



The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Nazarian at LFredN@aol.com.

Author Disclosure

Drs Fuh, Forrster, Pourat, Capouya, Berman, Brachlow, Enrione, and Bode did not disclose any financial relationships relevant to these cases.

Frequently Used Abbreviations

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CBC:	complete blood count
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
ECG:	electrocardiography
ED:	emergency department
EEG:	electroencephalography
ESR:	erythrocyte sedimentation rate
GI:	gastrointestinal
GU:	genitourinary
Hct:	hematocrit
Hgb:	hemoglobin
MRI:	magnetic resonance imaging
WBC:	white blood cell

Case 1 Presentation

A 16-year-old girl presents to the ED complaining of 1 day of worsening lower abdominal cramps, vaginal discharge, nausea, and vomiting. The pain is worse during urination. Analgesics provide only minor relief, and positioning does not alter the pain. She denies having any diarrhea or fever.

She experienced similar, milder symptoms 1 year ago that resolved spontaneously. She has asthma and seasonal allergies. Her menarche was at age 11 years, her last menstrual period was 2 weeks ago, and her periods are regular. She has been heterosexually active for 1 year, with three partners, uses condoms occasionally, and denies oral or anal sex.

On physical examination, her temperature is 100°F (37.7°C), heart rate is 108 beats/min, respirations are 16 breaths/min, and blood pressure is 111/60 mm Hg. There is diffuse lower abdominal tenderness, worse on the right side, but no rebound tenderness or guarding. On pelvic examination, she has cervical and adnexal tenderness on palpation.

Her WBC count is $29.8 \times 10^3/\text{mCL}$ ($29.8 \times 10^9/\text{L}$), with 88.5% neutrophils, 9% bands, and 7.9% lymphocytes; Hgb level is 13.4 g/dL (134 g/L); Hct is 38.8% (0.388); and platelet count is $219 \times 10^3/\text{mCL}$ ($219 \times 10^9/\text{L}$). Blood chemistry findings are within normal limits. A urine pregnancy test is negative. Urinalysis shows blood and leukocytes.

The patient is admitted for intravenous antibiotic treatment of pelvic inflammatory disease (PID). The next day, cervical cultures are positive for *Neisseria gonorrhoeae*. Tests for human immunodeficiency virus and syphilis are negative.

After 2 days of therapy, the patient's pain improves, but she continues to have lower abdominal pain,

more localized to the right lower quadrant. Abdominal and pelvic ultrasonography reveal the diagnosis.

Case 2 Presentation

A 6-year-old boy who has been receiving piperacillin/tazobactam antimicrobial therapy for osteomyelitis of his left talus for 17 days presents to the ED with 3 days of fever, chills, and diffuse abdominal pain. He has had no illness contacts, and the peripheral intravenous central catheter (PICC) line used to administer the antibiotic is intact and functional.

On examination, the child's temperature is 102.5°F (39.2°C), and he appears toxic. His respiratory rate is 22 breaths/min, heart rate is 90 beats/min, and blood pressure is 84/60 mm Hg. He has no abdominal tenderness or masses and has normal bowel sounds. There is no palpable lymphadenopathy in his cervical, axillary, or inguinal regions. He has no neck stiffness or meningeal signs. His PICC line site appears uninfamed. The remainder of the physical findings are normal.

Electrolytes, liver function tests, and levels of amylase and lipase are normal. He has a total WBC count of $1 \times 10^3/\text{mCL}$ ($1 \times 10^9/\text{L}$), with an absolute neutrophil count (ANC) of 160/mcL, Hgb of 10.8 g/dL (108 g/L), Hct of 28.8% (0.288), and platelet count of $149 \times 10^3/\text{mCL}$ ($149 \times 10^9/\text{L}$). Blood cultures from the PICC and peripheral blood show no growth. A radiograph of the abdomen is read as normal.

Case 3 Presentation

A 3½-month-old girl has experienced 2 days of progressive lethargy, decreased appetite, spitting up, and worsening respiratory distress requiring intubation at an outlying hospital.

The infant was born at term with-

out complications. She has been well and is developing normally. Her mother is 17 years old and unmarried. The father is not involved, and the pregnancy was unplanned. The patient lives with her mother, grandfather, and two uncles.

On physical examination, the baby is intubated, chemically paralyzed, sedated, and connected to a ventilator. Her heart rate is 145 beats/min, respiratory rate is 30 breaths/min, blood pressure is 100/55 mm Hg, and temperature is 94.5°F (34.8°C). Pulses are 2+ distally and centrally. Her skin is pale and gray, and the capillary refill takes greater than 3 seconds. She has trace deep tendon reflexes, decreased muscle tone, and 3-mm pupils that react briskly to light. The remaining physical findings are normal.

Laboratory values include: sodium, 144 mEq/L (144 mmol/L); potassium, 3 mEq/L (3 mmol/L); chloride, 121 mEq/L (121 mmol/L); bicarbonate, 5 mEq/L (5 mmol/L); BUN, 3 mg/dL (1.1 mmol/L); creatinine, 1.3 mg/dL (114.9 μmol/L); glucose, 521 mg/dL (28.9 mmol/L); calcium, 9.8 mg/dL (2.5 mmol/L); anion gap, 18 mEq/L (18 mmol/L); ammonia, 349 mcg/dL (249 μmol/L); lactic acid, >30 mEq/L; serum osmolality, 420 mOsm/Kg; and osmolar gap, 102 mOsm/Kg. Arterial blood gas determination reveals pH, 6.79; PCO₂, 29 mm Hg; PO₂, 200 mm Hg; bicarbonate, 4 mEq/L (4 mmol/L); and base excess, -28 mEq/L.

An additional test reveals the diagnosis.

Case 4 Presentation

A 7-week-old girl is transferred to the intensive care unit (ICU) from an outside ED, where she had been seen for a 1-week history of worsening

cough, congestion, and increased secretions. The ED staff intubated her because of a poor respiratory drive and inability to handle her secretions.

The baby has had a poor, uncoordinated suck since birth, and her feeding difficulties have worsened. She seems generally weak and much less active than her sibling. No sedatives or paralytics were needed during intubation due to her decreased movement and hypotonia. The baby has had no fever, vomiting, constipation, or seizure activity, and there is no family history of similar conditions.

She was born at term without complications. Her mother denies any drug use or infections but did note a feeling of decreased fetal movement near term, at which time ultrasonography was performed and reported as normal. In the ICU, intubated but not sedated, the infant's vital signs are stable, but she shows little spontaneous movement and has globally decreased tone. Her fontanelle is soft and flat, pupils are equal and reactive, and cranial nerves are intact. Her lung sounds are slightly coarse, and her upper airway is congested. She has normal reflexes and withdraws to pain appropriately.

A sequential evaluation establishes her diagnosis.

Case 1 Discussion

Ultrasonography showed a noncompressible tubular structure consistent with acute appendicitis. A surgeon was consulted, and an appendectomy was performed. After recovering from surgery, the patient was sent home on oral doxycycline to complete a 14-day treatment of the PID.

The Conditions

Both appendicitis and PID are common causes of lower abdominal pain in adolescent females. In some cases,

periappendicitis actually may be a complication of PID.

PID comprises a spectrum of inflammatory disorders of the upper female genital tract. It affects 11% of women in the reproductive age group, with adolescents having the highest incidence. Risk factors include promiscuity, intrauterine device placement, and a history of having sexually transmitted diseases or previous PID. Ascending sexually transmitted bacteria are implicated in the pathophysiology of PID, with *Chlamydia trachomatis* and *Neisseria gonorrhoea* being the primary pathogens, although anaerobes and other agents can cause the condition.

Symptoms usually begin about 1 week after the onset of menstruation and include dull, continuous lower abdominal pain. There may be fever, vomiting, abnormal vaginal discharge, or irregular bleeding. Symptoms may be very mild or absent, a condition called silent PID.

Acute appendicitis is the most common childhood condition requiring emergency surgery. Adolescents have the highest age-specific incidence. Appendicitis develops most commonly as a result of the obstruction of the appendiceal lumen, often by a fecalith. The obstruction causes mucosal edema and bacterial growth. Luminal obstruction is followed by continued production of mucus, with increases in luminal pressure and subsequent compromise of lymphatic flow, venous circulation, and finally arterial flow. Periappendicitis also may develop as a complication of PID.

Clinical symptoms of appendicitis depend on the phase at presentation and usually include abdominal pain, nausea, and fever. The pain initially is periumbilical but subsequently localizes to the right lower quadrant. In the case of a retrocecal appendix, the pain may be lateral. True pelvic ap-

pendicitis may present with no lower abdominal findings by history or physical examination. If the appendix perforates, the pain may lessen temporarily and then worsen and become generalized as peritonitis develops.

Differential Diagnosis

The differential diagnosis of lower abdominal pain in an adolescent female must include many conditions. Rupture of an ovarian cyst usually is unilateral, although these lesions may occur bilaterally. Affected patients generally are afebrile, except in the case of infected cysts. Torsion of the ovary is a surgical emergency that also tends to be unilateral. Normal and ectopic pregnancy can be ruled out with a pregnancy test or ultrasonography, which also can rule out ovarian cysts and torsed ovaries, although ultrasonography may not yield abnormal findings, especially early in the course of torsion. Urinary tract infections also must be considered, but the pain in these conditions usually is suprapubic or in the flank. Other causes of lower quadrant abdominal pain that must be considered are mesenteric adenitis, constipation, psoas abscess, tubo-ovarian abscess, Crohn disease, and gastroenteritis. A good history and physical examination can narrow the list considerably.

Treatment

PID treatments must be effective against *N gonorrhoeae* and *C trachomatis* and provide broad-spectrum coverage for anaerobes, gram-negative facultative bacteria, and streptococci. Treatment must begin as soon as a diagnosis is presumed to prevent long-term sequelae. Hospitalization is suggested in severe cases, which includes patients who have symptoms of nausea, vomiting, or high fever; surgical emergencies;

pregnancy; nonresponsiveness to medical therapy; inability to tolerate an oral regimen; or presence of a tubo-ovarian abscess. Parenteral regimens include cefotetan or cefoxitin plus doxycycline or, as an alternative, clindamycin plus gentamicin. Ambulatory regimens include ofloxacin or levofloxacin with or without metronidazole. Alternatives are ceftriaxone, cefoxitin with probenecid, or another third-generation cephalosporin together with doxycycline, with or without metronidazole.

Clinical improvement should occur within 3 days; otherwise, hospitalization, additional diagnostic tests, and possibly surgical intervention are warranted. Sexual partners must be treated empirically and reported to the local health department.

The definitive treatment for appendicitis is appendectomy. Patients should receive fluid resuscitation and preoperative antibiotics. A combination of ampicillin, clindamycin (or metronidazole), and gentamicin is recommended. Alternative regimens include imipenem/cilastatin, ticarcillin/clavulanate, piperacillin/tazobactam, ampicillin/sulbactam, cefoxitin, and cefotetan. If no perforation is suspected, a second-generation cephalosporin is sufficient. A subset of patients who present days after perforation may have a localized abscess. Initial treatment includes antibiotics, CT-guided drainage, and appendectomy in 8 to 12 weeks.

Lessons for the Clinician

An extensive diagnostic list can be made for a patient who presents with abdominal pain. A thorough history must be taken and a physical examination performed, including pelvic and rectal examinations. Clinicians should avoid treating abdominal pain with narcotics, which could mask the true diagnosis. Laboratory tests and

imaging studies should help significantly in narrowing the possibilities. Complications of delayed treatment of PID include predisposition to ectopic pregnancy, infertility, and chronic pelvic pain. In the case of appendicitis, delay may lead to perforation, sepsis, shock, and dehiscence. This patient also demonstrates that more than one significant disorder can occur simultaneously. (*Beng R. Fuh, MD, Esther E. Forrster, MD, Monica Pourrat, MD, Howard University Hospital, Washington, DC*)

Case 2 Discussion

After discontinuation of antibiotic therapy and careful observation, the boy's WBC count rebounded the following morning to $1.8 \times 10^3/\text{mL}$ ($1.8 \times 10^9/\text{L}$), with an ANC of 306/ mL . In the absence of any antibiotic therapy, all hematologic values continued to climb to normal ranges as the patient improved clinically. It was believed that this patient's severe leukopenia and fever were induced by a reaction to the extended-spectrum beta-lactam antibiotic he was receiving intravenously.

The Effect

Hematologic adverse effects of antibiotics are not rare and are not restricted to beta-lactam antibiotics. Adverse effects from this particular group of drugs are observed commonly because of their frequent use in clinical pediatrics; they include leukopenia, anemia, thrombocytopenia, and Coombs (direct antibody test)-positive hemolysis.

Beta-lactam-induced leukopenia was observed first in 1946 in an adult being treated with penicillin. The phenomenon has been reported in patients who have received prolonged courses of beta-lactam and extended-spectrum beta-lactam antibiotics. This group of antibiotics in-

cludes penicillin, semisynthetic penicillins, cephalosporins, and those drugs combined with either clavulanic acid or tazobactam. The antibiotic courses generally are for 2 weeks or longer, and the drugs are administered either orally or intravenously. Hematologic effects are more common with antibiotics in the penicillin family compared with the cephalosporins.

Pathophysiology

The neutropenia induced by beta-lactam and extended-spectrum beta-lactam antibiotics is believed to result from a reversible depletion of myeloid precursors in the bone marrow. Total WBC and ANC concentrations decrease gradually over 1 to 2 weeks, and in some instances, both thrombocytopenia and anemia can result. The lymphocyte count remains relatively stable, and lymphopoiesis is not affected. When the antibiotic is discontinued, the WBC count, Hgb level, Hct, and platelet count gradually increase. The patient also should show dramatic signs of clinical improvement.

The specific mechanism through which these drugs induce the arrest in myelopoiesis is poorly understood. Investigation is limited because cases are rare, sporadic, and transient. In some situations, antineutrophil antibodies are detected and have been characterized as being both auto-antibodies and drug-dependent antibodies detectable only in the presence of the offending drug.

Fever

Drug fever was another key feature of this child's clinical presentation. Drug fever can be caused by a number of agents, including diuretics, antiepileptics, antiarrhythmics, sedatives, and less commonly, antibiotics; it is considered a hypersensitivity reaction to the drug. Beta-lactams are

among the most common antibiotics causing drug fever, but rash generally is not present. Drug fever is a diagnosis of exclusion in a patient who has experienced temperatures of 102°F (39°C) or greater and has negative blood cultures. Shaking chills should not be observed unless an antipyretic has been administered.

Implications

The clinical situations in which these drug effects may occur include prolonged courses of treatment for sinusitis, pneumonia associated with cystic fibrosis, osteomyelitis, intra-abdominal abscesses, neck abscesses, and infections in immunocompromised individuals. Affected patients can be encountered in both the hospital and outpatient setting. Accordingly, patients receiving a protracted course of antibiotics must be monitored because of the potential adverse effects.

Other Offenders

Hematologic adverse effects of antibiotics are not uncommon and are not restricted to the beta-lactam group. Other common offenders are the sulfamethoxazole component of trimethoprim-sulfamethoxazole (TMP-SMX), chloramphenicol, and vancomycin. Sulfonamides such as TMP-SMX can cause an acute hemolytic anemia in individuals who have glucose-6-phosphate dehydrogenase (G6PD) deficiency. Megaloblastic anemia also has been reported with the use of TMP-SMX and is the result of a folate deficiency. Chloramphenicol can cause anemia through two very different mechanisms. One effect is dose-dependent, in which the drug suppresses the bone marrow by inhibiting mitochondrial protein synthesis, resulting in anemia, leukopenia, and thrombocytopenia. These effects may occur singly or in combination. Life-threatening aplastic

anemia also can result from chloramphenicol therapy and is an idiosyncratic reaction that occurs weeks to months after completion of therapy and is not dose-related. Vancomycin has been reported to cause neutropenia and fever through a proposed autoimmune mechanism.

Therapy

When an antibiotic causes anemia (including by hemolysis), neutropenia, thrombocytopenia, and drug fever through dose-related mechanisms, removing the antibiotic is curative without the need for marrow-stimulating factors. Clinicians must exclude other causes of fever and bone marrow depression before determining that a drug effect is the causative mechanism. When these antibiotic reactions occur and the drug must be stopped, culture results and sensitivities should be studied carefully and an alternative broad-spectrum antibiotic chosen. In patients who have G6PD deficiency, avoidance of sulfonamides is recommended. The megaloblastic anemia seen with sulfonamides can be treated with folate supplementation in the diet.

Lessons for the Clinician

In this case, febrile neutropenia, which has many potential causes and clinical outcomes, was caused by reaction to a medication. When the drug was removed, both the fever and neutropenia resolved. Although a diagnosis of exclusion, drug-induced fever and neutropenia always should be kept in mind. Patients receiving therapy with beta-lactam antibiotics for more than 2 weeks, whether orally or parenterally, should be followed with weekly CBCs to evaluate their hematologic status. (*Jared D. Capouna, MD, David Berman, DO, University of*

South Florida, All Children's Hospital, St. Petersburg, Fla.)

Case 3 Discussion

The severe acidosis with significant anion and osmolar gaps prompted an evaluation for inborn errors of metabolism. Urine organic acid testing revealed a massive peak for glycolic acid, a metabolite of ethylene glycol. A postdialysis serum ethylene glycol concentration was elevated at 21.1 mcg/mL, confirming the diagnosis of ethylene glycol toxicity.

Mechanical ventilation and cardiovascular support with inotropic and vasopressor drugs were administered for stabilization. Multiple boluses of sodium bicarbonate were provided in an unsuccessful attempt to correct the metabolic acidosis. Hemodialysis then was performed for ongoing metabolic acidosis, lactic acidosis, and hyperammonemia. The infant had multiple seizures on the day of admission that were controlled with phenytoin. Following 2 weeks of hospitalization, the infant stabilized and was discharged into foster care.

The baby's mother subsequently admitted to being the perpetrator. She had a history of emotional distress during childhood associated with trauma, abandonment, violence, and runaway behaviors. Further questioning revealed that a family dog had died of ethylene glycol toxicity. Subsequent to her baby's intentional poisoning, the mother had attempted suicide with ethylene glycol. Evaluation for other injuries consistent with child abuse, including skeletal survey, ophthalmology evaluation, and cranial MRI, showed no injury.

Differential Diagnosis

The profound metabolic acidosis and large anion gap in this infant led to

suspicion of an inborn error of metabolism, such as methylmalonic or propionic acidemia. Ethylene glycol ingestion was suspected when the urine organic acid analysis revealed a massive peak for glycolic acid, a product of ethylene glycol metabolism. The differential diagnosis of acidosis in an infant is vast and includes sepsis, lactic acidosis from anaerobic metabolism, inborn errors of metabolism, toxic ingestion, renal failure, diabetic ketoacidosis, and adrenal crisis.

Several causes of an elevated anion gap acidosis can be recalled by using the mnemonic MUDPILES (methanol, uremia, diabetic ketoacidosis, paraldehyde, phenformin, isoniazid, iron, infection, inborn errors, lactic acidosis, ethanol, ethylene glycol, salicylates, starvation ketoacidosis).

The Agent

Ethylene glycol is the major ingredient in most radiator and deicing solutions. It is sweet, odorless, colorless, and severely toxic. Death has been reported following three swallows of 95% ethylene glycol (15 mL) by a child weighing 10 kg. In 2002, 5,102 cases of ethylene glycol ingestion were reported in the United States, 610 of which were in children 6 years of age and younger.

Care must be taken when using gas chromatography to diagnose ethylene glycol ingestion. In one famous case, a mother was accused falsely of murdering her child by ethylene glycol poisoning. She subsequently gave birth to a child who had propionic aciduria. The gas chromatographic peak that had been identified earlier as ethylene glycol actually was due to propionic acid, and charges against the mother were dropped. Conversely, a case was reported in which repeated ethylene glycol intoxication was misinterpreted as an inborn error of metabolism with recurrent infantile metabolic acidosis. Glycolic

acid may be elevated in inborn errors of metabolism, but typically at much lower levels. Comprehensive toxicology screenings do not include ethylene glycol routinely.

Pathophysiology

On ingestion, ethylene glycol is absorbed rapidly from the GI tract. An osmolar gap occurs directly after ingestion, before the osmotically active ethylene glycol is metabolized. The osmolar gap compares the serum osmolality, measured by freezing point depression, and the calculated serum osmolality by using the formula $2 \times \text{sodium} + \text{BUN}/2.8 + \text{glucose}/18$. The specimen should be sent simultaneously for the measured and calculated osmolality. An osmolar gap greater than 10 mOsm/kg is abnormal and indicates the presence of osmotically active substances not accounted for by the calculated formula. Unmeasured osmoles are solutes that permeate membranes and are known as ineffective osmoles because they do not affect extra- and intracellular water balance. Examples include methanol, mannitol, isopropyl alcohol, ethanol, sorbitol, glycerol, acetone, paraldehyde, contrast dyes, and the substances elevated in states of hyperproteinemia and hypertriglyceridemia.

Alcohol dehydrogenase metabolizes more than 85% of ethylene glycol to glycolic acid, which produces a profound acidosis and significant anion gap acidosis. The anion gap measures the balance of anions and cations and is calculated by sodium – (bicarbonate + chloride). A normal anion gap ranges from 8 to 12 mEq/L (8 to 12 mmol/L). Glycolic acid metabolizes to oxalic acid, which combines with calcium and forms calcium oxalate crystals in the urine. Urinalysis detects calcium oxalate crystals. Hypocalcemia also may result. A Wood's lamp examination

of the urine may be helpful in the analysis of patients who have suspected ethylene glycol ingestion while awaiting the results of a confirmative ethylene glycol assay.

Management

Agents for treating ethylene glycol ingestion include ethanol, fomepizole (4-methylpyrazole), and hemodialysis. Ethanol and fomepizole act as competitive substrates of alcohol dehydrogenase to prevent the metabolism of ethylene glycol to its toxic metabolites. Fomepizole has a greater affinity for alcohol dehydrogenase and fewer adverse effects, such as altered mental status and hypoglycemia, compared with ethanol. Fomepizole also has reliable pharmacokinetic properties. The United States Food and Drug Administration has not approved the use of fomepizole for children, but multiple case reports demonstrate its safety and efficacy in children.

Toxic Ingestion

The risk of ingestion varies with the age of the child, which may provide a clue to the cause or motivation of a toxic ingestion. Accidental poisoning peaks in toddlers 2 to 3 years of age and is rare in infants younger than 1 year of age (0.1% to 8%) and in children 6 to 10 years of age (2% to 4%). This ethylene glycol ingestion in a 3-month-old baby occurred outside the age range most common for accidental poisonings. This child is the youngest case of ethylene glycol ingestion reported; the previous youngest case also was intentional and occurred in a 6-month-old.

Although intentional poisoning of children is less common than accidental poisoning, typically it is more lethal due to the products and quantities used. In a review of 48 cases of intentional child poisonings, 17% of the children died. In 30% of those

cases, poisoning persisted despite hospitalization. Child abuse by battering accompanied intentional poisonings in 20% of the cases. Cases of intentional ingestion should include a thorough search for abuse, including radiographic studies looking for skeletal fractures.

Presenting signs and symptoms of intentional ingestions are as numerous as the motivations causing the poisoning and the toxic substances. Motivations range from a caregiver seeking amusement to someone wanting to sedate a child. Intentional ingestions often are undisclosed, making early diagnosis and treatment challenging. Accidental ingestions more often are declared to medical personnel. In one series of 24 pediatric cases, all accidental ingestions were reported within 5 minutes of ingestion.

In general, when signs and symptoms remain unexplained by the history or by a classic symptom complex, child abuse should be suspected. Persistent, unexplained metabolic acidosis has been the only sign of a toxic ingestion in multiple cases. In one review, the most common agent of abuse was excessive salt with water restriction, followed by excessive water, barbiturates, and tranquilizers.

Lessons for the Clinician

Ethylene glycol is a potent toxin. Early detection is essential because prompt treatment may prevent considerable morbidity and mortality. An osmolar gap occurs in the initial phase of ethylene glycol ingestion; an anion gap acidosis develops as ethylene glycol forms toxic metabolites. Intentional toxic ingestion may occur in any age, group, or situation. Social stressors often are associated with child abuse. In cases of intentional ingestion, a full evaluation for other abuse is essential. (*Allison E. Brachlow, MD, Inova Fairfax Hospi-*

tal for Children, Falls Church, Va.; Maria A. Enrione, MD, Children's Hospital Medical Center of Akron, Ohio)

Suggested Reading

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EDITOR'S NOTE. This case was chosen from those submitted to the American Academy of Pediatrics (AAP) Residents Section Clinical Case Presentation program in 2004.

The decision as to which case should be published took into consideration not only the teaching value and excellence of writing of the case but also the content needs of the journal. Another case will be chosen from the 10 finalists presented at this year's AAP National Conference and Exhibition and published in 2006. —LFN

Case 4 Discussion

This child presented with respiratory failure due to hypoventilation and decreased respiratory drive. It was clear that this state was caused by the infant's underlying generalized and severe hypotonia.

Differential Diagnosis

Neonatal hypotonia results from a number of conditions, including central hypotonia, spinal cord and anterior horn cell disorders, neuromuscular junction disorders, congenital myopathies, muscular dystrophies, metabolic and multisystem diseases, and benign congenital hypotonia.

In this patient, the initial evaluation yielded a normal CBC, comprehensive metabolic panel, and thyroid function tests. She also had normal levels of creatine kinase, aldolase, ammonia, amino acids, and organic acids. Blood, urine, and CSF cultures were negative. A cranial MRI was read as normal.

The history and physical findings, in particular, combined with the initial normal laboratory and MRI findings, helped to narrow the differential diagnosis.

Anterior horn cell disorders such as spinal muscular atrophy cause absent deep tendon reflexes and often present with tongue fasciculations. There was no history of constipation, muscle weakness, or honey ingestion to support botulism, a relatively common neuromuscular junction disorder. The normal aldolase and

creatinine kinase concentrations and negative family history made a case against both congenital myopathies and muscular dystrophies.

Metabolic diseases, such as carnitine deficiency, peroxisomal disorders, and glycogen metabolic disorders, are less likely with normal screening laboratory findings and the lack of multisystem involvement.

The most common cause of neonatal hypotonia is central and includes hypoxic encephalopathy, infection or sepsis, intracranial hemorrhage, hypoglycemia, hypothyroidism, and chromosomal abnormalities such as trisomy 21, Turner syndrome, and Prader-Willi syndrome. The normal laboratory values and imaging results help to rule out most of these.

Eventually, high-resolution chromosome analysis and fluorescent in situ hybridization (FISH) probe results were positive for Prader-Willi syndrome.

Clinical Picture

Prader-Willi syndrome often presents in a neonate who has central hypotonia and a poor suck. Affected infants rarely present with respiratory failure but frequently require gavage feeding to avoid failure to thrive (FTT). Starting at the age of 1 year, hyperphagia ensues, and a battle against obesity begins.

Prader-Willi syndrome has a prevalence of about 1 in 12,000 births and is the most common genetic cause of obesity. The fundamental physiologic defect is a hypothalamic flaw that results in a lack of satiety. The condition affects both sexes and all races. Diagnostic clinical criteria include both major and minor criteria, as well as supportive findings.

Major criteria include: neonatal hypotonia with poor suck, feeding problems, and FTT in infancy; onset of rapid weight gain between 12 months and 6 years of age, which

causes obesity; hyperphagia and foraging for food; hypogonadism; characteristic facial features (dolichocephaly, almond-shaped eyes, down-turned mouth); and developmental delay with mental retardation. Molecular genetic testing confirms the diagnosis.

Minor criteria include decreased fetal movement or infantile lethargy, sleep apnea, short stature, hypopigmentation, small hands or feet, characteristic behavior problems (temper tantrums, obsessive-compulsive behaviors, opposition, rigidity), skin picking, esotropia and myopia, thick viscous saliva, and speech articulation defects.

Supportive findings include scoliosis and kyphosis, early adrenarache, high pain threshold, unusual skill with jigsaw puzzles, and osteoporosis. Affected children also have a very high incidence of type 2 diabetes mellitus, hypertension, and other problems related to the obesity. A diagnostic checklist for Prader-Willi syndrome and a wealth of other information can be found on the Prader-Willi Syndrome Association Web site (www.pwsausa.org).

Laboratory Findings

Clinical suspicion leads to genetic testing, which confirms the diagnosis. Prader-Willi syndrome provides an example of the effects of genetic imprinting or the differential expression of genetic information, depending on the parent of origin. The condition results from the lack of a paternally derived gene normally present on chromosome 15. This situation can be caused by a deletion, maternal uniparental disomy where both copies are inherited from the mother, or an imprinting mutation wherein gene expression is inhibited. Sophisticated genetic testing, including high-resolution chromosome analysis, FISH probe, and DNA

methylation testing, helps identify the abnormality.

A Related Condition

A closely related genetic disorder, Angelman syndrome, results when information on the maternally derived chromosome 15 is either missing or malfunctioning. Although genetically considered a “sister” syndrome to Prader-Willi syndrome, the two disorders have very different clinical manifestations. Historically referred to as “happy puppets,” children who have Angelman syndrome are characterized by severe mental retardation, midface hypoplasia, seizures, uncontrollable bouts of laughter, and jerky, ataxic movements. Such children often have generalized hypotonia but no associated obesity or hyperphagia.

Treatment

Although early intervention for Prader-Willi syndrome is directed at avoiding FTT by giving gavage feedings and at promoting normal development, later management centers on preventing obesity and its associated morbidity and mortality. A multidisciplinary team that in-

cludes geneticists, endocrinologists, nutritionists, and primary care physicians is needed. There must be stringent dietary restrictions, including limiting access to food, which often involves locking kitchen cabinets and refrigerators. Encouragement of healthy food choices and exercise is essential. A normal life span may be achieved if obesity and its related complications are avoided.

Debate continues regarding the role of growth hormone (GH) in the treatment of the obesity. Most recent studies show some benefit in terms of improved height velocity, decreased fat mass, improved body composition, and even improved behavior and appetite control. GH must be used in conjunction with measures that reduce energy intake and increase energy expenditure. The safety of GH has been a concern, specifically because of case reports of fatalities related to sleep apnea and sudden death. Consultation and coordination with an endocrinologist and Prader-Willi experts is recommended.

Because these children require coordination of their complex care, clinicians should be aware of the medical home Web site of the American

Academy of Pediatrics as a source for identifying regional family-centered resources (www.medicalhomeinfo.org).

Lessons for the Clinician

The clinician should be able to recognize the constellation of symptoms that raises suspicion of Prader-Willi syndrome and leads to genetic testing. Hypotonia and poor suck in a neonate or a history of those signs combined with global developmental delay in a 2- to 6-year-old child warrant an investigation. In older children, the development of excessive eating and obesity and the onset of behavior problems suggest Prader-Willi syndrome. Prader-Willi syndrome must be considered in the obese adolescent and adult in the context of mental retardation and hypothalamic hypogonadism. As with most disease processes, early diagnosis and intervention through a comprehensive team approach are the keys to successful management and improvement. (*Ryan S. Bode, MD, Phoenix Children's Hospital/Maricopa Medical Center, Phoenix, Ariz.*)