Altered Mental Status: A Case Report of Toxic Leukoencephalopathy Following Heroin Exposure

Abstract

Toxic leukoencephalopathy is a very rare complicated illness that causes diffuse white matter destruction, and as a result may appear to mimic psychiatric disorders. Multiple causes have been identified including nerve related injury from exposure to a toxin. When symptoms do present, they typically improve after the offending agent has been eliminated. However, the clinical presentation demonstrated in this report is unique in that the syndrome appeared to get worse several weeks after the toxin was removed as the patient was in the hospital. Research indicates that supportive supplements and vitamins can be used to facilitate neurological recovery. This report outlines a case of toxic leukoencephalopathy following heroin overdose that was effectively treated with vitamin supplementation. The clinical course of the patient also highlights the importance of performing a full medical workup for any patient presenting with acute psychiatric-type symptoms, so that a challenging diagnosis with appropriate treatment can be appreciated.

Introduction

Altered mental status can have many causes, which can make accurate diagnosis challenging. When changes in mental status are very dramatic, especially in the context of concurrent substance use, it may seem logical to pin the etiology on psychiatric causes. However, organic causes need to be ruled out first to address any potential life-threatening conditions that may be inducing the change in mental status. One rare cause of acute mental
status change is toxic leukoencephalopathy, a disease of diffuse white matter deterioration due to the inhalation of environmental toxins and drugs of abuse.\textsuperscript{1} Although uncommon, it is an important consideration in the undifferentiated comatose patient who fails to wake following drug overdose, or has unexplained neurological symptoms with a history of drug exposure. While not much is known about the illness, treatment has been aimed at agents that can aid in fast neurological recovery. In this report, we look at the clinical course, diagnosis, and effective treatment of toxic leukoencephalopathy with vitamin C in a 25-year-old female with altered mental status following heroin overdose.

**Objective:**

The objective of this case report is to analyze a 25-year-old female patient who developed toxic leukoencephalopathy following heroin overdose, and was significantly improved with the use of vitamin C.

**Methods:**

Relevant medical literature was analyzed. The patient was interviewed throughout hospitalization and additional information was collected from electronic medical records.

**Case presentation**

The patient is a 25-year-old woman who presented to the hospital for acute liver failure after being found down by her boyfriend in the middle of the night for an indeterminate amount of time. The patient’s boyfriend provided collateral information regarding her use of heroin which had been extensive over the previous few months. The patient was intubated on hospital day two due acute respiratory failure from volume overload. She was admitted to the ICU, where she was also diagnosed with rhabdomyolysis and acute kidney injury, which was
treated with hemodialysis. The patient was extubated after five days and was unable to answer questions. Soon after she was re-intubated due to hypoxia for one day. Following extubation, she was able to follow some commands. After seven dialysis treatments, the patient’s mental status progressively improved, and she was able to talk in full sentences and hold a reality-based conversation. At the time, the patient was subsequently downgraded to the medical floor.

Psychiatry was consulted soon after on hospital day eighteen for reported anxiety and depression, with a history of clonazepam prescription. On initial psychiatric assessment, the patient admitted to several similar overdose episodes in the past. She also admitted to continuous cocaine and alcohol use, stemming from stress associated with her job. She had no suicidal ideations, attempts or previous hospitalizations. On initial mental status exam, she did not appear anxious or depressed, and her withdrawal symptoms were well controlled. Thought process was logical, and she was focused on getting better to be with her young son at home. No hallucinations or otherwise bizarre behaviors were noted. The patient was oriented to person, place and time. Judgment and insight appeared good. At the time, the patient was still in acute kidney injury, and due to her clear sensorium and acute medical issues, no psychiatric medications were recommended at that time. Psychiatry intended to follow the patient through her hospital course for support and continued monitoring of her mental status.

The patient had creatinine levels above 2 and dialysis treatments were continued. She was alert and oriented for the next five days upon psychiatric follow-up. However, on the following day, her mental status deteriorated to the point where she was not answering questions and refused to cooperate during any examination. Three days after this
presentation, the patient was staring into space with a blank stare and displaying bizarre postural tone including hitting her thigh against the bed. The patient became catatonic with prominent muscle rigidity and muteness. Psychiatric recommendation was to repeat EKG and then to give Risperdal 1mg twice a day standing dose for agitation and Haldol 1mg every 8 hours as needed intramuscular for severe agitation. Head CT revealed no abnormalities, vital signs showed heart rate of 116, and medical work up for change in mental status, including serum ammonia, were negative. Neurology was consulted and assessed her symptoms to be psychiatric in nature. The primary team requested continued psychiatry input as well. The psychiatric team was concerned that the unresolved tachycardia was due to surreptitious drug use supplied by a visitor. Recommendations now called for lorazepam IV three times a day due to presumed catatonia and possible opiate withdrawal. Serum drug screen was ordered due to inability to obtain a urine sample. The patient tolerated the initial lorazepam dose well without adverse effects, with slight improvement in her mental status. The patient did well overnight and the lorazepam frequency was increased to four times daily the following day.

On psychiatric follow up, her tachycardia resolved and the serum drug screen was negative (testing for amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, PCP, cannabis, methadone and opiates). However, her mental status did not improve as expected, and she developed upper extremity tremors that later generalized. At the time, the patient stopped talking completely, blankly stared, and remained rigid. Due to lack of improvement, the psychiatry team suspected an organic cause of her symptoms and ordered a brain MRI, with request of the neurology team to do additional testing. Full autoimmune workup was then performed along with lumbar puncture, and testing for West Nile virus, syphilis, polyoma virus,
HIV, and HSV. The patient was subsequently upgraded to the ICU for sedation to get the MRI testing. The results of the MRI are shown in figures 1 and 2. In this patient, the cerebellum was mostly affected, showing decreased diffusion bilaterally. (Figure 3). Upon neurology follow-up, she was given a diagnosis of toxic leukoencephalopathy.

Figure 1. T2 MRI images showing diffuse abnormal white matter hyperintensities in the periventricular regions. These abnormalities are depicted by the arrows.
Figure 2. T2 MRI hyperintensity signals in the bilateral subcortical white matter areas. The abnormalities are symmetrical and diffuse in nature as depicted by the arrows.

Figure 3. Diffusion Weighted Imaging (DWI) of the cerebellum. This hyper-intensity flair shows reduced bilateral diffusion.
Case outcome

Following the diagnosis, the patient was given supportive therapy including vitamin C 500mg daily, folic acid 1mg daily, and thiamine 100mg daily. She was slowly asked yes and no questions to assess her understanding of her medical situation. Patient had gradually been becoming more verbal and able to respond to her environment. For the next week, the patient continued to improve and started answering more open-ended questions. At that point, psychiatry’s recommendation was for transfer to a neuro-cognitive rehabilitation facility. A follow up MRI was performed and showed similar pattern of white matter damage as the initial testing. Patient continued to improve and was discharged a few days later.

Differential Diagnosis

Imaging showed diffuse white matter deterioration. Given the patient’s history and hospital course, differential diagnosis included vanishing white matter syndrome, acute disseminating encephalomyelitis (ADEM), toxic leukoaraiosis, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy, and toxic leukencephalopathy. Despite these disorders all showing diffuse white matter damage, toxic leukoencephalopathy was the primary diagnosis due to the recent exposure to heroin.

Discussion

Toxic leukoencephalopathy is a rare condition characterized by progressive damage to the white matter of the brain. Prevalence of this illness is very low as cases are often underreported, especially in circumstances of heroin overdose often resulting in death. Causes can be variable and include exposure to drugs, environmental toxins, chemotherapeutic agents, carbon monoxide, methanol, ethylene, toluene, ethanol, ecstasy, and
paradichlorobenzene. Disease severity varies among patients due to differing exposure times, concentration and purity of the inciting agent. Clinical features can present as confusion, somnolence, headaches, inattention, forgetfulness, change in personality, difficulty with cognitive function, dementia, coma, and even death. These symptoms can range from very subtle to severe neurological impairment, depending on the extent of brain involvement. In this patient, as the deterioration was extensive with multiple areas of involvement, this may also correlate with the variety and severity of symptoms presented.

The exact mechanism and pathophysiology of toxic leukoencephalopathy remains unknown and may depend on the source of toxicity. Because not every person who uses heroin develops toxic leukencephalopathy, it is possible, in the rare heroin-related cases, that an unknown contaminant, which may vary by region, producer, or distributor, could be responsible for causing the brain changes. Evidence also shows that white matter damage may occur directly from toxic injury on the myelin sheath or indirectly from capillary endothelial injury or a combination of both.

Toxic leukoencephalopathy is best diagnosed by magnetic resonance imaging because of advancements that allow for greater detection of white matter abnormalities. Typically, imaging findings will display diffuse bilateral white matter abnormalities in the periventricular (figure 1), subcortical, (figure2), cerebellar, and posterior cerebral white matter. Abnormalities are also observed in the posterior limb of the internal capsule, and cerebellar peduncles. DWI can also be used to evaluate affected brain structures and will typically show reduced diffusion in the cerebellum (figure 3). This finding may explain the patient’s postural instability and poor coordination that was observed. These diffusion reductions may be related to pathologic
intramyelinic edema or toxic demyelination derived from the build-up of substances related to the toxin exposure. ¹¹

Treatment for this condition should target reversible causes, and is otherwise largely symptomatic. ¹² Clinical recovery can be evident when the offending agent is removed or stopped. Uniquely, in this patient, neurologic symptoms worsened during the middle of hospitalization course, roughly two weeks after the proposed offending agent was removed. This clinical course may be best explained by delayed apoptosis of oligodendrocytes. This phenomenon has been described in similar conditions including carbon monoxide poisoning. The delayed onset of apoptosis has been theorized to be due to the toxic build-up of free radicals over a period of time after contaminant exposure. ¹³ The clinical recovery may be explained by gradual regeneration and elasticity of the white matter, especially following administration of vitamins E and C. Along these lines, these vitamins have been proposed to be helpful in neurologic recovery due to their antioxidant effects which can increase neurotropic secretion of cytokines, improving nerve nutritional states. ¹⁴ Patient may fully recuperate depending upon the extent of white matter damage, but little is known on this topic. Future research may look at potential biomarker targets that may predict overall prognosis and recovery.

Conclusion

Toxic leukoencephalopathy is a very rare illness that can occur following heroin overdose. The syndrome is characterized by diffuse, symmetrical white matter deterioration. The patient in this case was successfully treated with supportive treatments including Vitamin C. This case highlights a clinical course of toxic leukoencephalopathy in a unique way, with
symptoms getting profoundly worse after the offending agent was eliminated several weeks before presentation. Without the extensive exploration of organic causes, it is possible that this patient would have been given a psychiatric diagnosis. Although rare, toxic leukoencephalopathy is an important consideration for unexplained neurological symptoms in the setting of a toxin exposure, as neurological damage may become irreversible if appropriate testing and treatment are not administered.

References