Child Neurology Open
Volume 5: 1-3

DOI: 10.1177/2329048X18792441
journals.sagepub.com/home/cno
SAGE

A Case of Delayed-Onset Posthypoxic Leukoencephalopathy in a Pediatric Patient

Kristen Smolinsky, MD[1] and Ivona Sediva, MD[2]

Abstract

We present a 16-year-old female status post traumatic brain injury from severe motor vehicle crash with prolonged extrication. Initially with a Glasgow Coma Scale of 4 and blood pressure of 80/40, she required emergent intubation. Head computed tomography was notable for skull fracture with hematoma, diffuse axonal injury, and 6-mm midline shift with right uncal herniation. On hospital day 1, she underwent decompressive R hemicraniectomy. She received neuroprotective treatment including a hypocarbic, hypernatremic state with close blood pressure monitoring for appropriate cerebral perfusion. On hospital day 4, patient was extubated and weaned off pressors and hypertonic saline. On hospital day 6, she was able to get out of bed to a chair, was speaking some words, following commands, and tolerating bites of food. On hospital day 8, she developed sudden agitation, combativeness, confusion, and could no longer follow commands. Magnetic resonance imaging now demonstrated confluent restricted diffusion consistent with acute changes. Imaging and examination findings were consistent with delayed-onset posthypoxic leukoencephalopathy.

Keywords

Posthypoxic Leukoencephalopathy, severe hypoxic brain injury, altered mental status, pediatric

Received May 1, 2018. Received revised June 26, 2018. Accepted for publication July 12, 2018.

Delayed-onset posthypoxic leukoencephalopathy is a rare condition in which a patient who has suffered severe anoxic brain injury develops delayed neurologic sequelae secondary to demyelination in the white matter of the cerebral hemispheres. The overall findings are believed to be related to one of the following 3 clinical situations described by Plum and Posner[1]: anoxic anoxia (oxygen fails to reach the blood due to low environmental tension or pulmonary function), anemic anoxia (low oxygen carrying capacity of blood as in carbon monoxide poisoning), or ischemic anoxia (failure of cerebral blood flow).

Presentation classically consists of a period of full neurologic recovery, followed by decompensation 7 to 21 days after the inciting incident. Neurologic sequelae may include disorientation, amnesia, hyperreflexia, parkinsonism, or psychosis.

Reported cases have been seen in cardiac arrest, overdoses of opioids or benzodiazepines, carbon monoxide poisoning, and strangulation. One case study followed 2360 victims who suffered acute anoxic injuries secondary to carbon monoxide poisoning. Sixty-five of those people were diagnosed with delayed neurologic sequelae based on initial anoxic injury, presentation of delayed symptoms, and computed tomography (CT) findings. Ages of these patients ranged from 34 to 80 years (mean, 56.1 years), with the peak incidence in the sixth and seventh decades.[2] There were no reported cases in the pediatric population during the literature review.

The pathophysiology of this phenomenon is still unclear, but theories include direct myelinotoxic injury, delayed apoptosis of oligodendrocytes, genetic predisposition leading to disruption of enzymes required for myelin turnover, or the inability of cerebral white matter to compensate for hypoperfusion due to weaker blood supply in comparison to gray matter or posterior fossa.[3]

[1] Brown University Pediatric Program, Hasbro Children's Hospital, Providence, RI, USA
[2] Division of Pediatric Intensive Care, Hasbro Children's Hospital, Providence, RI, USA

Corresponding Author:
Kristen Smolinsky, MD, Hasbro Children's Hospital, 593 Eddy St, Providence, RI, USA.
Email: ksmo21@aol.com

Case Study

This is the case of a 16-year-old female who was admitted to the pediatric intensive care unit after suffering traumatic brain injury in a severe motor vehicle crash with prolonged extrication. At the scene of the accident, she was found to have a Glasgow Coma Scale of 4 and a blood pressure of 80/40. She was emergently intubated and life-flighted to a level I trauma center. Initial head CT was notable for a right-sided depressed parietal skull fracture, right frontotemporal hematoma, multiple hyperdense punctate foci in the gray–white junction consistent with diffuse axonal injury, and 6-mm right-to-left midline shift with findings suggestive of right uncal herniation.

She was emergently taken to the operating room for decompressive right hemicraniectomy and subsequently admitted to the pediatric intensive care unit. Standard neuroprotective management was initiated including ventilator management to maintain a goal CO_2 of 35 to 40. She was treated with hypertonic saline to maintain blood sodium levels with a goal of 150 to 155 and vasopressors were initiated to maintain a goal mean arterial pressure of >65. Postoperative CT was obtained on hospital day 2, which showed residual midline shift and persistent punctate foci of hemorrhage, but no additional signs of injury.

On hospital day 4, she was extubated with stable hemodynamics and weaned off both vasopressors and hypertonic saline. Sodium at that time was 156 and her neurologic status steadily improved over the next few days. On hospital day 6, she could get out of bed to chair, was speaking some words, following commands, and tolerating bites of food. Sodium at this time was 145. On hospital day 7, she required increased normal saline due to brisk urine output and a drop in her serum sodium to 139. On hospital day 8, she developed acute worsening in her mental status with increasing agitation, combativeness, confusion, and inability to follow commands. Her urine output remained brisk and her serum sodium continued to drop to 131 by the end of the day. Hyponatremia was thought to be secondary to cerebral salt wasting, but the cause of her sudden change in mental status was unclear.

Repeat CT and magnetic resonance imaging (MRI) were obtained to investigate the cause of altered mental status. Imaging demonstrated persistent foci with more intense fluid-attenuated inversion recovery signal abnormalities in the corpus callosum as well as contusion within the right temporal and frontal lobes with more intense flair signal abnormality consistent with progression of findings from imaging on initial presentation.

Additionally, MRI showed confluent restricted diffusion with minimal associated fluid-attenuated inversion recovery signal abnormality involving the corpus callosum, as well as the white matter in the right frontoparietal lobes, right temporal lobe, and left parietal lobe. Given the discrepancy between the intensity of restricted diffusion and minimal fluid-attenuated inversion recovery signal, these findings were believed to represent an acute change as opposed to progression of old injuries and consistent with delayed-onset posthypoxic leukoencephalopathy. She was started on amantadine therapy, which has shown promising benefits in treatment of this condition.

She remained in the hospital for 18 days and was subsequently discharged to rehab. At that time, she had spontaneous movements of her extremities, could sit unsupported for short periods of time, write her name, and follow simple commands. She remained nonverbal, however, and continued to require moderate to maximum assistance with activities of daily care including feeding, brushing her teeth, and dressing. She was continued on amantadine while at rehab, and at her neurosurgical follow-up 4 months later, she had made significant advancements with speech, able to answer all questions on her own, and could now ambulate flat terrain and stairs with assistance.

Discussion

Delayed posthypoxic leukoencephalopathy is a demyelinating syndrome which is represented by neurologic decline after initial recovery in the setting of a hypoxic ischemic event. The case described above represents a classic presentation of this rare condition. It is reasonable to assume that our patient had suffered severe hypoxic event during her prolonged extrication with an initial blood pressure recorded as 80/40 and Glasgow Coma Scale of 4. She showed a period of rapid neurologic recovery which was followed by sudden neurologic decline 8 days after the initial injury. Imaging at that time showed an acute change, not consistent with any original injuries.

Delayed-onset posthypoxic leukoencephalopathy is diagnosed only after excluding other causes of neurologic decline. In our patient, hyponatremia was high on the differential as a possible source given her rapid drop of serum sodium from 145 on hospital day 6 to a level of 131 at the end of hospital day 8. It is true that the patient was at her peak level of neurologic recovery with the optimized serum sodium on hospital day 6 and she began to become symptomatic over the time period of dropping sodium. However, it is more likely that her dropping sodium was a *symptom* of the new brain injury rather than the cause. Clinical manifestations of acute hyponatremia typically take the form of nausea, malaise, headache, lethargy, obtundation, and eventually seizures.[4] Our patient, however, presented with severe agitation, combativeness, and confusion. With appropriate correction of serum sodium over the next 48 to 72 hours, patient showed no recovery of function previously demonstrated. Rate of decline in serum sodium was also considered. The general pathophysiology of central pontine myelinolysis is related to sudden shifts in fluid from the extracellular compartment to the myelin sheath. This leads to intramyelinic edema, osmotic injury, and local release of myelinotoxic factors causing oligodendrocyte failure and death. These changes take 2 to 3 days to develop, and our patient showed symptomatic change concurrently with dropping sodium levels.[4] Furthermore, we typically assume that a safe correction rate of serum sodium is 4 to 8 mmol/L/d, and the

patient never had a drop of serum sodium greater than 8 mmol/L in a 24-hour period.

The prognosis of delayed-onset posthypoxic leukoencephalopathy is unclear as some studies demonstrate severe decompensation with fatal outcomes, while others report substantial recovery. Most cases, however, do seem to have lasting cognitive deficits.[3] Given the uncertainty in pathophysiology of this disease, treatment options remain limited. Early supportive care and rehabilitation are currently the mainstays of treatment. Since delayed-onset posthypoxic leukoencephalopathy is not well known or understood, the differential diagnosis of altered mental status in the setting of hypoxic brain injury still remains broad and other more common causes should always be explored.

Some research has been done with the use of amantadine in treatment of patients with traumatic brain injury and has shown promising benefits. One case report discusses the use and benefits of amantadine specifically in treatment of a patient with delayed-onset posthypoxic leukoencephalopathy after unintentional methadone and diazepam overdose. The theory behind these benefits revolves around increased dopaminergic activity in the brain.[5] Lack of recognition of this condition, however, makes any research in this field extremely limited.

Conclusion

Severe hypoxic brain injury has been found to be associated with delayed-onset white matter injury leading to an encephalopathic presentation. While it has more commonly been described with drug overdoses and carbon monoxide poisoning, it also has been seen in trauma with disruption of cerebral blood flow. It is often difficult to recognize this condition given the many confounding factors which present in such critically ill patients. Therefore, it is possible that there are more actual cases than reported. It is clear that there needs to be greater awareness of this phenomenon to prompt further research into the causes, prevention, and potential treatment options.

Author Contributions

K. Smolinsky contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. I. Sediva contributed to conception, design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

On behalf of all authors I certify that the work submitted is original, has not been plagiarized, and has not been published anywhere else. We have no conflicts of interest to report.

References

1. Plum F, Posner JB. *Diagnosis of Stupor and Coma*. Philadelphia, PA: F.A. Davis Co; 1966:128-129.
2. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. *Arch Neurol*. 1983;40(7):433-435.
3. Shprecher D, Mehta L. The syndrome of delayed post-hypoxic leukoencephalopathy. *Neurorehabilitation*. 2010;26(1):65-72.
4. Hannon MJ, Thompson CJ. Neurosurgical hyponatremia. *J Clin Med*. 2014;3(4):1084-1104.
5. Arciniegas DB, Frey KL, Anderson CA, Brousseau KM, Harris SN. Amantadine for neurobehavioural deficits following delayed post-hypoxic encephalopathy. *Brain Inj*. 2004;18(12):1309-1318.