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Sickle cell disease treatment: It's not just a battle with pain

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Editor's note: *Complications of sickle cell disease are a common presentation to the emergency department (ED). Emergency physicians (EPs) and nurses must treat complications of this disease process aggressively. It is the minority of patients who abuse the use of the ED, accused of being drug seekers, victims of adverse social situations, and poor follow-up. These patients should not distract the EP in the evaluation of this dangerous disease process. Patients may present with life-threatening complications including vasoocclusive crisis, stroke, acute chest syndrome, bone-marrow infarction, osteomyelitis, and sepsis. The diagnosis and management of these complications will be outlined in this issue. Appropriate management can prevent life-threatening complications and unnecessary litigation.*

Introduction

Sickle cell anemia is the most prevalent heritable hematologic disease affecting humans.[1] An estimated 8% of the U.S. African-American population carries the sickle cell gene. One in 625 is expected to be homozygous for sickle cell hemoglobin (HbSS, with two alpha hemoglobin chains and two sickle hemoglobin chains), manifesting sickle cell disease (SCD). Approximately 70,000 Americans are expected to suffer from sickle cell disease.[2] Individuals heterozygous for sickle cell hemoglobin (HbAS) are described as having the sickle cell trait. Sickle cell anemia (SCA) is an autosomal disease caused by the replacement of glutamine with valine at the sixth amino acid position of the beta globin fraction of hemoglobin. Hemoglobin S molecules, when deoxygenated, undergo a polymerization of intracellular fibers that causes a morphologic change of the round

red blood cell (RBC) into the shape of a sickle. Due to these fibers, sickle cells have decreased deformability and internal viscosity. Sickle erythrocyte dehydration also occurs. Deoxygenation and sickling of the RBC increases calcium permeability and consequently activates the channel, resulting in cellular potassium loss and dehydration. The antifungal clotrimazole specifically inhibits this and may have a therapeutic role.[3]

In addition, sickle cell membranes have more adhesive qualities than normal red blood cells causing them to attach more readily to endothelial cells. The changes in shape, viscosity, and adhesiveness lead to sludging of sickled RBCs within the microcirculation, causing obstruction and subsequent tissue ischemia. These conditions of hypoxia, acidosis, and dehydration lead to further sickling of RBCs. Patients with the sickle trait or variants have a normal life span with only rare crises. They are at risk, however, for sudden death during exertion.[4]

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Severe Crisis and Death

Case #1. ***Wright v. City of Los Angeles.***[5] The family brought action against the city, police department officers, and fire department paramedics to recover damages for a suspect's wrongful death on theories of negligence, false imprisonment, and assault and battery; for negligent infliction of emotional distress; for intentional infliction of emotional distress; and for deprivation of constitutional rights. This action arose from the death of Jerry Eugene Wright Jr., age 20. On May 19, 1979, witnesses saw Mr. Wright being picked up by a large man and being slammed against the side of a car, beaten, punched, and hit. He claimed he was being robbed. A third man came out of an apartment and hit the large man, who then fell under the car. It appeared Mr. Wright was having difficulty moving and seemed exhausted. Mr. Wright started the car, it rolled backward then stopped, possibly having rolled over the large man.

When police arrived, Mr. Wright did not comply with demands to exit the car; he slouched down, leaning back in the driver's seat. The officers got Mr. Wright out onto the parkway, half on the grass, half in the gutter. One of the officers then kicked him into the gutter. A witness reported seeing him lying face down on the grass parkway, hands cuffed behind his back.

Mr. Wright apparently complained of head pain and asked for water. An ambulance with two paramedics arrived. The paramedics came within three to five feet of Mr. Wright and were overheard to say, "He's loaded," and "He's OK." They then left. Witnesses stated they never saw the paramedics touch Mr. Wright to take his pulse or blood pressure. He never was given water even though he continued to ask for it.

Mr. Wright complained of the handcuffs being too tight. A police officer stated he could not remove the cuffs despite his mother's request. Mr. Wright appeared to begin to doze off. An officer used his foot to turn Mr. Wright over, causing him to hit his head on the curb, and after shining his flashlight in Mr. Wright's eyes, the officer stated that Mr. Wright was on drugs. Family members nearby insisted this was not the case.

Mr. Wright's pulse was being assessed periodically by a woman in the crowd, who stated that he was aspirating. Upon rolling him over, foam was seen coming from his mouth. An officer nearby removed

the handcuffs and called for another ambulance, which arrived 15-20 minutes later. The paramedics pulled a sheet over Mr. Wright's head. No attempts at cardiopulmonary resuscitation (CPR) were performed before or after the ambulance arrived.

Police officers stated at trial that Mr. Wright was not cooperative, appeared intoxicated and incoherent at times, possibly from phencyclidine (PCP). He had upper body rigidity/muscle tension with trouble controlling his body. Witnesses stated that Mr. Wright stated he hurt all over and asked for an ambulance. The paramedic who evaluated Mr. Wright stated he performed a brief 60-second examination, visual examination at the scene to determine if there was a life-threatening situation. He noted the need for repeated questioning to elicit a response from Mr. Wright. The paramedic did not ask orientation questions or take his vital signs. He could not recall touching his skin. He told the officer that a doctor should see Mr. Wright before being booked.

Dr. Barry Freed Silverman, a board-certified pathologist, reviewed the autopsy report. It was his opinion that Mr. Wright's death was secondary to massive intravascular sickling from an underlying sickle cell trait disorder. A gross autopsy revealed no cause of death, and toxicology studies demonstrated no evidence of alcohol, PCP, or other drugs in the body. Microscopic and histology studies revealed massive intravascular sickling of essentially every red blood cell of every organ sampled. He further opined that clinical manifestations of a vasoocclusive crisis include severe pain and anemia that could lead to dyspnea, shock, and even death. He concluded that stress could have induced a massive vasoocclusive crisis in this individual with only the sickle cell trait, as his organs were requiring more oxygen than normal during the altercation.

On cause of action for wrongful death resulting from negligence, the jury found in favor of the plaintiffs. The appeals court confirmed this finding and let the $2 million award of the original jury stand.

Discussion

The burden of proof in a lawsuit against emergency medical technicians and paramedics is that the plaintiff must prove gross and flagrant negligence — rather than ordinary negligence — as is the standard for physicians and nurses. This added protection is provided in almost all states to pre-hospital providers. The gross negligence standard has been described as willful and wanton, or with utter disregard for the patient. In this case, the paramedics' care was grossly negligent. The initial paramedics' evaluation occurred from no closer than 3 feet. They did not ask any questions regarding orientation, take any history, nor perform even a basic physical examination, including vitals. The second group of paramedics attempted no cardiac resuscitation; they merely placed a sheet over the patient. Had the initial paramedics performed a history and physical exam, the patient's death may have been prevented and the paramedics may have been saved from litigation. When medical providers' actions are so cavalier, it's easy for the plaintiff's attorney to win.

Evaluation of the sickle cell patient with a vasoocclusive crisis begins with a focused history and physical examination. Records of the patient's past pattern of crises, complications, baseline laboratory values, medications, and surgeries should be sought. Therapeutic interventions include rehydration, correction of hypoxemia if present, and analgesia. Oral or intravenous (IV) isotonic or hypotonic fluids correct red cell dehydration and, along with oxygenation, discourage and reverse sickling. Further workup is warranted if fever is present. Proper emergency medical service evaluation and care would have resulted in the establishment of IV access, administration of IV fluids, and rapid transport to a hospital for further evaluation and treatment that may have been lifesaving. Even minimal examination would have revealed an individual in shock and in need of immediate medical assistance and emergency care.

Sickle Cell in Pediatric Patients

Case #2. *Wells vs. Lurate*.[6] Parents Marvin and Annette Wells brought a medical malpractice action against Dr. Robert Lurate for the physician's treatment of their son. The Eleventh Judicial District Court entered judgment for the physician; the parents appealed the decision. Marvin Wells Jr., a 14-month-old sickle cell anemia patient, was given doses of penicillin daily as part of his treatment for the disease. On the afternoon of Nov. 3, 1990, the child's mother noticed that he had a fever and gave him acetaminophen instead of the usual dose of penicillin. The child reportedly was active during the late afternoon. He awoke from a nap at 7:30 p.m.; again his mother noted his being feverish,

irritable, and in visibly worsened condition. She brought him to DeSoto General Hospital ED in Mansfield, LA.

The ED physician on duty, Dr. Lurate, performed a history and physical examination of the child. Vital signs revealed a respiratory rate of 68 breaths per minute, with a temperature of 103.5° F and a pulse rate of 120 beats per minute. Auscultation revealed diffuse rhonchi in the lungs. Dr. Lurate prescribed IV fluids and supplemental oxygen, and ordered a complete blood count (CBC). The child improved with nonlabored breathing. The child appeared stable to both Dr. Lurate and attending nurse, Ms. Alicia Williams. Hemoglobin level was 4.5 g/dL; hematocrit was 15.5%.

Dr. Lurate contacted the pediatric ED at Louisiana State University Medical Center (LSUMC) in Shreveport, consulting with Dr. Terry Kendrick, the pediatrician on duty. After being informed of the child's physical condition, Dr. Kendrick recommended that the child be brought to LSUMC as quickly as possible, as his condition required intensive care unit (ICU) facilities not available at DeSoto General. Dr. Lurate reported that Mansfield did not have ambulance service available, and that the closest ambulance would take an hour to arrive from Logansport. Dr. Lurate told Dr. Kendrick that the child appeared stable, and so they decided that the quickest means of transporting the patient to LSUMC was by private car. The IV fluids and oxygen were discontinued, and the child's vital signs were not rechecked before transport. The child left in a private car at 10:45 p.m. for the approximately 45-minute trip to LSUMC. Several miles outside Shreveport, the child began having seizures. Upon arrival at LSUMC ED, shortly after midnight, the child was comatose. The patient was transferred to the pediatric ICU. Despite treatment, the child's heart stopped at 3:40 a.m., and CPR was not successful. The cause of death was recorded as overwhelming pneumococcal sepsis and septic shock.

A medical review panel formed at the request of the plaintiffs found that the defendant failed to follow accepted emergency medical standards in his treatment of the plaintiffs' child. At trial, the jury found that Dr. Lurate had not breached the standard of care, thereby foreclosing its consideration of the remaining issues of causation and damages.

In their appeal, the plaintiffs argued the jury was wrong in finding Dr. Lurate not negligent. They contended he breached the standard of care by not administering antibiotics and a blood transfusion, and by transporting the child in a private car without oxygen or IV fluids. Dr. Robert West, the plaintiffs' emergency medicine expert, testified that Dr. Lurate breached the standard of care by failing to initiate antibiotic treatment for a child with sickle cell disease presenting with a high fever and an elevated white blood cell (WBC) count. The plaintiffs' pediatrics expert Dr. David Beckton testified that the child should have received antibiotics soon after his arrival at the ED.

Dr. Lurate stated he routinely does not give antibiotics to patients before identifying a source of infection because of the risk of a reaction. Dr. Lurate testified that if the patient had a viral infection, there was a chance antibiotics would not destroy a resistant strain, which would then continue to spread in the patient's body. He stated he did not give parenteral antibiotics because of the possibility that a spinal tap would be performed and antibiotics would preclude identification of an organism. Dr. Lurate also stated that he believed the child had received his prescribed penicillin because the mother stated that he had not missed any doses.

Drs. Beckton and West testified that the child should have received a blood transfusion. Dr. West, however, was unaware of the DeSoto General Hospital's blood bank capacity. Dr. Beckton stated that a type and match normally is required, but O-negative blood can be given in an emergency. Dr. Lurate stated that the lab tests take more than an hour to type and match. The blood bank could not screen for antibodies and might not have the proper blood type available after the process. He stated that even the LSUMC facilities took 1½ hours to transfuse the child.

Dr. Lurate also was criticized for transporting the child via private car — not an ambulance — with the discontinuation of oxygen and fluids reducing the child's chance of survival. Dr. West stated that it was negligent to send the child in a private car because other options usually are available. On cross-examination, he admitted he did not have personal knowledge of ambulance service at DeSoto General. Dr. Beckton testified he would have maintained the oxygen. He acknowledged it could not reverse the pneumococcal infection, nor would it affect the child's blood capacity to carry oxygen to the organs.

The pediatric expert for the defendant Dr. Kendrick,

who also had extensive pediatric emergency experience, testified that fluids and oxygen for the duration of the trip would not have made any difference in the outcome. The defendant's other pediatric expert, Dr. William Haynie, testified that the removal of the oxygen made no difference in the chance of survival as the oxygen-carrying capacity of the blood was diminished severely, secondary to sickle cell disease and pneumococcal infection. He stated it was a judgment call on the part of Drs. Lurate and Kendrick because none of the options were good. He further stated Dr. Lurate's treatment of the child met the standard of care. Dr. Kendrick also stated Dr. Lurate's treatment met the emergency medicine standard of care.

Dr. Lurate testified he was alarmed by the child's hemoglobin level of 4.5 and consulted with specialist Dr. Terry Kendrick, who stated it was necessary to get the child to LSUMC pediatric ED as soon as possible. After discussing transportation options and lack of pediatric intensive care/pediatricians at DeSoto General, the doctors decided private auto transport was their best option.

The appellate court concluded that the jury had heard conflicting expert testimony regarding Dr. Lurate's treatment of the child meeting the standard of care and could reasonably conclude that he had rendered appropriate emergency medical care, choosing the best available means to preserve the child's survival given the circumstances. The court felt the jury was not clearly wrong in its evaluation of expert testimony or its finding that Dr. Lurate was not negligent.

Discussion

Sickle cell anemia causes functional hyposplenism. The splenic sinusoids filter blood through capillaries as small as one micron, sequestering senescent or rigid red blood cells from the circulation. Macrophages ingest bacteria from within the capillary network. Presentation of their antigens to the immunoglobulin-producing B lymphocytes stimulates production of opsonizing antibody.

Repeated episodes of obstruction of splenic sinusoids by sickled cells leads to splenic infarction, fibrosis, and subsequent loss of reticuloendothelial function. After 3 to 5 years of age, autosplenectomy presumably has occurred. Also contributing to an immunodeficient state is a lack of humoral immunity against encapsulated organisms. Prior to penicillin prophylaxis and routine *Haemophilus influenzae* type B vaccination, severe sepsis and meningitis in children with SCA was uncommon before 6 months of age, most prevalent from ages 1 to 2 years, and less frequent after ages 5 to 6 years.[7]

Post-splenectomy (including functional splenectomy) sepsis is a rapidly fatal illness mostly due to encapsulated bacteria. The highest incidence of sepsis in children with SCA occurs after infantile splenectomy. The most common organism is *Streptococcus pneumoniae*. *Haemophilus influenzae* and *Neisseria meningitidis* are found less commonly, the former due to routine vaccination.

Clinically, the child may appear toxic and acutely ill, possibly with tachycardia and hypotension. The sensorium may be altered secondary to hypotension or meningitis. A primary source of infection may be localized, such as pneumonia, otitis media, pharyngitis, or sinusitis. Laboratory studies often show an altered (elevated or depressed) WBC count with left shift, possibly toxic granulation and Dohle bodies. Peripheral blood smear may show intravascular bacteria. Thrombocytopenia, disseminated intravascular coagulopathy, and organ failure are other possible findings.

The history of fever at home in this child with SCD, his poor response to fluids, and the laboratory finding of anemia indicate a high likelihood of sepsis. Life support measures and broad-spectrum antibiotics with activity against beta-lactamase *H. influenzae* and penicillin-resistant *Streptococcus pneumoniae* should be instituted rapidly. Even if the family in this case had been compliant with penicillin dosing, this should not have changed the physician's management, as IV antibiotics are indicated. Ceftriaxone, vancomycin, chloramphenicol, fluoroquinolones, and macrolides are all possible antibiotic choices that depend upon patient allergies, the severity of illness, age, and comorbidities. **There never should be a delay in administration of antibiotics while awaiting diagnostic procedures, including lumbar puncture (LP).** Inotropic agents often are necessary as fluids may induce only a transient hemodynamic response. The clinical course of patients with SCA and sepsis likely will be complicated with high, early mortality.

Patients will be better served with initial treatment in the ED, such as in this case, with IV fluids, IV antibiotics, and inotropes if necessary, while awaiting appropriate medically assisted transport. All EDs

— rural and urban — should have transfer arrangements with either an air ambulance service (particularly with the rapid increase in helicopter programs nationwide) or a ground-based ambulance service. In this case, had the patient experienced a seizure in the safe confines of the ED, medications could have been administered, his airway stabilized, and other lifesaving measures performed. Patients transferred by car present not only a potential for negligence claim, but also federal penalties under the Emergency Medical Treatment and Labor Act (EMTALA). Don't transfer patients by car to an accepting ICU. The transferring doctor is responsible under both negligence laws and EMTALA for the safety of the patient until his/her arrival at the accepting hospital.

Blood transfusions given to sickle cell disease patients improve oxygen-carrying capacity of blood and dilute circulating sickled RBCs, improving microvascular perfusion. Transfused blood for patients with sickle cell should be free of sickle cells, anti-red blood cell and Rh compatible, matched phenotypically for C, E, and K antigens, leukocyte reduced, and possibly irradiated.[8] Complications of transfusion in sickle cell patients include allergic and febrile reactions, hemolytic reactions, alloimmunization against the above antigens, iron overload, immunosuppression, as well as transmission of infectious disease. While a potential complication, transfusions should not be withheld to those in need. Indications for transfusion include symptomatic anemia due to aplastic crisis, acute hemorrhage, acute splenic or hepatic sequestration, acute chest syndrome, multiple organ failure syndrome, sepsis and meningitis, or acute neurological event. Exchange transfusion should be considered in acute cerebrovascular accident (CVA), acute chest syndrome, acute priapism unresponsive to routine therapy, and prior to surgery — this after correction of a hemoglobin level of 6 g/dL or lower by simple transfusion.[9]

Acute splenic sequestration is the second most common cause of death in children younger than 5 years of age. The presentation is hypovolemic shock with splenic enlargement. Often following a viral infection, sickled cells obstruct splenic outflow, which leads to pooling of blood in the spleen. Major sequestration crisis is defined by hemoglobin declination greater than 3 g/dL from baseline or to a value less than 6 g/dL total. Minor sequestration crisis is defined by splenic enlargement with a hemoglobin level greater than 6 g/dL. As the bone marrow is responsive, the reticulocyte count will be elevated. Treatment involves red cell transfusion or exchange transfusion. Resistant cases may require splenectomy.

Neurologic Issues in Sickle Cell Disease

Case #3. *Cooper v. Sams, et al.* In *Cooper* the mother of a sickle cell patient who suffered brain damage, brought a medical malpractice and products liability suit against physicians, a nurse, a hospital, and drug manufacturers. Prior to trial, Ms. Cooper voluntarily dismissed the case against the physicians and Nurse McCain and settled with the hospital for $100,000. After settlement, the plaintiff proceeded against Louisiana Patient's Compensation Fund for damages in excess of $100,000, and the Fund filed a third-party demand against manufacturers Taylor and Janssen. The trial court granted summary judgment in favor of Taylor and Janssen and dismissed them. A jury trial was held to determine damages, if any, owed to Cooper by the Fund.

On April 11, 1985, Darrell Cooper, a 21-year-old with known sickle cell anemia, was admitted to St. Frances Cabrini Hospital with fever and rash thought to be due to either an allergic reaction to an over-the-counter antacid or an infection. His condition worsened over the next several days, and he began to exhibit symptoms of sickle cell pain (vasoocclusive) crisis. He also had severe abdominal pain and vomiting. On the night of April 22, he had an emergency cholecystectomy by Dr. Weldon that was uneventful.

Shortly after midnight, he was returned to the ICU on a ventilator accompanied by anesthesiologist Dr. Lewis and nurse anesthetist McCain. At 1 a.m., he experienced a tonic-clonic reaction (per Dr. Lewis) or seizure (per Nurse McCain) and was given valium with good control of the movements. At 1:20 a.m., he began to fight the endotracheal tube and was given fentanyl to further sedate him. During the next two hours, he experienced more seizure activity and escalating fevers. Dr. Weldon ordered phenytoin, though he was not informed of the patient's temperature or other vital signs. Upon arriving at the bedside at 3:45 a.m., Dr. Sams, an internist, immediately poured ice all over Mr. Cooper's body. He ordered medications and treatments including dantrolene sodium, "which seemed to be the antidote that finally brought the fever down after it climbed over 108 degrees," according to Dr. Sams.

The patient lapsed into a semicomatose state for

several days, possibly suffering a stroke. Thereafter, it was determined he had suffered permanent brain damage affecting his cognitive function with physical weakness on his right side. He began to recognize family members and was later taught how to read and write again. He did not remember his college experience nor was he able to live independently, and his condition was compared with that of a second-grader by his brother.

While still hospitalized, his physicians — in consultation with other specialists — attempted to determine what happened to cause the fever and subsequent brain damage. Possible etiologies included infection, a CVA, or ischemia affecting that part of the brain that regulates temperature (either leading to the fever or resulting from the high fever or sickle cell crisis). Cerebral computerized tomography (CT) scans did not confirm a stroke, and his brain damage was considered diffuse. The plaintiff suggested malignant hyperthermia or status epilepticus causing the fever as possible etiologies and argued that this was caused by the fentanyl. (The court rejected this argument, as it is the anesthetic of choice for patients prone to malignant hyperthermia).

The plaintiff's expert, Dr. Speeg, who practices general internal medicine and pediatrics, stated that failure to promptly treat the symptoms of hyperthermia (i.e., the fever) caused the patient's neurologic damages. The patient's treating hematologist, Dr. Ule, discussed the disease process of sickle cell anemia including its neurologic complications such as strokes, but felt she was not qualified to state whether a high fever could induce brain damage. She stated, "We have clinical suspicions as to the cause" of the fever and seizures, yet never revealed them.

The jury found that the negligence of hospital was the sole cause of Mr. Cooper's damages, and judgment was rendered in favor of Mr. Cooper and against the Fund, awarding $13,279,905 to cover bodily injury, permanent disability, economic loss, loss of consortium, and medical expenses.

On appeal, after oral arguments were heard, Mr. Cooper and the Fund settled the damages portion of the case.

Discussion

While the etiology of Mr. Cooper's permanent neurologic deficit is unclear, CVA is highly probable. Cerebrovascular changes are reported in 25% of SCD patients, though only 7-9% present with classic neurologic signs. By age 20 years, stroke (CVA) has occurred in 11% of SCD children; a slight majority (54%) were infarcts in one study.[11] There is a second peak in brain infarction in individuals 50 and older. Intracranial hemorrhage is less common in young children, but more common in older children and adults.

Presentation of stroke in SCD includes focal seizure, hemiparesis, or other neurologic signs. CT or magnetic resonance imaging (MRI) identifies infarct or hemorrhage. Lumbar puncture should be considered to rule out infection of the central nervous system if there is no evidence of elevated intracranial pressure.

Treatment options are transfusion and exchange transfusion with the goal being to reduce sickle cell concentration to less than 30% of total hemoglobin. It is now the standard of care to continue long-term transfusion therapy to reduce the incidence of recurrent stroke — to as low as 10% — in children. There is no consensus on when to discontinue transfusion therapy. The National Heart, Lung, and Blood Institute encourages transcranial Doppler ultrasonography (TCD) of asymptomatic children with SCD to identify those with elevated internal or middle carotid artery mean velocities. These children are at 10-20 times the baseline risk of stroke (10% per year) compared with children with SCD not selected by TCD. The role of hydroxyurea in stroke prevention has not been established.

Adult SCD patients with stroke deserve consideration of IV tissue plasminogen activator (tPA) administration in the usual three-hour time window from onset if there are no other contraindications including hemorrhage. Adults also may be placed on antiplatelet and anticoagulants for prevention.

Bone-Marrow Infarction in Sickle Cell Disease

Case #4. ***Moore v. University of Cincinnati Hospital.***[12] The mother of a sickle cell beta thalassemia (SC-beta thal) patient who died, appealed her dismissed wrongful-death claim against the hospital. On June 1, 1989, Jamie Moore, a 25-year-old male was diagnosed with an asthma exacerbation and admitted from the ED at the University of Cincinnati Hospital. His asthmatic condition stabilized, and he was noted to have normal blood tests. On June 4, he began complaining of musculoskeletal pain and was diagnosed with vasoocclusive/sickle cell pain crisis

and given meperidine. His condition worsened on June 6, and had a "downward trend on repeat CBC." His pain medication was switched to morphine, 6 mg every three hours, as ordered by Dr. Kay Johnson. At 5:30 p.m., he received his first dose, and his pain seemed relieved. He became agitated by 7:30 p.m., pulling at his IV lines. He suffered a cardiac arrest at 9:15 p.m., was resuscitated, then subsequently arrested again, and was pronounced dead at 10:25 p.m. The autopsy report indicated he died as a result of a sickle vasoocclusive crisis that was complicated by bone-marrow infarction and resulting fat embolization.

The patient's mother, Ms. Mary Moore, filed a complaint against the hospital consisting of a survival action and a cause of action for wrongful death, both alleging negligence and failure to obtain informed consent with resultant pain and suffering. Ms. Moore's expert, Dr. Oswaldo Castro, testified about sickle cell disease, the potential for bone-marrow infarction and fat embolization, and blood transfusions. He testified that a blood transfusion would have been Jamie Moore's only chance of survival, but it was difficult to say whether it was more probable that he would have survived had he received a transfusion. Indeed, of his patients who had received transfusions, only one-third survived. The court of appeals ruled the appellant (Ms. Moore) failed to establish proximate cause, as this was less than the 50% likelihood as required by the Ohio Supreme Court in loss-of-chance theory of recovery cases of action for wrongful death where medical malpractice is alleged.

The court of appeals found merit in the argument regarding survival action only; that the decedent should recover for pain and suffering as a result of the hospital's failure to administer pain medication as ordered (i.e., every three hours). The second dose of morphine should have been given at 8:30 p.m. and noted in hospital records. The case was remanded for further proceedings on the survival action, only with regard to pain and suffering due to failure to administer the 8:30 p.m. morphine dose.

Discussion

Pain is probably the driving force behind most ED visits by sickle cell patients. The severe pain of a potential vasoocclusive crisis needs to be addressed while investigating the usual signs and symptoms. Hydration, oxygenation (if hypoxemic), antibiotics (if indicated), as well as pain control, are indicated. Sickling cells obstruct the microvasculature. Hypoxic tissues release mediators of inflammation that initiate painful stimuli transmitted along A and C peripheral fibers. Psychosocial factors also are important modifiers. Assessment relies mainly on patient self-report using various scales appropriate for the age of the patient. Nonopioid analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs such as ibuprofen and ketorolac, tramadol, topical agents, and corticosteroids are all possible options for minor to moderate SCA pain. For reported severe pain, opioid analgesics are the standard, and include agonists, partial agonists, and mixed agonist-antagonists. There may be enhancement of analgesic effect with delay or prevention of tolerance to opioids if small doses of antagonists are used in combination with an agonist.[13] Analgesic adjunctive agents include antihistamines, benzodiazepines, antidepressants, and anticonvulsants.

SCD patients have a high incidence of infection. Osteomyelitis is the second most common childhood infection. *Salmonella* and *Staphylococcus aureus* are the usual causative agents. Bone infarction and osteomyelitis both present with fever, bone pain, and soft-tissue swelling. There is great difficulty distinguishing between these two conditions. In children, presumptive treatment for infection with IV antibiotics for osteomyelitis often is begun while awaiting culture results from blood and bone aspiration. EPs should never delay antibiotics to await culture results or lumbar puncture. Proximity or apparent joint involvement requires immediate drainage to avoid long-term morbidity. Plain radiographs help rule out fracture and bone tumors, but often are not helpful differentiating infarction from infection, as radiologic evidence of osteomyelitis may not appear for 10-14 days from onset. MRI or contrast-enhanced CT may be required to localize an area for culture. Response to treatment with fluids and analgesics and changing clinical course may aid the clinician in final diagnosis.

Mr. Moore initially was admitted for an asthma exacerbation and vasoocclusive pain crisis; however, when his symptoms worsened despite treatment, one's suspicion for bone-marrow infarction should have been raised. Fundoscopic examination may reveal refractory bodies (fat globules). Urine sediment may contain fat globules. Fat globules also may be found in sputum macrophages or bronchial washings.

Treatment is with exchange transfusion with or without heparin and corticosteroids.

Chest Syndrome in Sickle Cell Disease

Case #5. ***Webb v. Tulane Medical Center Hospital and Abe Andes, MD.***[14] In this case, the mother of a sickle cell anemia patient, who died following cardiopulmonary arrest in hospital, sued the hospital and physician. The Civil District Court, Parish of Orleans, dismissed the claim against the physician and entered judgment awarding damages to plaintiff on the claim against the hospital. The hospital appealed, and the plaintiff answered the appeal by alleging error in dismissal of claim against the physician.

Rodney Comeaux, a 23-year-old male with sickle cell anemia had chronic poor health suffering continual bouts of pneumonia and sickle cell crisis. In June 1988, he had complaints of chest and abdominal pain. Dr. Andes admitted him to Tulane Medical Center Hospital (TMC) where he was radiographed and treated with analgesics and IV antibiotics. He was discharged July 6, 1988, with pulmonary infarction vs. pneumonia, prescribed Keflex, (cephalexin) with follow-up July 12 at 2:30 p.m.

Mr. Comeaux appeared several hours early at Dr. Andes' SCD clinic on the 12th, where he couldn't be seen due to Dr. Andes attending to previously scheduled patients. He went to his mother's office (she was Deputy Director of Health for New Orleans at that time) where an internist named Dr. Lutz worked. Dr. Lutz accompanied Mr. Comeaux to TMC's ED, where a diagnosis of multiple bilateral pulmonary infarctions was made. After admission, Dr. Andes examined Mr. Comeaux at 4 p.m. in his hospital room. He advised packed-red-blood-cell (PRBC) transfusion, but Mr. Comeaux refused on the basis of a fear of HIV risk. By the morning of July 13, his temperature had steadily increased with thick, yellow sputum production. Pulmonologist Dr. John Hill suspected pulmonary infarction with pneumonia, ordering sputum testing and chest radiographs. Dr. Andes felt the antibiotics were having little effect on the chest pain and fever. Mr. Comeaux agreed to a transfusion late in the afternoon on July 13.

Dr. Andes ordered two units with transfusion beginning at 12:45 a.m. on July 14, and was completed sometime after 8 a.m. Temperature at 4 a.m. was noted to be 103.8º F. Dr. Andes examination at 8:30 a.m. noted continued shortness of breath and chest pain, basically unchanged. At noon, a temperature of 103.2º F was noted. Dr. Andes ordered an arterial blood gases (ABG) measurement because of continued chest and stomach pain and labored breathing. This was drawn at 12:50 p.m. The patient went into cardiopulmonary arrest at 1 p.m., was resuscitated after 30-35 minutes, but remained comatose having suffered irreparable brain damage. Life support was removed July 21, and the patient died. There was no disagreement that the patient aspirated his emesis.

A medical review panel found no negligence by either Dr. Andes or the hospital. The panel concluded the patient suffered natural consequences relating to his SCD. The plaintiff's lawsuit was tried by a judge who exonerated Dr. Andes, but found TMC at fault for nursing negligence. A Dr. Seiler testified that during transfusion, a patient should be monitored physically every 20 minutes. Nursing notes and charting did not establish adequate attendance to Mr. Comeaux, and there were temperatures hovering at 104ºF from the start of transfusion to the moment of arrest. Also, the patient's respiration rate was dangerously high the entire period. The trial judge felt that given the temperature, respiration rate, and the patient's condition of pulmonary infarction and/or acute chest syndrome, he should have been observed more frequently by TMC nursing. Though Dr. Andes stated the nursing staff complied with Tulane's protocol, the court embraced Dr. Seiler's testimony that the protocol failed to meet the standard of care. Dr. Lutz testified that Mr. Comeaux was not monitored adequately.

The court stated that Dr. Andes did not breach standard of care for a hematologist, and evidence established that the diagnosis of pulmonary infarction was reasonable. The court stated that it believed that the patient had acute chest syndrome though the distinction regarding treatment is not extremely meaningful as evidence established that PRBC transfusion is appropriate treatment for either condition. The court found Mr. Comeaux 20% at fault for refusing transfusion.

TMC appealed. The appeals court reviewed expert testimony by hematologists on both sides and concluded that simple transfusion was an acceptable treatment for pulmonary infarction or an acute chest syndrome, and there was no evidence of fluid overload. The court reversed the portion of the judgment holding TMC liable for nursing negligence and

affirmed the portion dismissing plaintiff's claims against Dr. Andes.

Discussion

While nursing protocols apparently were followed, they arguably may not have been sufficient to meet the standard of care in monitoring this critically ill patient, leading to prolonged litigation for the hospital. This case illustrates the complications that sickle cell patients may encounter. An adverse outcome — or as in this case, a patient's death — does not necessarily equate to malpractice against the physician or nursing staff. Acute chest syndrome (ACS) defines acute episodes of fever, chest pain, hypoxemia, cough or hemoptysis, tachypnea, wheezing, chills, worsening anemia, leukocytosis, and new pulmonary infiltrates in patients with sickle cell disease.[15,16] Young children are more likely to have isolated upper or middle lobe disease, while adults have lower lobe infiltrates and more frequent pleural effusions.[17] Multilobular pulmonary disease is indistinguishable from acute (adult) respiratory distress syndrome, which may be the end result. Bilateral or multilobular infiltrates warrant a worse prognosis. ACS is second to vasoocclusive pain crises as the most common cause of hospitalization, and it is the most common cause of death for SCA patients. It is usually a self-limiting condition that resolves with treatment, but can be associated with respiratory failure. Mortality rates were documented at 1.1% for children and 4.3% for adults in one study.[18]

Risk factors for ACS include leukocytosis, high hemoglobin levels, low fetal hemoglobin (HbF) levels, high pain rate, SCD, sickle beta thalassemia, fever, age, rib or vertebral infarction, pregnancy, aseptic hip necrosis, analgesic use, acute anemic event, and cold weather.[19, 20] Etiologies include infection, pulmonary embolism, atelectasis, excessive hydration leading to pulmonary edema, bronchospasm or reactive airway disease, dehydration, or hypoxia. Community-acquired pneumonia is the leading cause of infection, usually caused by chlamydia, mycoplasma, respiratory syncytial virus, *Streptococcus pneumoniae, Haemophilus influenza,* but also *Staphylococcus aureus*.[21] Pulmonary embolism resulting from long bone-marrow infarction leading to fat embolism may be more common than previously thought.[22,23] Peripheral thromboembolism is uncommon despite the hypercoagulable state in SCD.[24] This state appears to cause more stimulation of cellular adhesion and activation of the inflammatory system than initiation of thrombotic cascade.[25, 26] Atelectasis may be due to splinting secondary to rib or vertebral infarction, or it may be secondary to hypoventilation due to overzealous or inadequate pain management.[27]

The pathophysiology of ACS is unclear. Ventilation-perfusion mismatch secondary to hyperreactive airways leads to hypoxemia and acidosis causing further RBC sickling. Sickled RBCs adhese to endothelial cells within the small- or medium-sized pulmonary vessels and occlude microvascular flow resulting in pulmonary infarction.[28-30] Free fatty acids liberated from membrane phospholipids are believed to cause pulmonary endothelial damage resulting in a leak syndrome similar to acute respiratory distress syndrome (ARDS) if severe.[31]

The work-up for an ACS includes serial chest radiographs, deep sputum (from induction or bronchoalveolar lavage), microscopic analysis and culture, blood culture, ABG measurement, and hemoglobin level monitoring. Ventilation-perfusion scans or spiral chest CT, and ruling out of deep venous thrombosis of the lower extremities or pelvis may be indicated.

Therapeutic management focuses upon treating potential infection and infarction concurrently, as the two are difficult to distinguish, and each may lead to the development of the other. An IV, third-generation cephalosporin in combination with a macrolide or a fluoroquinolone is recommended to cover typical and atypical pathogens.[32] Careful hydration, judicious analgesic use, oxygen, and incentive spirometry and transfusion therapy are conventional management in ACS. Simple transfusion and partial or complete exchange transfusion decrease the proportion of sickled RBCs. Corticosteroids may be beneficial in children[33] but may hypertrophy fat in adults, increasing the chances of fat embolization as well as inducing or worsening avascular necrosis.[34]

Conclusion

Sickle cell disease patients often present to the ED with pain complaints, although a thorough evaluation for the complications of SCD is warranted to both provide appropriate care and avoid litigation. A detailed history is essential to evaluate the patient and should include the prior frequency of pain episodes, past complications of SCD including ACS, stroke,

TIAs, cholecystectomy, asthma or reactive airway disease, and past transfusion therapy. Signs and symptoms of infection may help stratify the presenting complaint further.

Life threats include CVA, pulmonary infarction or infection predisposing to an acute chest syndrome, and infection/sepsis. Other life threats in this functionally asplenic population include splenic sequestration, transient aplastic crisis, and bone infarction, potentially leading to fat embolization. Evaluation and treatment will depend upon the patient's presenting symptoms. EPs and nurses must remain vigilant in seeking out and treating complications of sickle cell disease to reduce morbidity and mortality.

Endnotes

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CE/CME Questions

1. Which of the following statements is *false*?

A. Pain secondary to vasoocclusive crisis is the most common reason for seeking medical attention in patients with sickle cell anemia.
B. The use of parenteral fluids and non-narcotic analgesics is warranted only in pain crises related to sickle cell anemia.
C. Fever in a patient with SCD indicates sepsis until proven otherwise.
D. Coverage with parenteral broad spectrum antibiotics should be instituted as quickly as possible in the face of fever or history of fever at home in the child with SCD.

2. All of the following conditions are indications for simple blood transfusion in SCD *except*:

A. Symptomatic anemia due to sepsis, aplastic crisis, acute splenic or hepatic sequestration.
B. Acute chest syndrome, hemoglobin level greater than 10 g/dL.
C. Acute priapism not responsive to routine therapy, hemoglobin level less than 6 g/dL.
D. Acute chest syndrome, hemoglobin level less than 6 g/dL.

3. Which of the following statements describing ACS is *false*?

A. In children, the upper lobes often are affected; in adults, the lower lobes often are filled with pleural effusions.
B. Features include fever, elevated WBC, hypoxemia, leukocytosis, and new infiltrates on chest x-ray.
C. It is the most common cause of death in patients with SCD.
D. It is easily differentiated from pulmonary infarction and treatment is radically different.

4. In SCD patients with extremity pain, the EP should be concerned with bone-marrow infarction, osteomyelitis, and vasooclussive crisis. Which one of the following statements is true?

A. These conditions are easily distinguished with simple laboratory tests and radiographs.
B. The only treatment necessary is fluids, oxygen, and analgesics.
C. Radiographs are taken to distinguish osteomyelitis from infarction.
D. The clinical course may help distinguish among these entities.

Answers: 1. B; 2. B; 3. D; 4. D.

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