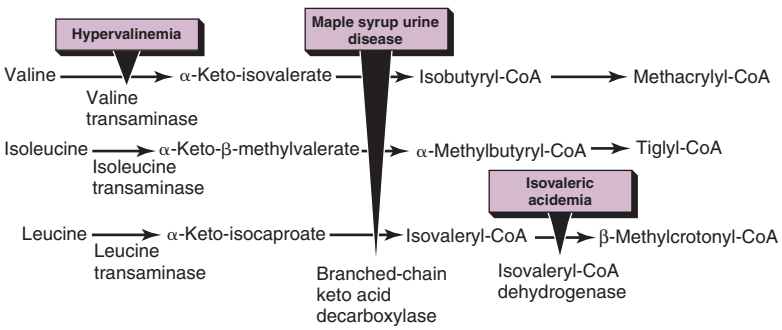

Fig. 1.1 Branched-chain Amino Acid Metabolism. 1. Transaminase system; 2. branched-chain α-ketoacid dehydrogenase; 3. isovaleryl-CoA dehydrogenase; 4. α-methyl branched-chain acyl-CoA dehydrogenase; 5. propionyl-CoA carboxylase (biotin cofactor); 6. methylmalonyl-CoA racemase; 7. methylmalonyl-CoA mutase (adenosylcobalamin cofactor).

of hyperammonemia, organic acidemia, or valproic acid treatment establishes the diagnosis.

Management. No therapy has proven to be effective. Hemodialysis provides only temporary relief of the encephalopathy, and diet therapy has not been successful in modifying the course. Diazepam, a competitor for glycine receptors, in combination with choline, folic acid, and sodium benzoate, may stop the seizures. Oral administration of sodium benzoate at doses of 250–750 mg/kg/day can reduce the plasma glycine concentration into the normal range. This substantially reduces but does not normalize CSF glycine concentration. Carnitine 100 mg/kg/day may increase the glycine conjugation with benzoate. It has been reported that dextromethorphan 5–35 mg/kg/day divided into four doses is helpful in lowering levels of glycine.[6]

Urea cycle disturbances. Carbamoyl phosphate synthetase (CPS) deficiency, ornithine transcarbamylase (OTC) deficiency, citrullinemia, argininosuccinic acidemia, and argininemia (arginase deficiency) are the disorders caused by defects in the enzyme systems responsible for urea synthesis. A similar syndrome results from deficiency of the cofactor producer N-acetylglutamate synthetase (NAGS). Arginase deficiency does not cause symptoms in the newborn. OTC deficiency is an X-linked trait; transmission of all others is by autosomal recessive inheritance.[7] The estimated prevalence of all urea cycle disturbances is 1:30,000 live births.

Clinical features. The clinical features of urea cycle disorders are due to ammonia intoxication (Box 1.5). Progressive lethargy, vomiting, and hypotonia develop as early as the first day after delivery, even before the initiation of protein feeding. Progressive loss of consciousness and seizures follow on subsequent days. Vomiting and lethargy correlate well with plasma ammonia concentrations greater than 200 μg/dL (120 μmol/L). Coma correlates with concentrations greater than 300 μg/dL (180 μmol/L) and seizures with those greater than 500 μg/dL (300 μmol/L). Death follows quickly in untreated newborns. Newborns with partial deficiency of CPS and female carriers of OTC deficiency may become symptomatic after ingesting a large protein load.

BOX 1.5 Causes of Neonatal Hyperammonemia

- Liver failure
- Primary enzyme defects in urea synthesis
  - Argininosuccinic acidemia
  - Carbamyl phosphate synthetase deficiency
  - Citrullinemia
  - Ornithine transcarbamylase deficiency
- Other disorders of amino acid metabolism
  - Glycine encephalopathy
  - Isovaleric acidemia
  - Methylmalonic acidemia
  - Multiple carboxylase deficiency
  - Propionic acidemia
- Transitory hyperammonemia of prematurity

Diagnosis. Suspect the diagnosis of a urea cycle disturbance in every newborn with a compatible clinical syndrome and hyperammonemia without organic acidemia. Hyperammonemia can be life threatening, and diagnosis within 24 hours is essential. Determine the blood ammonia concentration and the plasma acid–base status. A plasma ammonia concentration of 150 mmol/L strongly suggests a urea cycle disorder. Quantitative plasma amino acid analysis helps differentiate the specific urea cycle disorder. Molecular genetic testing is available for some disorders, but others still require liver biopsy to determine the level of enzyme activity. The most common cause of hyperammonemia is difficult phlebotomy with improper sample processing. Accurate serum ammonia testing requires a good phlebotomist, sample placement on ice, and rapid processing.

Management. Treatment cannot await specific diagnosis in newborns with symptomatic hyperammonemia due to urea cycle disorders. The treatment measures include reduction of plasma ammonia concentration by limiting nitrogen intake to 1.2–2.0 g/kg/day and using essential amino acids for protein; allowing alternative pathway excretion of excess nitrogen with sodium benzoate and phenylacetic acid; reducing the amount of nitrogen in the diet; and reducing catabolism by introducing calories supplied by carbohydrates and fat. Arginine concentrations are low in all inborn errors of urea synthesis except for arginase deficiency and require supplementation.

Even with optimal supervision, episodes of hyperammonemia may occur and may lead to coma and death. In such cases, intravenous (IV) administration of sodium benzoate, sodium phenylacetate, and arginine, coupled with nitrogen-free alimentation, are appropriate. If response to drug therapy is poor, then peritoneal dialysis or hemodialysis is indicated.

Benign Familial Neonatal Seizures

This condition should be suspected in neonates or infants with multifocal brief motor seizures and otherwise normal function, especially when a family history of similar events is present. This is associated with mutations that affect the potassium or the sodium channels. The mutation is located on the gene *KCNQ2* (locus 20q13.3) found in 50% of cases, *KCNQ3* (locus 8q24) found in 7% of cases, and *SCN2A* (locus 2q23-q24.3).[8,9]

Clinical features. Brief multifocal clonic seizures develop during the first week, sometimes associated with apnea. Delay of onset may be as long as 4 weeks. With or without treatment, the seizures usually stop spontaneously within the first months of life. Febrile seizures occur in up to one-third of affected children; some have febrile seizures without first having neonatal seizures. Epilepsy develops later in life in as many as one-third of affected newborns. The seizure types include nocturnal generalized tonic-clonic seizures and simple focal orofacial seizures.

Diagnosis. Suspect the syndrome when seizures develop without apparent cause in a healthy newborn. Laboratory tests are normal. The EEG often demonstrates multifocal epileptiform discharges and may be normal interictally. A family history of neonatal seizures is critical to diagnosis but may await discovery until interviewing the grandparents; parents are frequently unaware that they had neonatal seizures. The detection of one of these mutations found in more than 60% of this phenotype may abbreviate further diagnostic testing and be of some reassurance as most cases are benign; however, poor outcomes have been described. Predictive testing in siblings or children of affected family members would not change management.[8,9]

Management. Treat with anticonvulsants. Oxcarbazepine at doses of 20 mg/kg/day for a couple of days and titrated to 40 mg/kg/day can be helpful. The duration of treatment needed is unclear. We often treat infants for about 9 months, after which we discontinue treatment if the child remains seizure-free and the EEG has normalized. In my experience levetiracetam is often ineffective in this condition.

Bilirubin Encephalopathy

Unconjugated bilirubin is bound to albumin in the blood. *Kernicterus,* a yellow discoloration of the brain that is especially severe in the basal ganglia and hippocampus, occurs when the serum unbound or free fraction becomes excessive. An excessive level of the free fraction in an otherwise healthy newborn is approximately 20 mg/dL (340 μmol/L). Kernicterus was an important complication of hemolytic disease from maternal–fetal blood group incompatibility, but this condition is now almost unheard of in most countries. The management of other causes of hyperbilirubinemia in full-term newborns is not difficult. Critically ill premature infants with respiratory distress syndrome, acidosis, and sepsis are the group at greatest risk. In such newborns, lower concentrations of bilirubin may be sufficient to cause bilirubin encephalopathy, and even the albumin-bound fraction may pass the blood–brain barrier.

Clinical features. Three distinct clinical phases of bilirubin encephalopathy occur in full-term newborns with untreated hemolytic disease. Hypotonia, lethargy, and a poor sucking reflex occur within 24 hours of delivery. Bilirubin staining of the brain is already evident in newborns during this first clinical phase. On the second or third day, the newborn becomes febrile and shows increasing tone and opisthotonic posturing. Seizures are not a constant feature but may occur at this time. Characteristic of the third phase is apparent improvement with normalization of tone. This may cause second thoughts about the accuracy of the diagnosis, but the improvement is short-lived. Evidence of neurological dysfunction begins to appear toward the end of the second month, and the symptoms become progressively worse throughout infancy.

In premature newborns, the clinical features are subtle and may lack the phases of increased tone and opisthotonos.

The typical clinical syndrome after the first year includes extrapyramidal dysfunction, usually athetosis, which occurs in virtually every case; disturbances of vertical gaze, upward more often than downward in 90%; high-frequency hearing loss in 60%; and mental retardation in 25%. Survivors often develop a choreoathetoid form of cerebral palsy.

Diagnosis. In newborns with hemolytic disease, the basis for a presumed clinical diagnosis is a significant hyperbilirubinemia and a compatible evolution of symptoms. However, the diagnosis is difficult to establish in critically ill premature newborns, in whom the cause of brain damage is more often asphyxia than kernicterus. The MRI may show the targeted areas in the basal ganglia.

Management. Maintaining serum bilirubin concentrations below the toxic range, either by phototherapy or exchange transfusion, prevents kernicterus. Once kernicterus has occurred, further damage can be limited, but not reversed, by lowering serum bilirubin concentrations. Diazepam and baclofen are often needed for management of dystonic postures associated with the cerebral palsy.

Drug Withdrawal

Marijuana, cocaine, alcohol, narcotic analgesics (hydrocodone and oxycodone), hypnotic sedatives (lorazepam, alprazolam), and central nervous system (CNS) stimulants (amphetamine or methylphenidate) are the nonprescribed drugs most commonly used during pregnancy. Marijuana and alcohol do not cause drug dependence in the fetus and are not associated with withdrawal symptoms, although ethanol can cause fetal alcohol syndrome. Hypnotic sedatives, such as barbiturates, do not ordinarily produce withdrawal symptoms unless the ingested doses are very large. Phenobarbital has a sufficiently long half-life in newborns that sudden withdrawal does not occur. The prototype of narcotic withdrawal in the newborn is with heroin or methadone, but a similar syndrome occurs with

codeine and propoxyphene. Cocaine and methamphetamine also cause significant withdrawal syndromes.

Similar symptoms are common with the use of prescribed drugs in pregnancy such as selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, sertraline, citalopram, escitalopram, and paroxetine. Symptoms may include continuous crying, irritability, jitteriness, feeding difficulties, fever, tachypnea, hypoglycemia, and seizures. The onset of symptoms is between hours and days and may last 2–4 weeks. It is not clear if this represents a serotonin syndrome or withdrawal from SSRIs. For this reason, some suggest the term *serotonin discontinuation syndrome* or *prenatal SSRI exposure syndrome*. Some infants benefit from a short-term course of chlorpromazine.[10]

Clinical features. Symptoms of opiate withdrawal are more severe and tend to occur earlier in full-term (first 24 hours) than in premature (24–48 hours) newborns. The initial feature is jitteriness, present only during the waking state, which can shake an entire limb. Irritability, a shrill, high-pitched cry, and hyperactivity follow. The newborn seems hungry, but has difficulty feeding and vomits afterward. Diarrhea and other symptoms of autonomic instability are common.

Myoclonic jerking is present in 10%–25% of newborns undergoing withdrawal. Whether these movements are seizures or jitteriness is not clear. Definite seizures occur in fewer than 5%. Maternal use of cocaine during pregnancy is associated with premature delivery, growth retardation, and microcephaly. Newborns exposed to cocaine, in utero or after delivery through the breast milk, often show features of cocaine intoxication including tachycardia, tachypnea, hypertension, irritability, and tremulousness.

Diagnosis. Suspect and anticipate drug withdrawal in every newborn whose mother has a history of substance abuse. Even when such a history is not available, the combination of jitteriness, irritability, hyperactivity, and autonomic instability should provide a clue to the diagnosis. Careful questioning of the mother concerning her use of prescription and nonprescription drugs is imperative. Blood, urine, and meconium analyses identify specific drugs.

Management. Symptoms remit spontaneously in 3–5 days, but appreciable mortality occurs among untreated newborns. Benzodiazepines or chlorpromazine 3 mg/kg/day may relieve symptoms and reduce mortality. Secretion of morphine, meperidine, opium, and methadone in breast milk is insufficient to cause or relieve addiction in the newborn. The following medications and doses may be used for narcotic withdrawal: oral morphine 0.04 mg/kg every 3–4 hours, oral methadone 0.05–0.1 mg/kg every 6 hours, or oral clonidine 0.5–1 μg/kg every 3–6 hours.[10] Levetiracetam 40 mg/kg/day is a good option for seizures.

The occurrence of seizures in itself does not indicate a poor prognosis. The long-term outcome relates more closely to the other risk factors associated with substance abuse in the mother.

Hypocalcemia

The definition of hypocalcemia is a blood calcium concentration less than 7 mg/dL (1.75 mmol/L). The onset of hypocalcemia in the first 72 hours after delivery is associated with low birth weight, asphyxia, maternal diabetes, transitory neonatal hypoparathyroidism, maternal hyperparathyroidism, and the DiGeorge syndrome (DGS). Later-onset hypocalcemia occurs in children fed improper formulas, in maternal hyperparathyroidism, and in DGS.

Hypoparathyroidism in the newborn may result from maternal hyperparathyroidism, or it may be a transitory phenomenon of unknown cause. Hypocalcemia occurs in less than 10% of stressed newborns and enhances their vulnerability to seizures, but it is rarely the primary cause.

DGS is associated with microdeletions of chromosome 22q11.2.[11] Disturbance of cervical neural crest migration into the derivatives of the pharyngeal arches and pouches explains the phenotype. Organs derived from the third and fourth pharyngeal pouches (thymus, parathyroid gland, and great vessels) are hypoplastic.

Clinical features. The 22q11.2 syndrome encompasses several similar phenotypes: DGS, *velocardiofacial syndrome* (VCFS), and Shprintzen syndrome. The acronym CATCH is used to describe the phenotype of cardiac abnormality, T-cell deficit, clefting (multiple minor facial anomalies), and hypocalcemia.[12] The identification of most children with DGS is in the neonatal period with a major heart defect, hypocalcemia, and immunodeficiency. Diagnosis of children with VCFS comes later because of cleft palate or craniofacial deformities.

The initial symptoms of DGS may be due to congenital heart disease, hypocalcemia, or both. Jitteriness and tetany usually begin in the first 48 hours after delivery. The peak onset of seizures is on the third day, but a 2-week delay may occur. Many affected newborns die of cardiac causes during the first month; survivors fail to thrive and have frequent infections secondary to the failure of cell-mediated immunity.

Diagnosis. Newborns with DGS come to medical attention because of seizures and heart disease. Seizures or a prolonged Q-T interval brings attention to hypocalcemia. Molecular genetic testing confirms the diagnosis.

Management. Management requires a multispecialty team including cardiology, immunology, medical genetics, and neurology. Plastic surgery, dentistry, and child development contribute later on. Hypocalcemia generally responds to parathyroid hormone or to oral calcium and vitamin D.

Hypoglycemia

A transitory, asymptomatic hypoglycemia is detectable in 10% of newborns during the first hours after delivery and before initiating feeding. Asymptomatic, transient hypoglycemia is not associated with neurological impairment later in life. Symptomatic hypoglycemia may result from stress or inborn errors of metabolism (Box 1.6).

Clinical features. The time of onset of symptoms depends upon the underlying disorder. Early onset is generally associated with perinatal asphyxia, maternal diabetes, intracranial hemorrhage, and late onset with inborn errors of metabolism. Hypoglycemia is rare and mild among newborns with classic MSUD, ethylmalonic-adipic aciduria, and isovaleric acidemia, and is invariably severe in those with 3-methylglutaconic aciduria, glutaric aciduria type 2, and disorders of fructose metabolism.

The syndrome includes any of the following symptoms: apnea, cyanosis, tachypnea, jitteriness, high-pitched cry, poor feeding, vomiting, apathy, hypotonia, seizures, and coma. Symptomatic hypoglycemia is often associated with later neurological impairment.

Diagnosis. Neonatal hypoglycemia is defined as a whole blood glucose concentration of less than 20 mg/dL (1 mmol/L) in premature and low-birth-weight newborns, less than 30 mg/dL (1.5 mmol/L) in term newborns during the first 72 hours, and less than 40 mg/dL (2 mmol/L) in full-term newborns after 72 hours. Finding a low glucose concentration in a newborn with seizures prompts investigation into the cause of the hypoglycemia.

Management. IV administration of glucose normalizes blood glucose concentrations, but the underlying cause must be determined before providing definitive treatment.

BOX 1.6 Causes of Neonatal Hypoglycemia

- **Primary transitional hypoglycemia**[a]
  - Complicated labor and delivery
  - Intrauterine malnutrition
  - Maternal diabetes
  - Prematurity
- **Secondary transitional hypoglycemia**[a]
  - Asphyxia
  - Central nervous system disorders
  - Cold injuries
  - Sepsis
- **Persistent hypoglycemia**
  - Aminoacidurias
  - Maple syrup urine disease
  - Methylmalonic acidemia
  - Propionic acidemia
  - Tyrosinosis
- **Congenital hypopituitarism**
- **Defects in carbohydrate metabolism**
  - Fructose 1, 6-diphosphatase deficiency
  - Fructose + intolerance
  - Galactosemia
  - Glycogen storage disease type 1
  - Glycogen synthase deficiency
- **Hyperinsulinism**
- **Organic acidurias**
  - Glutaric aciduria type 2
  - 3-Methylglutaryl-CoA lyase deficiency

[a]Denotes the most common conditions and the ones with disease-modifying treatments

Hypoxic-Ischemic Encephalopathy

Asphyxia at term is usually an intrauterine event, and hypoxia and ischemia occur together; the result is hypoxic-ischemic encephalopathy (HIE). *Acute systemic and severe asphyxia* often leads to death from circulatory collapse. Survivors are born comatose. Lower cranial nerve dysfunction and severe neurological handicaps are the rule.

Less severe and systemic, prolonged asphyxia is the usual mechanism of HIE in surviving full-term newborns.[13] The fetal circulation accommodates to reductions in arterial oxygen by maximizing blood flow to the brain, and to a lesser extent the heart, at the expense of other organs.

Clinical experience indicates that fetuses may be subject to considerable hypoxia without the development of brain damage. The incidence of cerebral palsy among full-term newborns with a 5-minute Apgar score of 0 to 3 is only 1% if the 10-minute score is 4 or higher. Any episode of hypoxia sufficiently severe to cause brain damage also causes derangements in other organs. Newborns with mild HIE always have a history of irregular heart rate and usually pass meconium. Those with severe HIE may have lactic acidosis, elevated serum concentrations of hepatic enzymes, enterocolitis, renal failure, and fatal myocardial damage.

Clinical features. Mild HIE is relatively common. The newborn is lethargic but conscious immediately after birth. Other characteristic features are jitteriness and sympathetic overactivity (tachycardia, dilatation of pupils, and decreased bronchial and salivary secretions). Muscle tone is normal at rest, tendon reflexes are normoreactive or hyperactive, and ankle clonus is usually elicited. The Moro reflex is complete, and a single stimulus generates repetitive extension and flexion movements. Seizures are not an expected feature, and their occurrence suggests concurrent hypoglycemia, the presence of a second condition or a more significant HIE.

Symptoms diminish and disappear during the first few days, although some degree of over-responsiveness may persist. Newborns with mild HIE are believed to recover normal brain function completely. They are not at greater risk for later epilepsy or learning disabilities.

Newborns with *severe HIE* are stuporous or comatose immediately after birth, and respiratory effort is usually periodic and insufficient to sustain life. Seizures begin within the first 12 hours. Hypotonia is severe, and tendon reflexes, the Moro reflex, and the tonic neck reflex are absent as well. Sucking and swallowing are depressed or absent, but the pupillary and oculovestibular reflexes are present. Most of these newborns have frequent seizures, which may appear on EEG without clinical manifestations. They may progress to status epilepticus. The response to antiepileptic drugs is usually incomplete. Generalized increased intracranial pressure characterized by coma, bulging of the fontanelles, loss of pupillary and oculovestibular reflexes, and respiratory arrest often develops between 24 and 72 hours of age.

The newborn may die at this time or may remain stuporous for several weeks. The encephalopathy begins to subside after the third day, and seizures decrease in frequency and eventually may stop. Jitteriness is common as the child becomes aroused. Tone increases in the limbs during the succeeding weeks. Neurological sequelae are expected in newborns with severe HIE.

Diagnosis. EEG and MRI are helpful in determining the severity and prognosis of HIE. In mild HIE, the EEG background rhythms are normal or lacking in variability. In severe HIE, the background is always abnormal and shows suppression of background amplitude. The degree of suppression correlates well with the severity of HIE. The worst case is a flat EEG or one with a burst-suppression pattern. A bad outcome is invariable if the amplitude remains suppressed for 2 weeks or a burst-suppression pattern is present at any time. Epileptiform activity may also be present but is less predictive of the outcome than is background suppression.

MRI with diffusion-weighted images are helpful to determine the full extent of injury. The basal ganglia and thalamus are often affected by HIE.

Management. The management of HIE in newborns requires immediate attention to derangements in several organs and correction of acidosis. Clinical experience indicates that control of seizures and maintenance of adequate ventilation and perfusion increases the chance of a favorable outcome. A treatment approach involves either whole body or selective head cooling.[14,15] My preference is whole body cooling as this allows a better EEG recording, which is essential for the management of seizures. The continuous EEG monitoring is needed as seizures are often subclinical in newborns.

A separate section details the treatment of seizures in newborns. The use of IV levetiracetam is promising[16] and is our first choice. Seizures often cease spontaneously during the second week, and long-term anticonvulsant therapy may not be necessary. The incidence of later epilepsy among infants who had neonatal seizures caused by HIE is 30%–40%. Continuing antiepileptic therapy after the initial seizures have stopped does not seem to influence, significantly if at all, whether the child goes on to develop epilepsy as a lifelong condition.

Organic Acid Disorders

Characteristic of organic acid disorders is the accumulation of compounds, usually ketones, or lactic acid that causes acidosis in biological fluids.[17] Among the dozens of organic acid disorders are abnormalities in vitamin metabolism, lipid metabolism, glycolysis, the citric acid cycle, oxidative metabolism, glutathione metabolism, and 4-aminobutyric acid metabolism. The clinical presentations vary considerably and several chapters contain descriptions. Defects in the further metabolism of branched-chain amino acids are the organic acid disorders that most often cause neonatal seizures. Molecular genetic testing is clinically available for detection of several of these diseases, including MSUD, propionic acidemia, methylmalonic acidemia, biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, isovaleric acidemia, and glutaric acidemia type 1.

Isovaleric Acidemia

Isovaleric acid is a fatty acid derived from leucine. The enzyme isovaleryl-CoA dehydrogenase converts isovaleric acid to 3-methylcrotonyl-CoA (see Fig. 1.1). Genetic transmission is autosomal recessive inheritance. The heterozygote state is detectable in cultured fibroblasts.

Clinical features. Two phenotypes are associated with the same enzyme defect. One is an acute, overwhelming disorder of the newborn; the other is a chronic infantile form. Newborns with the acute disorder are normal at birth but within a few days become lethargic, refuse to feed, and vomit. The clinical syndrome is similar to MSUD except that the urine smells like "sweaty feet" instead of maple syrup. Sixty percent of affected newborns die within 3 weeks. The survivors have a clinical syndrome identical to the chronic infantile phenotype.

Diagnosis. The excretion of isovaleryl-lysine in the urine detects isovaleric acidosis. Assays of isovaleryl-CoA dehydrogenase activity utilize cultured fibroblasts, and molecular testing is available. The clinical phenotype correlates not with the percentage of residual enzyme activity, but with the ability to detoxify isovaleryl-CoA with glycine.

Management. Dietary restriction of protein, especially leucine, decreases the occurrence of later psychomotor

retardation. L-Carnitine, 50 mg/kg/day, is a beneficial supplement to the diet of some children with isovaleric acidemia. In acutely ill newborns, oral glycine, 250–500 mg/day, in addition to protein restriction and carnitine, lowers mortality. Arachidonic acid, docosahexaenoic acid, and vitamin B_{12} may become deficient and require supplementation in patients treated with dietary restriction of protein.[18]

Methylmalonic Acidemia

D-Methylmalonyl-CoA is racemized to L-methylmalonyl-CoA by the enzyme D-methylmalonyl racemase and then isomerized to succinyl-CoA, which enters the tricarboxylic acid cycle. The enzyme D-methylmalonyl-CoA mutase catalyzes the isomerization. The cobalamin (vitamin B_{12}) coenzyme adenosylcobalamin is a required cofactor. Genetic transmission of the several defects in this pathway is by autosomal recessive inheritance. *Mutase deficiency* is the most common abnormality. Propionyl-CoA, propionic acid, and methylmalonic acid accumulate and cause hyperglycinemia and hyperammonemia.

Clinical features. Affected children appear normal at birth. In 80% of those with complete mutase deficiency, the symptoms appear during the first week after delivery; those with defects in the synthesis of adenosylcobalamin generally show symptoms after 1 month. Symptoms include lethargy, failure to thrive, recurrent vomiting, dehydration, respiratory distress, and hypotonia after the initiation of protein feeding. Leukopenia, thrombocytopenia, and anemia are present in more than one-half of patients. Intracranial hemorrhage may result from a bleeding diathesis. The outcome for newborns with complete mutase deficiency is usually poor. Most die within 2 months of diagnosis; survivors have recurrent acidosis, growth retardation, and cognitive impairment.

Diagnosis. Suspect the diagnosis in any newborn with metabolic acidosis, especially if associated with ketosis, hyperammonemia, and hyperglycinemia. Demonstrating an increased concentration of methylmalonic acid in the urine and elevated plasma glycine levels helps confirm the diagnosis. The specific enzyme defect can be determined in fibroblasts. Techniques for prenatal detection are available.

Management. Some affected newborns are cobalamin responsive and others are not. Management of those with mutase deficiency is similar to propionic acidemia. The long-term results are poor. Vitamin B_{12} supplementation is useful in some defects of adenosylcobalamin synthesis, and hydroxocobalamin administration is reasonable while awaiting the definitive diagnosis. Maintain treatment with protein restriction (0.5–l.5 g/kg/day) and hydroxocobalamin (1 mg) weekly. As in propionic acidemia, oral supplementation of L-carnitine reduces ketogenesis in response to fasting.

Propionic Acidemia

Propionyl-CoA forms as a catabolite of methionine, threonine, and the branched-chain amino acids. Its further carboxylation to D-methylmalonyl-CoA requires the enzyme propionyl-CoA carboxylase and the coenzyme biotin (see Fig. 1.1). Isolated deficiency of propionyl-CoA carboxylase causes propionic acidemia. Transmission of the defect is autosomal recessive.

Clinical features. Most affected children appear normal at birth; symptoms may begin as early as the first day after delivery or delayed for months or years. In newborns, the symptoms are nonspecific: feeding difficulty, lethargy, hypotonia, and dehydration. Recurrent attacks of profound metabolic acidosis, often associated with hyperammonemia, which respond poorly to buffering is characteristic. Untreated newborns rapidly become dehydrated, have generalized or myoclonic seizures, and become comatose.

Hepatomegaly caused by a fatty infiltration occurs in approximately one-third of patients. Neutropenia, thrombocytopenia, and occasionally pancytopenia may be present. A bleeding diathesis accounts for massive intracranial hemorrhage in some newborns. Children who survive beyond infancy develop infarctions in the basal ganglia.

Diagnosis. Consider propionic acidemia in any newborn with ketoacidosis or with hyperammonemia without ketoacidosis. Propionic acidemia is the probable diagnosis when the plasma concentrations of glycine and propionate and the urinary concentrations of glycine, methylcitrate, and β-hydroxypropionate are increased. While the urinary concentration of propionate may be normal, the plasma concentration is always elevated, without a concurrent increase in the concentration of methylmalonate.

Deficiency of enzyme activity in peripheral blood leukocytes or in skin fibroblasts establishes the diagnosis. Molecular genetic testing is available. Detecting methylcitrate, a unique metabolite of propionate, in the amniotic fluid and by showing deficient enzyme activity in amniotic fluid cells provides prenatal diagnosis.

Management. The newborn in ketoacidosis requires dialysis to remove toxic metabolites, parenteral fluids to prevent dehydration, and protein-free nutrition. Restricting protein intake to 0.5–l.5 g/kg/day decreases the frequency and severity of subsequent attacks. Oral administration of L-carnitine reduces the ketogenic response to fasting and may be useful as a daily supplement. Intermittent administration of nonabsorbed antibiotics reduces the production of propionate by gut bacteria.

Herpes Simplex Encephalitis

Herpes simplex virus (HSV) is a large DNA virus separated into two serotypes, HSV-1 and HSV-2. HSV-2 is associated

with 80% of genital herpes and HSV-1 with 20%. The overall prevalence of genital herpes is increasing and approximately 25% of pregnant women have serological evidence of past HSV-2 infection. Transmission of HSV to the newborn can occur in utero, peripartum, or postnatally. However, 85% of neonatal cases are HSV-2 infections acquired during the time of delivery. The highest risk for perinatal transmission occurs when a mother with no prior HSV-1 or HSV-2 antibodies acquires either virus in the genital tract within 2 weeks prior to delivery (first-episode primary infection). Postnatal transmission can occur with HSV-1 through mouth or hand by the mother or other caregiver.

Clinical features. The clinical spectrum of perinatal HSV infection is considerable. Among symptomatic newborns, one-third have disseminated disease, one-third have localized involvement of the brain, and one-third have localized involvement of the eyes, skin, or mouth. Whether infection is disseminated or localized, approximately half of infections involve the CNS. The overall mortality rate is over 60%, and 50% of survivors have permanent neurological impairment.

The onset of symptoms may be as early as the fifth day, but is usually in the second week. A vesicular rash is present in 30%, usually on the scalp after vertex presentation and on the buttocks after breech presentation. Conjunctivitis, jaundice, and a bleeding diathesis may be present. The first symptoms of encephalitis are irritability and seizures. Seizures may be focal or generalized and are frequently only partially responsive to therapy. Neurological deterioration is progressive and characterized by coma and quadriparesis.

Diagnosis. Culture specimens are collected from cutaneous vesicles, mouth, nasopharynx, rectum, or CSF. Polymerase chain reaction (PCR) is the standard for diagnosing herpes encephalitis. The EEG is always abnormal and shows multifocal spikes, initially more than the periodic triphasic pattern seen in older populations. The periodic pattern of slow waves usually suggests a destructive underlying lesion similar to stroke. The CSF examination shows a lymphocytic leukocytosis, red blood cells, and an elevated protein concentration.

Management. The best treatment is prevention. Cesarean section should be strongly considered in all women with active genital herpes infection at term, whose membranes are intact or ruptured for less than 4 hours.

IV acyclovir is the drug of choice for all forms of neonatal HSV disease. The dosage is 60 mg/kg/day divided in three doses, given intravenously for 14 days in skin/eye/mouth disease and for 21 days for disseminated disease. All patients with CNS HSV involvement should undergo a repeat lumbar puncture at the end of IV acyclovir therapy to determine that the CSF is PCR negative and normalized. Therapy continues until documenting a negative PCR. Acute renal failure is the most significant adverse effect of parenteral acyclovir. Mortality remains 50% or greater in newborns with disseminated disease.

Trauma and Intracranial Hemorrhage

Neonatal head trauma occurs most often in large term newborns of primiparous mothers. Prolonged labor and difficult extraction is usual because of fetal malpositioning or fetal-pelvic disproportion. A precipitous delivery may also lead to trauma or hemorrhage. Intracranial hemorrhage may be subarachnoid, subdural, or intraventricular. Intraventricular hemorrhage is discussed in Chapter 4.

Idiopathic cerebral venous thrombosis. The causes of cerebral venous thrombosis in newborns are coagulopathies, polycythemia, and sepsis. Cerebral venous thrombosis, especially involving the superior sagittal sinus, also occurs without known predisposing factors, probably due to the trauma even in relatively normal deliveries.

Clinical features. The initial symptom is focal seizures or lethargy beginning any time during the first month. Intracranial pressure remains normal, lethargy slowly resolves, and seizures tend to respond to anticonvulsants. The long-term outcome is uncertain and probably depends upon the extent of hemorrhagic infarction of the hemisphere.

Diagnosis. CT venogram or MRI venogram are the standard tests for diagnosis. CT venogram is a more sensitive and accurate imaging modality; however, MRI is preferred due to the absence of radiation.

Management. Anticoagulation may decrease the risk of thrombus progression, venous congestion leading to hemorrhage and stroke, and facilitate re-canalization of the venous sinus. Response to therapy varies widely, and dosages of low molecular weight heparin frequently require readjustment to maintain therapeutic anti-Xa levels of 0.5–1 U/mL. A starting dose of 1.7 mg/kg every 12 hours for term infants, or 2.0 mg/kg every 12 hours for preterm infants, may be beneficial.[19] Ultimately therapeutic decisions must incorporate treatment of the underlying cause of the thrombosis, if known.

Primary subarachnoid hemorrhage

Clinical features. Blood in the subarachnoid space probably originates from tearing of the superficial veins by shearing forces during a prolonged delivery with the head molding. Mild HIE is often associated with SAH, but the newborn is usually well, when suddenly an unexpected seizure occurs on the first or second day of life. Lumbar puncture, performed because of suspected sepsis, reveals blood in the CSF. The physician may suspect a traumatic lumbar puncture; however, red blood cell

counts in first and last tube typically show similar counts in SAH, and show clearing numbers in traumatic taps. Most newborns with SAHs will not suffer long-term sequelae.

Diagnosis. CT is useful to document the extent of hemorrhage. Blood is present in the interhemispheric fissure and the supratentorial and infratentorial recesses. EEG may reveal epileptiform activity without background suppression. This suggests that HIE is not the cause of the seizures, and that the prognosis is more favorable. Clotting studies are needed to evaluate the possibility of a bleeding diathesis.

Management. Seizures usually respond to anticonvulsants. Specific therapy is not available for the hemorrhage, and posthemorrhagic hydrocephalus is uncommon.

Subdural hemorrhage

Clinical features. Subdural hemorrhage is usually the consequence of a tear in the tentorium near its junction with the falx. Causes of tear include excessive vertical molding of the head in vertex presentation, anteroposterior elongation of the head in face and brow presentations, or prolonged delivery of the after coming head in breech presentation. Blood collects in the posterior fossa and may produce brainstem compression. The initial features are those of mild to moderate HIE. Clinical evidence of brainstem compression begins 12 hours or longer after delivery. Characteristic features include irregular respiration, an abnormal cry, declining consciousness, hypotonia, seizures, and a tense fontanelle. Intracerebellar hemorrhage is sometimes present. Mortality is high, and neurological impairment among survivors is common.

Diagnosis. MRI, CT, or ultrasound visualizes the subdural hemorrhages.

Management. Small hemorrhages do not require treatment, but surgical evacuation of large collections relieves brainstem compression.

Pyridoxine Dependency

Pyridoxine dependency is a rare disorder transmitted as an autosomal recessive trait.[20] The genetic locus is unknown, but the presumed cause is impaired glutamic decarboxylase activity.

Clinical features. Newborns experience seizures soon after birth. The seizures are usually multifocal clonic at onset and progress rapidly to status epilepticus. Although presentations consisting of prolonged seizures and recurrent episodes of status epilepticus are typical, recurrent self-limited events including partial seizures, generalized seizures, atonic seizures, myoclonic events, and infantile spasms also occur. The seizures only respond to pyridoxine. A seizure-free interval up to 3 weeks may occur after pyridoxine discontinuation. Outcome may be improved and cognitive deficits decreased with early diagnosis and treatment.

Atypical features include late-onset seizures (up to age 2 years); seizures that initially respond to antiepileptic drugs and then do not; seizures that do not initially respond to pyridoxine but then become controlled; and prolonged seizure-free intervals occurring after stopping pyridoxine. Intellectual disability is common.

Diagnosis. Suspect the diagnosis in newborns with an affected older sibling, or in newborns with daily seizures unresponsive to anticonvulsants, with a progressive course, and worsening EEGs. Characteristic of the infantile-onset variety is intermittent myoclonic seizures, focal clonic seizures, or generalized tonic-clonic seizures. The EEG is continuously abnormal because of generalized or multifocal spike discharges and tends to evolve into hypsarrhythmia. An IV injection of pyridoxine 100 mg stops the clinical seizure activity and often converts the EEG to normal in less than 10 minutes. However, sometimes 500 mg is required. When giving pyridoxine IV, arousals may look like improvement in EEG since hypsarrhythmia is a pattern seen initially during sleep. Comparing sleep EEG before and after pyridoxine is needed to confirm an EEG response. CSF neurotransmitter testing is available to confirm the diagnosis.

Genetic testing may confirm mutations of the aldehyde dehydrogenase 7A1 *(ALDH7A1)* gene, which encodes antiquitin.[21]

Management. A lifelong dietary supplement of pyridoxine 50–100 mg/day prevents further seizures. Subsequent psychomotor development is best with early treatment, but this does not ensure a normal outcome. The dose needed to prevent mental retardation may be higher than that needed to stop seizures. Adult neurologists often become concerned about the possibility of pyridoxine induced neuropathy; however, we have never seen a child with B6 induced neuropathy even with high doses of pyridoxine and we have never found a case report of pyridoxine monotherapy induced neuropathy in adults. Most reports of pyridoxine induced neuropathy in adults are patients with chronic conditions and therapies that may induce neuropathy.

Folinic Acid Dependency

Folinic acid dependent seizures are similar to pyridoxine dependency seizures. A case report of Ohtahara syndrome responsive to folinic acid was negative for the known *ALDH7A1* mutation associated with folinic acid and pyridoxine dependent seizures and positive for a *STXBP1* gene.[22] We have treated a child who was negative for *ALDH7A1* and experienced seizures refractory to levetiracetam, fosphenytoin, and pyridoxine. The child and EEG normalized after a single dose of folinic acid, and the patient

remains asymptomatic and with normal development on folinic acid monotherapy.

Clinical features. Infants develop seizures during the first week of life that are not responsive to anticonvulsants or pyridoxine.

Diagnosis. A characteristic peak on CSF electrophoresis confirms the diagnosis.[23]

Management. Treat the disorder with folinic acid (NOT FOLIC ACID) supplementation 2.5–5 mg twice daily.

Incontinentia Pigmenti (Bloch–Sulzberger Syndrome)

Incontinentia pigmenti is a rare neurocutaneous syndrome involving the skin, teeth, eyes, and CNS. Genetic transmission is X-linked (Xq28) with lethality in the hemizygous male.[24]

Clinical features. The female-to-male ratio is 20:1. An erythematous and vesicular rash resembling epidermolysis bullosa is present on the flexor surfaces of the limbs and lateral aspect of the trunk at birth or soon thereafter. The rash persists for the first few months and a verrucous eruption that lasts for weeks or months replaces the original rash. Between 6 and 12 months of age, deposits of pigment appear in the previous area of rash in bizarre polymorphic arrangements. The pigmentation later regresses and leaves a linear hypopigmentation. Alopecia, hypodontia, abnormal tooth shape, and dystrophic nails may be associated. Some have retinal vascular abnormalities that predispose to retinal detachment in early childhood.

Neurological disturbances occur in fewer than half of the cases. In newborns, the prominent feature is the onset of seizures on the second or third day, often confined to one side of the body. Residual neurological handicaps may include cognitive impairment, epilepsy, hemiparesis, and hydrocephalus.

Diagnosis. The clinical findings and biopsy of the skin rash are diagnostic. The bases for diagnosis are the clinical findings and the molecular testing of the *IKBKG* gene.

Management. Neonatal seizures caused by incontinentia pigmenti usually respond to standard anticonvulsant drugs. The blistering rash requires topical medication and oatmeal baths. Regular ophthalmological examinations are needed to diagnose and treat retinal detachment.

Treatment of Neonatal Seizures

Animal studies suggest that continuous seizure activity, even in the normoxemic brain, may cause brain damage by inhibiting protein synthesis, breaking down polyribosomes, and via neurotransmitter toxicity. In premature newborns, an additional concern is that the increased cerebral blood flow associated with seizures will increase the risk of intraventricular hemorrhage. Protein binding of anticonvulsant drugs may be impaired in premature newborns and the free fraction concentration may be toxic, whereas the measured protein-bound fraction appears therapeutic.

The initial steps in managing newborns with seizures are to maintain vital function, identify and correct the underlying cause, i.e., hypocalcemia or sepsis, when possible, and rapidly provide a therapeutic blood concentration of an anticonvulsant drug when needed.

In the past, treatment of neonatal seizures had little support based on evidence. Conventional treatments with phenobarbital and phenytoin seem to be equally effective or ineffective.[25] Levetiracetam, oxcarbazepine, and lamotrigine have been studied in infants as young as 1 month of age, demonstrating safety and efficacy.[26–30]

When treating neonatal seizures we must first answer two questions: (1) Is the treatment effective? Neonates have a different chloride transporter in the first weeks of life, and opening the chloride pore by Gamma-aminobutyric acid (GABA) activation may result in a hyperexcitable state rather than anticonvulsant effect. Furthermore, neuromotor dissociation has been documented when using phenobarbital in neonates, causing cessation of clinical convulsions while electrographic seizures continue. (2) Are the seizures worse than the possible unknown and known negative effect of medications in the developing brain, such as apoptosis? A few brief focal seizures may be acceptable in the setting of a resolving neonatal encephalopathy.

Antiepileptic Drugs

Levetiracetam. The introduction of IV levetiracetam (100 mg/mL) provides a new and safer option for the treatment of newborns. Because levetiracetam is not liver metabolized, but excreted unchanged in the urine, no drug–drug interactions exist. Use of the drug requires maintaining urinary output. We consider it an excellent treatment option and recommend it as initial therapy. The initial dose is 30–40 mg/kg; the maintenance dose is 40 mg/kg/day in the first 6 months of life, and up to 60 mg/kg/day between 6 months and 4 years.[29] The maintenance dose is dependent on renal clearance. Reduce the dosage and dosing interval in neonates with hypoxic injury with associated lower renal function.

Oxcarbazepine. Oxcarbazepine suspension is a good option in neonates with functioning gastrointestinal tracts and a lower risk for necrotizing enterocolitis. Doses between 20 and 40 mg/kg/day for infants less than 6 months, and up to 60 mg/kg/day divided two or three times a day are adequate for older infants and young children.[26] We find this drug helpful in all localization related

epilepsies, but particularly in benign neonatal and infantile epilepsies, where levetiracetam is often less effective.

Phenobarbital. IV phenobarbital is a widely used drug for the treatment of newborns with seizures. However, its efficacy and safety are under review. The chloride transporters in newborns may convert phenobarbital into a proconvulsant or at least a less effective anticonvulsant. The possible antiseizure effect in this age group may be explained by extra-synaptic effects. A unitary relationship usually exists between the IV dose of phenobarbital in milligrams per kilogram of body weight and the blood concentration in micrograms per milliliter measured 24 hours after the load. A 20 μg/mL blood concentration is safely achievable with a single IV loading dose of 20 mg/kg injected at a rate of 5 mg/min. The usual maintenance dose is 4 mg/kg/day. Use additional boluses of 10 mg/kg, to a total of 40 mg/kg, for those who fail to respond to the initial load. In term newborns with intractable seizures from HIE the use of this drug to achieve a burst-suppression pattern is an alternative (likely extra-synaptic effect). The half-life of phenobarbital in newborns varies from 50 to 200 hours.

Phenytoin. *Fosphenytoin sodium* is safer than phenytoin for IV administration. Oral doses of phenytoin are poorly absorbed in newborns. The efficacy of phenytoin in newborns is less than impressive and concerns exist regarding potential apoptosis. A single IV injection of 20 mg/kg at a rate of 0.5 mg/kg/min safely achieves a therapeutic blood concentration of 15–20 μg/mL (40–80 μmol/L). The half-life is long during the first week, and the basis for further administration is current knowledge of the blood concentration. Most newborns require a maintenance dosage of 5–10 mg/kg/day. We prefer fosphenytoin over phenobarbital when levetiracetam fails. Options such as lacosamide and carbamazepine IV deserve investigation.

Duration of Therapy

Seizures caused by an acute, self-limited, and resolved encephalopathy, such as mild HIE, do not ordinarily require prolonged maintenance therapy. In most newborns, seizures stop when the acute encephalopathy is over. Therefore, discontinuation of therapy after a period of complete seizure control is reasonable unless signs of permanent cortical injury are confirmed by EEG, imaging, or clinical examination. If seizures recur, reinitiate antiepileptic therapy.

In contrast to newborns with seizures caused by acute resolved encephalopathy, treat seizures caused by cerebral dysgenesis or symptomatic epilepsies continuously as most of them are lifetime epileptic conditions.

PAROXYSMAL DISORDERS IN CHILDREN LESS THAN 2 YEARS OLD

The pathophysiology of paroxysmal neurological disorders (PNDs) in infants is more variable than in newborns (Box 1.7). Seizures, especially febrile seizures, are the main cause of PNDs, but apnea and syncope (breath-holding spells) are relatively common as well. Often the basis for requested neurological consultation in infants with PNDs is the suspicion of seizures. The determination of which "spells" are seizures is often difficult and relies more on obtaining a complete description of the spell than any diagnostic tests. Ask the parents to provide a sequential history. If more than one spell occurred, they should first describe the one that was best observed or most recent. After listening to the description of the event by a direct observer, the following questions should be included: What was the child doing before the spell?

BOX 1.7 Paroxysmal Disorders in Children Younger Than 2 Years

- **Apnea and Breath-holding**
  - Cyanotic[a]
  - Pallid
- **Dystonia**
  - Glutaric aciduria (see Chapter 14)
  - Transient paroxysmal dystonia of infancy
- **Migraine**
  - Benign paroxysmal vertigo[a] (see Chapter 10)
  - Cyclic vomiting[a]
  - Paroxysmal torticollis[a] (see Chapter 14)
- **Seizures[a]**
  - Febrile seizures
    - Epilepsy triggered by fever
    - Infection of the nervous system
    - Simple febrile seizure
  - Nonfebrile seizures
    - Generalized tonic-clonic seizures
    - Partial seizures
      - Benign familial infantile seizures
      - Ictal laughter
  - Myoclonic seizures
  - Infantile spasms
  - Benign myoclonic epilepsy
  - Severe myoclonic epilepsy
  - Myoclonic status
  - Lennox-Gastaut syndrome
  - Stereotypies (see Chapter 14)

[a]Denotes the most common conditions and the ones with disease-modifying treatments