Clinical Reasoning:

A case of altered mental status, not otherwise specified

Dionne E. Swor, DO
Frank R. Sharp, MD
Glen C. Jickling, MD

Correspondence to
Dr. Swor:
dswor@ucdavis.edu

SECTION 1

A 33-year-old right-handed woman presented with a 1-week history of rapid cognitive decline. The behavioral changes emerged gradually, with the first sign marked by erratic driving resulting in arrest. The patient was nonchalant about the detainment, which was out of character. In the preceding week, she had a precipitous decline in cognitive abilities, including a loss of interest in grooming, emotional outbursts, fecal and urinary incontinence, difficulty performing household chores, and jerky movements of her arms and legs impairing her ability to walk.

Of note, 1 month prior the patient had been hospitalized for an opioid (oxycodone) and benzodiazepine overdose, which resulted in aspiration pneumonia, hypoxic respiratory failure, and sepsis. The patient was hypotensive on arrival to the emergency department and required pressors, but never lost her pulse or had cardiac arrest. After 3 days on a ventilator, she regained consciousness, was extubated, and was noted to have dysarthria and confusion. Brain MRI revealed a very small watershed infarct in the right hemisphere (figure 1A). Her confusion and dysarthria resolved, and she was discharged home without

neurologic deficits. The patient then had a 3-week-long lucid interval prior to the start of her cognitive decline.

On presentation to the emergency department, the patient was alert and oriented to self, but not place or date. Affect was inappropriate and impulsive, with poor attention and distractibility. Executive function and memory were abnormal, but full cognitive assessment was limited by poor attention. Expressive and receptive language was normal. Cranial nerves were intact. Motor examination showed action myoclonus, slowing of rapid alternating movements, and bilateral motor apraxia. Muscle bulk and tone were normal with no signs of parkinsonism. Strength was normal and reflexes were 2+ throughout with downgoing plantar responses. Sensation was intact to light touch, pinprick, temperature, and vibration. She had dysmetria on finger to nose testing, and a mild ataxic gait. Romberg was present.

Questions for consideration:

1. Where would you localize these symptoms?
2. What tests should be ordered to help narrow the differential diagnosis?

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(A) MRI brain (fluid-attenuated inversion recovery [FLAIR] sequences) done on day 4 following the inciting hypoxic event. (B) MRI brain (FLAIR sequences) done on day 30 following the inciting hypoxic event shows bilateral white matter signal abnormalities in frontal, parietal, occipital, and temporal lobes. (C) MRI brain (FLAIR sequences) done 17 months following the inciting hypoxic event shows resolution of the white matter signal abnormalities seen previously.

SECTION 2

The patient's constellation of symptoms with deficits in attention, memory, executive function, and emotional lability in the absence of aphasia suggests bilateral dysfunction not involving language areas, and sparing the cortex. Altered mental status is a vague term used to signify a change in consciousness, where consciousness is defined as the state of full awareness of self and one's relationship with the environment. The differential diagnosis of altered mental status is broad and includes vascular insults, trauma, infection, toxic/metabolic derangements, neoplasms, seizure, structural abnormalities, degenerative processes, psychiatric disease, and iatrogenic etiologies. Action myoclonus can accompany a variety of disorders including metabolic derangements like uremia, and is highly characteristic of postanoxic encephalopathy, which is referred to as Lance Adams syndrome.¹ The memory deficits can be explained by either bilateral hippocampal involvement or bilateral temporal lobe white matter dysfunction. Bilateral motor apraxia suggests bilateral frontal lobe dysfunction affecting either gray or white matter. The bilateral limb and gait ataxia suggest either cerebellar involvement or

injury to the cerebellar connections to the basal ganglia or frontal lobes bilaterally.

To help narrow the differential, a MRI brain was performed, revealing symmetric, deep supratentorial, and patchy infratentorial white matter signal abnormalities (figure 1B) with mild restricted diffusion, and no gadolinium enhancement. Routine laboratory testing for inflammatory and toxic/metabolic derangements was normal. CSF studies demonstrated normal cell count, protein, and glucose, and a negative Gram stain and viral cultures. Viral encephalitis panel, paraneoplastic panel, and angiotensin-converting enzyme were sent from CSF and were negative. CSF was significant for an elevated myelin basic protein (14.8 ng/mL) supporting myelin injury. Serum studies for HIV, antinuclear antibodies, anti-phospholipid antibodies, and NMDA receptor antibody were negative. EEG showed generalized slowing, maximal in the frontal regions, consistent with a moderate encephalopathy.

Question for consideration:

1. What is the differential diagnosis of bilateral white matter changes on MRI?

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SECTION 3

The differential diagnosis of white matter changes is divided into 2 categories: symmetric white matter changes and asymmetric/multifocal white matter changes (figure 2). Symmetric white matter changes are characteristic of diseases causing diffuse white matter injury, such as infiltrative tumors, hereditary white matter disease, metabolic injury, and toxins.²

Asymmetric white matter changes or multifocal patterns are characteristic of vascular-mediated or inflammatory disorders or infections.²

Questions for consideration:

1. What is the most likely diagnosis based on imaging and the initial evaluation?
2. What treatment should be offered to the patient?

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Figure 2 Differential diagnosis of white matter changes on MRI based on most common locations²

ADEM = acute disseminated encephalomyelitis; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PML = progressive multifocal leukoencephalopathy.

SECTION 4

Based on the clinical history, MRI brain, and negative infectious, inflammatory, and metabolic testing, a diagnosis of delayed posthypoxic leukoencephalopathy (DPHL) was made. DPHL is a rare disorder characterized clinically by an anoxic brain injury, then recovery with a lucid interval, followed by acute leukoencephalopathy and cognitive decline days to weeks later. DPHL has been associated with carbon monoxide poisoning, with 2.8% of these patients going on to develop delayed neurologic sequelae.³ Other causes of anoxic injury associated with DPHL include cardiac arrest, strangulation, and overdose from opiates and benzodiazepines.^{4,5} It is notable that white matter is particularly vulnerable to hypoxia, with diffuse involvement of white matter irrespective of vascular territories.^{3–5} In contrast, areas of the brain most susceptible to hypoxic/ischemic injury include white matter within vascular border zones, neocortical layers 3, 5, and 6, and CA1 region of the hippocampus, thalamus, and cerebellum.⁶

The pathophysiology of the delay in DPHL remains unclear. One explanation for the delay may relate to the fact that the mean lucid interval coincides approximately with the replacement half-life for myelin lipids and proteins.⁷ Other suggested mechanisms include direct toxicity of carbon monoxide or heroin (heroin-associated delayed spongiform leukoencephalopathy)⁸ to oligodendrocytes as well as disruption of myelin-producing pathways due to pseudodeficiency of arylsulfatase A.⁹ The fact that a number of cases have shown significant recovery may relate to the ability of oligodendrocytes to repair their myelin sheaths, and oligodendrocyte progenitors to differentiate into mature myelin-forming oligodendrocytes.

Treatment of DPHL is largely supportive, with long-term physical, occupational, and cognitive therapy being most beneficial. A recent case reported a benefit in antioxidant therapy with coenzyme Q10, vitamin E, and vitamin B complex, which decreased the time to recovery in one patient with DPHL.¹⁰

Our patient benefitted greatly from physical and cognitive therapy. At her 6-month follow-up appointment, she continued to have cognitive deficits in memory and attention, but was nearly independent in her activities of daily living. At 1 year, she was completely independent, but continued to have minor

deficits in executive function and problem-solving, preventing her from returning to work. A repeat MRI brain at 17 months following the inciting anoxic event showed complete resolution of white matter signal abnormalities (figure 1C). The case highlights that in certain patients, a brief hypoxic insult can produce diffuse myelin injury irrespective of vascular boundaries. Further studies are needed to better understand this injury, and how the underlying processes of repair as observed in the presented patient can result in a good outcome.

AUTHOR CONTRIBUTIONS

Dionne E. Swor: concept and design, acquisition of data. Frank R. Sharp: critical revision of manuscript for important intellectual content. Glen C. Jickling: critical revision of manuscript for important intellectual content.

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DISCLOSURE

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