

Nicotine withdrawal as an unusual cause of terminal delirium

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Delirium is a neurocognitive and neuropsychiatric syndrome characterized by cognitive symptoms (eg, attention, perception, orientation, memory) and psychiatric symptoms (eg, hallucinations, delusions, agitation, apathy).^{1,2} Acute medical illness, trauma, surgery, substance use and withdrawal, and advanced illness are usual triggers of delirium. The prevalence ranges from 35% upon admission to inpatient palliative care units to highly prevalent (up to 88%) just before death across all palliative care settings.³ Terminal delirium is often referenced clinically, but there is no clear definition other than irreversible delirium in the days before death. The following case illustrates an uncommon syndrome—nicotine withdrawal combined with opioid-induced neurotoxicity—that was mistaken for terminal delirium.

Case

A 78-year-old woman with metastatic lung adenocarcinoma was admitted to hospital with increasing back pain and shortness of breath on exertion. Four months earlier she had stopped chemotherapy because of disease progression. On a scale of 0 to 10, she rated her pain as 6, dyspnea as 5, anorexia as 6, and confusion as 0. She had severe chronic obstructive pulmonary disease owing to a 100 pack-year smoking history, but she reported having quit smoking 3 years ago.

Examination findings revealed dehydration and reduced air entry with crackles over a known small pleural effusion. Her respiratory rate was 20 breaths/min and her oxygen saturation was 92% on room air. There were no signs of ascites or hepatomegaly, and her neurological examination findings were normal. She was oriented to person, place, and time.

Admission bloodwork results revealed anemia of chronic disease, normal electrolyte levels, lactate dehydrogenase at 289 U/L, γ -glutamyl transferase at 59 U/L, and alkaline phosphatase at 79 U/L. Total bilirubin was 9 μ mol/L, albumin was 38 g/L, and calcium was 2.25 mmol/L.

A hydromorphone subcutaneous infusion was initiated at 3 mg/h with breakthrough dosing. This replaced the 24-mg sustained-release hydromorphone taken twice daily orally and the 37- μ g/h fentanyl patch that the patient had been using before admission into a hydromorphone subcutaneous infusion that was nearly the same equivalent dose. Upon consultation, a respirologist suggested continuing her medications for chronic obstructive pulmonary disease and using opioids to treat the dyspnea.

On day 2 she was anxious, easily distracted, and confused. Multiple bone metastases in the spine and ribs were confirmed by x-ray scan.

On day 3 nurses noted agitation and auditory hallucinations, and the patient's daughter reported the confusion as new and abnormal. The patient required multiple doses of hydromorphone, salbutamol, and methotrimeprazine for agitation and dyspnea throughout the day and night.

On day 4 she remained agitated and dyspneic but reported the pain was now controlled. She was diagnosed with multifactorial delirium—likely terminal—owing to advancing illness. Investigation findings revealed no evidence of infection and no structural lesion in the brain. Medications considered nonessential were stopped. Regular administration of

Editor's key points

- ▶ Minimal evidence is available to help distinguish terminal delirium from a reversible cause of delirium. Identifying an imminent cause of death should be a key step in the diagnosis of terminal delirium.
- ▶ Nicotine withdrawal develops within 24 hours of abstinence, presenting with new-onset agitation or irritability, insomnia, restlessness, confusion, and anxiety, and may lead to delirium.
- ▶ Opioid toxicity can cause delirium because metabolites of morphine and hydromorphone excreted via the kidneys have the potential to be neurotoxic even in those with normal kidney function.
- ▶ When events do not proceed as expected, reviewing old charts and retaking the patient's history are recommended.

Points de repère du rédacteur

- ▶ Il existe peu de données probantes permettant de faire la distinction entre le delirium terminal et un delirium dont la cause est réversible. La détermination d'une cause imminente de décès devrait être une étape cruciale dans le diagnostic d'un delirium terminal.
- ▶ Le syndrome de sevrage à la nicotine se développe dans les 24 heures suivant l'abstinence, et il se manifeste par l'apparition soudaine de signes d'agitation ou d'irritabilité, d'insomnie, d'hyperactivité, de confusion et d'anxiété, et peut conduire au delirium.
- ▶ La toxicité des opioïdes peut causer un delirium, parce que les métabolites de la morphine et de l'hydromorphone excrétés par les reins ont le potentiel d'être neurotoxiques même chez les personnes dont la fonction rénale est normale.
- ▶ Lorsque la situation ne se déroule pas comme prévu, il est recommandé de passer en revue d'anciens dossiers et de refaire l'anamnèse du patient.

methotrimeprazine, with midazolam as needed for agitation, resulted in an intermittent calm state.

When emotional and respiratory distress continued, weekend staff switched to a midazolam infusion at 1 mg/h, which achieved calmness. Over the next week, staff changed frequently owing to Christmas holidays. A new resident noted the forecast decline was not occurring and some waking episodes. However, reducing the midazolam caused agitation and restlessness, so the dose was restored to a level that kept the patient calm.

After Christmas, staff felt a review was necessary. The patient was not dying and had complained of hunger; she ate dinner and asked when she was going to die. Hallucinations were ongoing. A review of old charts showed the patient had experienced confusion on morphine, despite having a normal estimated glomerular filtration rate. In reviewing the medical history with family, staff verified the patient had quit smoking 3 years ago, but the family revealed she had resumed smoking when she had been told she was terminally ill. Family members knew she had been “closet smoking” but were reluctant to contradict her story.

Given that the patient had smoked regularly until admission and that within 24 hours of abstinence she had developed new-onset agitation, irritability, insomnia, restlessness, confusion, and anxiety,⁴ staff realized the patient’s delirium was likely owing to nicotine withdrawal. A nicotine patch was initiated, presuming she had been smoking her previous habit of a pack a day. Opioid-induced neurotoxicity from increased doses of hydromorphone for her pain and dyspnea may have contributed to the delirium, so hydromorphone infusion was switched to an equivalent fentanyl infusion. Midazolam was tapered 24 hours after the initiation of these changes and stopped shortly after. She was calm, alert, and oriented, and she acknowledged that she had been smoking before admission. Her pain remained controlled on fentanyl, and she was switched to a patch with minimal hydromorphone as needed for breakthrough pain. She moved to hospice in the ensuing days and died there 2 months later.

Discussion


Nicotine withdrawal and delirium. Nicotine withdrawal produces affective, cognitive, and somatic symptoms, including irritability, anxiety, restlessness, difficulty concentrating, insomnia, and increased appetite.⁵ Symptoms begin within 24 hours of quitting, peak at 3 days, and resolve approximately 4 weeks after quitting.⁶ Insomnia, anxiety, and restlessness were predominant in our patient, and she requested food—the opposite of a person with advanced disease, where anorexia is the norm. Nicotine withdrawal can lead to delirium through its effect on acetylcholine receptors and through release of inflammatory cytokines and corticotropin-releasing factor.⁷

A prospective population-based cohort study⁸ followed 3908 older adult current smokers, *quitters* (study terminology), and lifelong abstainers for 6 years and looked at the incidence of delirium during hospitalization (excluding delirium secondary to alcohol and psychoactive substances). The risk of inpatient delirium did not differ between quitters and lifelong abstainers, but in a comparison of current smokers and quitters, a statistically significant hazard ratio of 3.22 suggested the delirium was associated with nicotine withdrawal.

A recent review⁹ concluded there is conflicting evidence that nicotine replacement therapy has a positive effect on outcome. However, most clinical studies have looked at nicotine withdrawal in the intensive care unit, where many other comorbidities are beyond control. In our case, the signs and symptoms of our patient matched the timing of nicotine withdrawal, and her agitation re-emerged with tapering down of the midazolam before nicotine replacement.

Opioid-induced neurotoxicity. Opioid toxicity can cause delirium¹⁰ because metabolites of morphine and hydromorphone excreted via the kidneys have the potential to be neurotoxic,¹¹ even in those with normal estimated glomerular filtration rates. The toxic metabolite hydromorphone-3-glucuronide can achieve a 3- to 4-fold increase in its maximum concentration, even at glomerular filtration rates less than 30 mL/min.¹² Risk factors for hydromorphone neurotoxicity also include rapid dose escalation, advanced age, dehydration, and medication interactions. Asking about prior experiences with opioids may reveal previous episodes of toxicity, leading an astute physician to rotate to another opioid less likely to cause toxicity.¹³

Conclusion

The trajectory of this patient’s illness—lung cancer with pleural effusion unresponsive to chemotherapy 4 months before admission—suggests she would be near the end of life. Confirmation bias may have played a role in clinicians believing this was terminal delirium despite investigations performed after admission not showing substantial organ failure. A review of factors related to mortality in a review of 121 consecutive delirium cases showed that being older, having more severe cognitive disturbance, and suffering from organ failure were more prevalent among those who died. While terminal delirium is frequently a diagnosis of exclusion of reversible causes, and there is little evidence to distinguish terminal delirium from reversible delirium,¹⁴ a plausible imminent cause of death should always be a prerequisite for the diagnosis. Determining an imminent cause of death should be included as a step in the diagnosis so that the absence of a cause may illuminate the need to consider other reversible factors in the delirium. 

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Competing interests

None declared

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References

1. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLulich AMJ, et al. Delirium. *Nat Rev Dis Primers* 2020;6(1):90. Erratum in: *Nat Rev Dis Primers* 2020;6(1):94.
2. Legesse B, Babadi B, Forester B. Management of neuropsychiatric symptoms in neurocognitive disorders. *Focus (Am Psychiatr Publ)* 2017;15(1):18-25. Epub 2017 Jan 11.
3. Watt CL, Momoli F, Ansari MT, Sikora L, Bush SH, Hosie A, et al. The incidence and prevalence of delirium across palliative care settings: a systematic review. *Palliat Med* 2019;33(8):865-77. Epub 2019 Jun 11.
4. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res* 2007;9(3):315-27.
5. McLaughlin I, Dani JA, De Biasi M. Nicotine withdrawal. *Curr Top Behav Neurosci* 2015;24:99-123.
6. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
7. Dinesh K, Ankit G, Sucheta T, Prerna K. Delirium and nicotine withdrawal. In: Preedy VR, editor. *Neuroscience of nicotine: mechanisms and treatment*. London, UK: Elsevier Inc; 2019. p. 221-8.
8. Hessler JB, Brønner M, Etgen T, Gotzler O, Förtl H, Poppert H, et al. Smoking increases the risk of delirium for older inpatients: a prospective population-based study. *Gen Hosp Psychiatry* 2015;37(4):360-4. Epub 2015 Mar 21.
9. Patwardhan S, Banerjee I. Nicotine withdrawal, the role of NRT in hospitalised smoker patients and its implications for Covid-19. *J Addict Sci* 2020;6(S1):S1-4.
10. Lim KH, Nguyen NN, Qian Y, Williams JL, Lui DD, Bruera E, et al. Frequency, outcomes, and associated factors for opioid-induced neurotoxicity in patients with advanced cancer receiving opioids in inpatient palliative care. *J Palliat Med* 2018;21(12):1698-1704. Epub 2018 Sep 27.
11. Kullgren J, Le V, Wheeler W. Incidence of hydromorphone-induced neuroexcitation in hospice patients. *J Palliat Med* 2013;16(10):1205-9. Epub 2013 Aug 9.
12. Davison SN, Mayo PR. Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. *J Opioid Manag* 2008;4(6):335-6, 339-44.
13. Corli O, Floriani I, Roberto A, Montanari M, Galli F, Greco MT, et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Ann Oncol* 2016;27(6):1107-15. Epub 2016 Mar 2.
14. Hui D, De La Cruz M, Bruera E. Palliative care for delirium in patients in the last weeks of life: the final frontier. *J Palliat Care* 2014;30(4):259-64.

This article has been peer reviewed.

Cet article a fait l'objet d'une révision par des pairs.

Can Fam Physician 2022;68:591-3. DOI: 10.46747/cfp.6808591