CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 26-2014: A 21-Month-Old Boy with Lethargy, Respiratory Distress, and Abdominal Distention

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PRESENTATION OF CASE

Dr. Daphne Morrison Ponce (Emergency Medicine): A 21-month-old boy was brought by ambulance to the emergency department at this hospital because of lethargy, respiratory distress, and abdominal distention.

The patient had been well until the day before admission, when fussiness, vomiting, and diarrhea developed, associated with decreased oral intake. He was taken to the emergency department at another hospital, where diagnoses of dehydration and gastroenteritis were made. He was treated with ondansetron, and intravenous fluids were administered. His condition markedly improved, and he was discharged home, with instructions to his parents to follow up the next day with a pediatrician.

That evening, the patient's parents noticed that the boy had respiratory grunting, increased work of breathing, progressive somnolence, and refusal of oral intake, without further stool output. The next morning, on the day of the current presentation, he was difficult to arouse and had recurrent vomiting and decreased urination. His parents took him to the pediatrician's office, where he appeared lethargic, with rapid respirations; emergency medical services (EMS) were called. The patient was in respiratory distress, with grunting and labored abdominal breathing. The blood pressure was 134/70 mm Hg, and the pulse was 177, regular, and strong; the respiratory rate was 56 breaths per minute, and the oxygen saturation was 99% while he was breathing oxygen through a nonrebreather face mask. The skin was pale, warm, and diaphoretic; the lungs were clear, and the extremities were limp. The weight was 14 kg. The blood glucose level was 231 mg per deciliter (13 mmol per liter). The patient was transferred by ambulance to the emergency department at this hospital.

The patient's history was obtained from the parents through a foreign-language interpreter. The patient was born without complication after a full-term gestation and had previously been healthy. His immunizations were current; he was receiving no other medications and had no known allergies. He lived with his parents and 3-year-old brother, who had been ill recently with similar but less severe symptoms. The parents reported no other contacts with ill persons and no ingestions; there were pill bottles at home, but all were closed and in a childproof drawer.

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On examination, the patient was moaning and minimally responsive, with writhing movements and withdrawal from pain. The temperature was 38.2°C, the blood pressure 124/76 mm Hg, and the pulse 172 beats per minute; hyperpneic (Kussmaul) respirations were variable at a rate of 32 breaths per minute, and the oxygen saturation was 98% while he was breathing oxygen at 15 liters per minute through a nonrebreather mask. The pupils were 3 mm in diameter, round, and reactive. The abdomen was distended and diffusely tender, with hypoactive bowel sounds. There were bounding pulses, with decreased capillary refill time. The remainder of the physical examination was normal. Trace stool obtained on rectal examination was guaiac-negative.

Monitoring and supportive measures were initiated. A bolus of normal saline was infused and was followed by an additional bolus because of hemodynamic instability. Blood levels of calcium, direct bilirubin, total protein, albumin, globulin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were normal; other test results are shown in Table 1. Ceftriaxone and ondansetron were administered, as were morphine sulfate for analgesia and lorazepam for agitation.

Consultation with pediatric surgeons was obtained. A radiograph of the chest was normal; an abdominal radiograph showed mild, diffuse gaseous distention and no evidence of bowel obstruction or pneumoperitoneum, and abdominal ultrasonography showed no evidence of intussusception. Rapid respirations and moaning continued, despite analgesia and anxiolytic medications. A nasogastric tube was placed because of increasing abdominal distention, and some coffee-grounds material was aspirated from the stomach; famotidine was administered. In addition, an infusion of 5% dextrose in a solution of 0.45% normal saline and potassium chloride was started after the infusion of a third bolus of normal saline. Additional patient history was obtained, sodium bicarbonate was administered, and a diagnostic test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Jean E. Klig: I am aware of the diagnosis in this case. This previously healthy, 21-month-old boy presented with clinically significantly altered mental status, respiratory distress, and abdominal distention. Since there was the potential for his condition to worsen rapidly, strategies for the initial evaluation and treatment of this child could have been lifesaving.

EMERGENCY EVALUATION AND MANAGEMENT

When a critically ill child presents to the emergency department, the initial focus is to rapidly evaluate the patient to determine whether there are any impending threats to life and to implement potentially lifesaving maneuvers. In this child, our priority was to assess his airway, breathing, and circulation (known as the ABCs of emergency medicine) for stability. The patient had a clear airway and had tachypnea without hypoxemia. He had tachycardia with evidence of decreased perfusion but was maintaining an adequate blood pressure. Although he appeared critically ill, there was no immediate indication for airway intubation or mechanical ventilation. Intravenous fluid boluses of normal saline were initiated because of the clinical signs of early shock.

Once we had assessed the ABCs, our next priority was to evaluate the DDDE, which stands for the patient's disability (neurologic status), dextrose (blood glucose level), drugs (possible exposures to drugs or toxins), and full exposure (complete examination of the patient, including monitoring and baseline laboratory tests).[1] The patient was moaning and responded to pain only; however, his glucose level was only mildly elevated (a finding consistent with systemic stress), and he had no overt signs of a drug or toxin exposure or trauma. Further investigation and synthesis of the patient's salient history and findings on physical examination proceeded in parallel with emergency resuscitative measures.

In constructing a differential diagnosis for this patient, it is vital to consider the timeline of his symptoms. The patient had been ill for less than 24 hours, and the first symptom was diarrhea, followed by vomiting and refusal of oral intake. By all accounts, the patient had improved with intravenous rehydration at another hospital, and his symptoms had worsened during the 12 hours after he returned home from that emergency department. During this time, progressive somnolence, grunting, and increasing abdominal distention developed. Possible limits to our obtaining key clinical information included a preverbal, neurologically compromised child, time demands on providers to address his clinical instability, and patient history taking that was

Table 1. Laboratory Data.*

Variable	Reference Range, Age-Adjusted†	On Presentation
Hematocrit (%)	33.9–39.0	34.8
Hemoglobin (g/dl)	10.5–13.5	11.8
White-cell count (per mm^3)	6000–17,500	40,600
Differential count (%)		
Neutrophils	25–49	81.0
Band forms	0–10	7.0
Lymphocytes	60–67	7.0
Monocytes	4–11	5.0
Platelet count (per mm^3)	150,000–450,000	567,000
Mean corpuscular volume (μm^3)	70–86	76
Sodium (mmol/liter)	135–145	139
Potassium (mmol/liter)	3.4–4.8	2.9
Chloride (mmol/liter)	100–108	105
Carbon dioxide (mmol/liter)	23.0–31.9	7.2
Plasma anion gap (mmol/liter)	3–15	27
Urea nitrogen (mg/dl)	5–20	13
Creatinine (mg/dl)	0.30–1.00	0.42
Glucose (mg/dl)	70–110	170
Phosphorus (mg/dl)	4.5–6.7	3.8
Magnesium (mg/dl)	1.7–2.4	2.7
Lactic acid (mmol/liter)	0.5–2.2	1.6
Venous blood gases		
Fraction of inspired oxygen		0.98 (15 liters/min)
pH	7.30–7.40	7.33
Partial pressure of carbon dioxide (mm Hg)	38–50	18
Partial pressure of oxygen (mm Hg)	35–50	35
Bicarbonate (mmol/liter)	24–30	10
Base excess (mmol/liter)		–13.6

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

hampered by parental distress and communication solely through a foreign-language interpreter, raising the possibility that nuances of answers by the parents may not have been conveyed. Further questioning of the parents yielded no additional information, so we proceeded to consider the combined differential diagnoses for a toddler with altered mental status and abdominal distention.

The differential diagnosis of acutely altered mental status in a toddler includes trauma (accidental or abuse), intussusception, infection (encephalitis or meningitis), poisoning (toxin), shock, accidental alcohol intoxication, encephalopathy, epilepsy as subclinical seizures, inborn errors of metabolism, ingestion of opiates, and uremia.[2,3]

A broad array of diagnostic entities can account for this patient's abdominal distention, including anatomical problems associated with bowel obstruction (intussusception or malrotation with

volvulus), trauma (hepatic or splenic laceration or pneumoperitoneum), gastroenterologic problems (protein-losing enteropathy, constipation, or intestinal ileus due to infection, electrolyte abnormalities, or toxin), infectious causes (appendicitis with peritonitis, acute bacterial and viral gastroenteritis, abscess, sepsis, pneumonia, or botulism), cancer (Wilms' tumor, neuroblastoma, leukemia, or lymphoma), and renal problems (hydronephrosis, obstructive uropathy, polycystic kidneys, or nephrotic syndrome).[4] When viewed in the context of the patient's altered mental status, a short list of diagnostic possibilities emerges that includes intussusception, infection, toxin, and trauma, with subclinical seizure as a less likely culprit.

It is helpful to consider each of the possible diagnoses on the basis of the patient's response to initial interventions. Perfusion improved after the administration of three boluses of normal saline, but otherwise the patient's clinical symptoms were unchanged by supportive respiratory measures, placement of an orogastric tube (with coffee-grounds material aspirated), and the administration of antibiotics, ondansetron, famotidine, morphine sulfate, and lorazepam. A bedside ultrasound evaluation of the abdomen that was performed by a pediatric radiologist revealed multiple air-filled loops of bowel but no intussusception, free fluid, or mass. A pediatric surgeon concurred that an abdominal process that would require surgery was unlikely. The differential diagnosis narrowed further as the patient's laboratory tests yielded a clinically significant anion-gap metabolic acidosis, with a venous pH of 7.33. The lactic acid level was normal, and an elevated white-cell count of 40,600 per cubic millimeter was presumed to reflect systemic stress rather than infection, although broad-spectrum antibiotics were administered after blood and urine cultures were obtained.

The differential diagnosis of an elevated anion-gap metabolic acidosis is detailed by the acronym "CAT MUDPILES" and includes cyanide, carbon monoxide, and congestive heart failure; aminoglycosides; theophylline; methanol; uremia; diabetic, alcoholic, or starvation ketoacidosis; paraldehyde, paracetamol (acetaminophen), and phenformin; iron, isoniazid, and inborn errors of metabolism; lactic acidosis; ethanol and ethylene glycol; and salicylate.[5] The more likely toxins in this scenario were acetaminophen, salicylates, iron, or methanol, with the last two less likely given a lack of toxin-specific symptoms or more marked metabolic acidosis. As we questioned the parents further at the bedside, the patient's older sibling mentioned that he had given pills to his brother. There was aspirin in a childproof bottle and loratadine in blister packs in the home. The salicylate level was reported shortly afterward and corroborated our clinical impressions. Treatment with sodium bicarbonate was initiated in consultation with the toxicology service and the dialysis team, and the patient was admitted to the pediatric intensive care unit (ICU).

DR. JEAN E. KLIG'S DIAGNOSIS

Acute salicylate poisoning.

DIAGNOSTIC TESTING

Dr. Morrison Ponce: The diagnostic test result was a serum salicylate level of 728 mg per liter (5.3 mmol per liter).

TOXICOLOGIC CONSIDERATIONS

Dr. Aaron B. Skolnik: This child presented with lethargy, respiratory distress, tachycardia, abdominal distention, and elevated body temperature. The presence of an elevated anion-gap metabolic acidosis quickly narrows the list of potential toxic exposures. Multiple toxins that cause an elevated anion-gap metabolic acidosis can be responsible for changes in mental status, respiratory distress, and tachycardia, but only salicylate poisoning is independently capable of causing hyperthermia, through the uncoupling of oxidative phosphorylation. In fact, hyperthermia is more common in fatal than in nonfatal salicylate poisoning, making elevated body temperature an important indicator of severe toxicity.[6]

TOXIC EFFECTS OF ACUTE SALICYLATE POISONING

The organ system most importantly affected by salicylate poisoning is the central nervous system (CNS). Neurotoxicity due to impaired ATP formation (and possibly exacerbated by low glucose levels in the cerebrospinal fluid)[7] may lead to agitation, combativeness, hallucinosis, lethargy, seizures, coma, cerebral edema, or death. It has been shown that levels of salicylate in the CNS correlate best with death in animals.[8] Any neurotoxic

effects are an indication of severe poisoning and should prompt aggressive management, as they did in this case once the diagnosis was known.[9]

In addition to its effects on the CNS, salicylate has a wide array of multisystem toxic effects, some of which were observed in this patient. Salicylate stimulates the respiratory center in the brain stem, resulting in respiratory alkalosis. Tinnitus or other changes in hearing are common with serum salicylate levels of 200 mg per liter (1.4 mmol per liter) or higher, although ototoxicity is not permanent.[10] Salicylate has corrosive effects on the gastrointestinal tract, commonly resulting in nausea and vomiting but occasionally in hematemesis; in this patient, the gastrointestinal manifestations were recurrent vomiting on the day of presentation and the coffee-grounds material aspirated from his stomach. The acute respiratory distress syndrome has been reported in persons with severe acute salicylate poisoning, but causality is difficult to prove because of the high incidence of aspiration in this population. Decreased myocardial ATP production, elevated body temperature, acidemia, and hypovolemia due to increased insensible losses may all contribute to sinus tachycardia, which was present in this patient.

DIAGNOSTIC TESTS

In most cases of salicylate poisoning, the diagnosis can be made on the basis of the history of salicylate ingestion, which the patient's older sibling initially withheld in this case. Ingestion of salicylate can be rapidly lethal and is often not managed optimally; therefore, I recommend instituting supportive treatment on the basis of a strong clinical suspicion for or history of ingestion alone, before laboratory confirmation.

The critical diagnostic test result in this case was the markedly elevated serum salicylate level, but salicylate levels must be interpreted in context. Owing to delayed gastric emptying and erratic absorption of oral salicylate, a single test that yields a normal salicylate level (generally considered to be 100 to 200 mg per liter) is insufficient to rule out serious poisoning. Since the volume of distribution of salicylate increases dramatically with a decrease in the serum pH, a falling salicylate level may actually indicate distribution into tissues, including the CNS, and may be associated with clinical worsening. In this case, the overdose occurred the night before admission, which suggests that there was enough time for the salicylate to distribute into the tissues and for there to be a high burden of the drug in the body at presentation. The patient's lethargy and hyperthermia were much more important indicators of severe poisoning than the absolute level of the drug. Serum salicylate levels in persons who die from salicylate poisoning are similar to those in persons who recover, and thus absolute levels alone should never be used to guide management.[11] That said, in most patients with serum salicylate levels of 1000 mg per liter (7.2 mmol per liter) or greater, an indication for hemodialysis usually develops during the course of their poisoning.

MANAGEMENT ISSUES

For a patient with acute salicylate poisoning, physicians must manage acute threats to life, arrange for hemodialysis (if indicated), attempt to keep salicylate out of the CNS, and augment the elimination of salicylate. This child had several indications for emergency hemodialysis. His depressed mental status was an important indicator of CNS toxicity, and he had hyperthermia. Patients with salicylate poisoning are equally subject to conventional indications for hemodialysis such as refractory metabolic acidosis, severe electrolyte disturbances, or volume overload associated with oliguria or anuria. Most toxicologists agree that a worsening clinical condition and an ongoing rise in salicylate levels in patients who are receiving maximal supportive care are also indications for hemodialysis. Hemodialysis works very well in the treatment of salicylate toxicity despite the drug's relatively high protein binding at therapeutic doses, in part because the binding is saturated in an overdose.[12]

Charcoal hemoperfusion is also an option for salicylate poisoning, but most centers do not have the capability to perform it.[13] This patient presented many hours after ingesting salicylate. Although activated charcoal absorbs salicylate well and can decrease absorption and enhance elimination of the drug, it is unlikely to be of value if gastric emptying has already occurred. In addition, a clear clinical benefit of activated charcoal in salicylate poisoning has not been shown, and I would avoid it in this case because of the high risk of aspiration.[14]

While the patient was awaiting hemodialysis, we provided supportive treatment by infusing a

solution of isotonic crystalloid to replace insensible losses and by alkalinizing his serum and urine. Although emphasis has been traditionally placed on alkalinizing the urine, alkalinizing the serum is more important. Salicylate that is not ionized can easily enter the CNS; the administration of sodium bicarbonate to alkalinize the serum to a pH of 7.50 to 7.55 can "trap" ionized salicylate in the serum and keep it out of the brain. A beneficial consequence of the administration of sodium bicarbonate is urinary alkalinization, which entraps ionized salicylate in the urine and enhances elimination. The acid–base balance should be frequently monitored to avoid overtreatment, which may cause excessive alkalosis. Checking the urine pH frequently (with a goal pH of 8) helps to determine whether the urinary alkalinization is successful. Hypoglycemia can occur in persons who have taken an overdose of salicylate, and glucose measurements help guide dextrose administration. Monitoring serum electrolytes is also important; many patients need potassium replacement, and it is critical to maintain normokalemia because potassium that is reabsorbed in the distal nephron is exchanged for protons, preventing successful urinary alkalinization.[15]

When hemodialysis is performed, it should be continued until the serum salicylate level is at least below the therapeutic upper limit of the normal range (200 mg per liter). For patients treated exclusively with alkalinization, therapy is discontinued when at least two consecutive salicylate levels are within the therapeutic range and each has declined by 20% of the previous value.

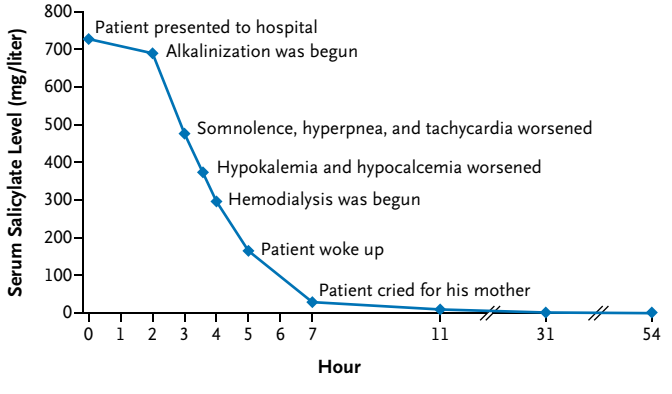

Figure 1. Clinical Course Relative to Serum Salicylate Level.

On presentation to the emergency department, the patient's serum salicylate level was 728 mg per liter. His subsequent clinical course is shown relative to time and serum salicylate level.

RENAL MANAGEMENT AND FOLLOW-UP

Dr. Amita Sharma: On arrival in the ICU, the patient was febrile and irritable. He had a normal respiratory rate but marked hyperpnea. Laboratory test results showed a very low serum bicarbonate level (7.2 mmol per liter), a potassium level of 2.6 mmol per liter, and an elevated anion gap of 27 mmol per liter. Urinalysis revealed 3+ ketones, trace glucose, a pH of 5.5, and a specific gravity of 1.015. Similar features have been described in a patient with diabetic ketoacidosis with infection.[16] However, this patient had no evidence of infection, and the salicylate level was 728 mg per liter.

The patient had already received two boluses of normal saline and had been started on an aggressive alkalinization regimen in the emergency department. Within an hour after his arrival in the ICU, his urine pH had increased from 5.5 to 7.5 and stayed in the range of 7.5 to 8, with urine output averaging 2 to 3 ml per kilogram per hour to aid renal elimination.[15] Salicylate is metabolized by at least five pathways. When a therapeutic dose is administered, salicyluric acid is conjugated with glycine (44%) and glucuronide (20%) to form the major pathways. When a toxic dose is administered, these major pathways become saturated and then follow zero-order kinetics. Renal elimination of unchanged salicylic acid becomes the major route of elimination,[17] albeit an inefficient one, because concomitant metabolic acidosis and acidic urine hamper urinary elimination.

Despite falling serum salicylate levels and robust alkalemia, the patient became more somnolent, hyperpneic, and tachycardic; these changes underscore the importance of continuing intensive clinical monitoring.[18] It is well established that the relationship between the serum salicylate level and tissue toxicity is not linear. While we were arranging for hemodialysis, the patient's hypokalemia and hypocalcemia worsened, and both conditions required multiple replacement boluses (Fig. 1).

Hemodialysis is an effective method of salicylate elimination, because the drug has a low molecular mass (138 kD), a low volume of distri-

bution (0.2 liters per kilogram of body weight), and a relatively high free fraction at toxic levels. In this patient, dialysis with a high-potassium and high-calcium bath helped to normalize the electrolyte levels, providing an added advantage over hemoperfusion or continuous therapies. He underwent dialysis for 4 hours and received additional alkalinization. The patient's condition continued to improve, and intubation was never required. When he was discharged home on hospital day 5, his condition was much improved and he was receiving no medications.

FINAL DIAGNOSIS

Salicylate poisoning.

This case was presented at the Emergency Medicine Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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