Delayed Toxic-Hypoxic Leukoencephalopathy After Posterior Reversible Encephalopathy Syndrome

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INTRODUCTION
Delayed toxic-hypoxic leukoencephalopathy (DTHL) is a rare and likely underrecognized clinico-radiological syndrome characterized by white matter damage after hypoxic-ischemic brain injury, usually in the context of toxic exposure. We describe the unusual case of a patient who developed posterior reversible encephalopathy syndrome (PRES) after two consecutive unintentional drug overdoses, followed by DTHL.

CASE PRESENTATION
A man in his thirties with polysubstance use disorder suffered an unintentional drug overdose after snorting fentanyl-laced cocaine. Upon evaluation by emergency medical services (EMS), the patient had apnea of unclear duration and decreased alertness. Following administration of naloxone, he returned to baseline within minutes. Thirty-six hours later, he had another unintentional overdose. EMS evaluation revealed oxygen saturation of 79% on ambient air and Glasgow Coma Scale of 8. At the emergency department, urine toxicology was positive for amphetamines, cannabinoids, cocaine, and fentanyl. Blood alcohol was undetectable. Non-contrast head CT was normal.

He was hospitalized for management of acute hypoxic respiratory failure (not requiring intubation), acute toxic-metabolic encephalopathy, aspiration pneumonitis, acute tubular necrosis, and rhabdomyolysis. On hospital day 8, he had two generalized tonic-clonic seizures. Same-day non-contrast brain MRI was consistent with PRES (Figure 1). Electroencephalogram revealed moderate, diffuse background slowing with no focal or epileptiform abnormalities. Encephalopathy and metabolic abnormalities gradually improved. Cognition returned close to baseline; however, impaired insight and judgment were present. He remained hospitalized for 40 days, largely from logistics of discharge planning. He had no access to recreational drugs during his hospitalization.

Less than 24 hours after discharge, family members brought the patient from home back to the hospital due to aggressive and disinhibited behavior, and worsening memory. Neuropsychological evaluation showed deficits across a range of functions, including amnestic memory functioning and significant frontal executive impairment. Toxic-metabolic workup, including urine toxicology screen, showed no abnormalities. Non-contrast head CT (not shown) demonstrated interval development of extensive subcortical white

Figure 1. Axial MRI of the brain consistent with posterior reversible encephalopathy syndrome (PRES). T2/fluid-attenuated inversion recovery (FLAIR) showed bilateral parieto-occipital, lateral temporal, and superior frontal predominant cortical and subcortical edema with additional foci of T2/FLAIR hyperintensity in the bilateral putamina and cerebellar hemispheres.
matter hypodensities. Non-contrast brain MRI (39 days after the initial MRI) now showed extensive, symmetric, and confluent white matter hyperintensities on T2/ fluid-attenuated inversion recovery (FLAIR) consistent with DTHL (Figure 2). A follow-up non-contrast brain MRI (75 days after the initial MRI, not shown), revealed modest reduction in the intensity of white matter lesions. Around the same time, repeat neuropsychological testing demonstrated marked improvement in memory and global functioning from the previous examination, although disinhibition and distractibility persisted. Apparently, the patient was still not back to his premorbid baseline.

DISCUSSION

Multiple encephalopathy syndromes can occur from exposure to toxins, and some have characteristic neuroimaging findings.4 One of these is PRES, which is likely caused by endothelial toxicity or injury. PRES may occur due to use of recreational drugs or certain medications, or from states such as uncontrolled hypertension, eclampsia, or sepsis.5,6 Common manifestations of PRES include encephalopathy, seizures, headache, or visual disturbances.6 MRI commonly shows T2/FLAIR hyperintensities in the parieto-occipital cortices and subcortical white matter, though other areas could be involved. Approximately 2% of PRES patients have concomitant acute toxic leukoencephalopathy, affecting the periventricular white matter. Both PRES and acute toxic leukoencephalopathy are potentially reversible clinico-radiological syndromes.7

DTHL is a rare neuropsychiatric syndrome occurring after hypoxic-ischemic brain injury. DTHL has often been described in the context of carbon monoxide poisoning or drug overdose.3,8-10 Its pathophysiology may be related to delayed effects from activation of the apoptotic cascade or dysmyelination following hypoxia.3 Clinically, DTHL typically follows a “biphasic” clinical presentation: an initial recovery from obtundation or coma gives place to a period of 2–40 days of clinical stability before the abrupt onset of symptoms such as cognitive impairment, upper motor neuron signs, gait disturbance, or psychosis.9,11 Given the delay between the acute hypoxic-ischemic event and the onset of neuropsychiatric symptoms, diagnosis of DTHL can be challenging. MRI shows extensive, symmetric, bilateral T2/FLAIR hyperintensities involving the subcortical white matter, sparing subcortical U-fibers. Associated restricted diffusion is common.3,9
Management of DTHL is symptomatic. Many patients experience gradual recovery over 3-12 months. However, “impaired attention or executive function, parkinsonism, or corticospinal tract signs can persist.”3,9 To the best of our knowledge, cases of PRES followed by DTHL in the context of recreational drug overdoses have not been previously published.

References

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