A 63-year-old woman with a history of multiple sclerosis and chronic musculoskeletal pain was found unresponsive in bed by her husband at about 1100 h. A year prior, the patient had been prescribed fentanyl patches for postoperative pain, which she did not use. Her usual daily medications included hydromorphone 9 mg 3 times per day, zopiclone 7.5 mg every night at bedtime and pregabalin 75 mg twice per day, all of which had been taken at the same dose at which they had been used for the last year, except for the hydromorphone. In the weeks before her presentation to hospital, the patient had not been taking her hydromorphone as prescribed because of adverse effects. At about 2300 h the evening before her arrival in the emergency department, the patient had reported increasing pain and applied three 12 µg fentanyl patches, doubling her daily morphine equivalent dose by the time she was found unresponsive 12 hours later. Her husband performed 10 minutes of cardiopulmonary resuscitation without checking for a pulse. When paramedics arrived, the patient had a pulse of 91 beats/min and was in normal sinus rhythm, with a blood pressure reading of 94/57 mm Hg and oxygen saturation of 84%. She awoke after naloxone infusion in the emergency department. Toxicology screening was positive for opiates only. Routine serology testing showed mild transient elevation in transaminase, troponin and creatine kinase levels. Over the following days, the patient showed profound anterograde amnesia and was unable to recall daily autobiographical details, despite meticulously recording them in a journal (Figure 1).

Neurologic examination identified anisocoria and mild spastic paraparesis, which were unchanged from a previously documented examination 3 years earlier. Her Montreal Cognitive Assessment score was 19/30: she lost 3 points for date, month and day; 5 points on delayed recall despite intact immediate recall; and 1 point on each of trails, cube and repetition. No prior cognitive testing was available for comparison. Gadolinium-enhanced magnetic resonance imaging (MRI) of the head performed on day 7 showed striking bilateral gyriform hippocampal hyperintensity on $T_2$-weighted imaging with corresponding restricted diffusivity on diffusion-weighted imaging (Figure 2), in addition to white-matter lesions compatible with multiple sclerosis that were stable on comparison with previous imaging. Electroencephalography done the same day showed no epileptiform activity. The patient’s cerebrospinal fluid profile was unremarkable, and results of polymerase chain reaction testing for herpes simplex virus were negative. Results of testing for arbovirus and syphilis, and a routine paraneoplastic antibody panel were also negative.

Magnetic resonance imaging of the head on day 12 showed complete resolution of the previously seen hippocampal diffusion...
in opioid-associated amnestic syndrome, the progression of opioid overdose potentially contributes to hippocampal injury from hypotension and respiratory depression in the context of hyperintensity within 12 days. Although hypoxic ischemic injury is not characteristic of typical cerebral infarction or ischemia. A recent letter by Barash and colleagues described 4 patients with opioid-associated amnestic syndrome and a history of heroin use who tested positive for fentanyl and norfentanyl, a fentanyl metabolite. In 2 patients, fentanyl was the only drug detected. Although none of the 4 patients were known to have used fentanyl, the toxicology findings were consistent with the presence of fentanyl in heroin, an increasingly common finding. Although the precise role that our patient’s prescription medications (including another opioid, hydromorphone) played in her clinical presentation cannot be delineated in this case, no medication was taken in excess of the routinely prescribed dose. Our findings support the hypothesis that fentanyl has a direct role in the development of opioid-associated amnestic syndrome, although this is controversial.

The hippocampi and deep grey nuclei are metabolically demanding structures and are vulnerable to a variety of ischemic, toxic and metabolic insults; however, the exact mechanism of the characteristic bilateral hippocampal injury in opioid-associated amnestic syndrome has not been shown. A rodent model of opioid neurotoxicity has been described, in which it was found that incomplete ischemia may be worsened by hippocampal hyperexcitability at the time of overdose, but this has not been reliably reproduced in subsequent experiments. In contrast, fentanyl has been shown to exert a direct toxic effect on the hippocampus and associated limbic structures of intubated rats, and as such potentially contributes to the development of opioid-associated amnestic syndrome even in the absence of profound hippocampal ischemia. Fentanyl use during general anesthesia has been associated with numerous reported cases of severe global amnesia during the postoperative period in absence of perioperative hemodynamic instability or any other demonstrable etiology. Interestingly, no case report identified fentanyl as a potential precipitant of acute amnestic syndrome, despite data from rodent models. This indicates that opioid-associated amnestic syndrome is potentially underrecognized in various clinical settings.

Several important clinical conclusions may be drawn from this case. First is the importance of testing for synthetic opioids in patients with a history of opioid use, as has been described by Barash and colleagues. Second, this case should alert clinicians to the possibility of an opioid-associated amnestic syndrome in cases of acute global amnesia and opioid overdose, including cases of prescription-fentanyl overdose. Finally, given the resolution of diffusion restriction observed in this case, early use of diffusion-weighted imaging may improve diagnosis in select patients with acute amnesia.

Discussion

A case series and subsequent alert by the Massachusetts Department of Public Health identified 13 cases of an opioid-associated amnestic syndrome between 2012 and 2016. Patients had acute-onset amnesia and evidence of opioid use on history or toxicology. All patients had a single MRI study by day 8 that showed bilateral hippocampal restricted diffusion, in keeping with infarction. Findings on our patient’s initial MRI were consistent with those in previous cases in the Massachusetts area.

After cerebral infarction, restricted diffusion may resolve within 8–14 days; however, \( T_2 \) hyperintensity typically persists for at least 1 month. Serial MRI in our patient showed complete resolution of the early hippocampal diffusion restriction and \( T_2 \) hyperintensity within 12 days. Although hypoxic ischemic injury from hypotension and respiratory depression in the context of opioid overdose potentially contributes to hippocampal injury in opioid-associated amnestic syndrome, the progression of changes on \( T_2 \) and diffusion-weighted imaging seen in this case, restriction and corresponding \( T_2 \) hyperintensities. Neuropsychological assessment showed mild executive impairment (felt to be in keeping with her known burden of subcortical demyelination) and severe anterograde amnesia. After discharge, the patient moved with her husband across the country to be closer to their children. A follow-up phone interview with the patient’s husband 4 months later confirmed persistent severe amnestic impairment in a novel environment that required constant monitoring by the family.

Figure 2: Serial magnetic resonance imaging (MRI) in opioid-associated amnestic syndrome. Gadolinium-enhanced MRI on day 7 shows bilateral gyriform hippocampal apparent diffusion coefficient hypointensity (A) with corresponding hyperintensity on diffusion-weighted imaging (B), indicating restricted hippocampal diffusivity (white arrows). Hippocampal \( T_2 \) hyperintensity (C; yellow arrows) along with subtle hippocampal gadolinium enhancement (D; red arrows) is also seen. Follow-up MRI on day 12 (performed without gadolinium despite request) shows resolution of hippocampal restricted diffusion (E) and resolution of \( T_2 \) hyperintensity (F).
The current case of opioid-associated amnestic syndrome after use of prescription fentanyl suggests that a contaminant or adulterant is not a necessary factor in the pathophysiology of this syndrome. Previous reports of the syndrome occurred in the United States; this report should alert clinicians in Canada and internationally who prescribe or administer opioids to opioid-associated amnestic syndrome and the potential role of fentanyl in its emergence.

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