

Lesson of the month: Oxycodone-induced leukoencephalopathy: a rare diagnosis

Authors: Eleanor Jones,^A Udayaraj Umasankar,^B Habeeba Mallu,^C Timothy Hampton,^D Angela Kulendran^B and Mehoor Patel^B

ABSTRACT

Oxycodone-induced leukoencephalopathy is a rare diagnosis that should be considered in unconscious patients with appropriate history. We describe a case of a 57-year-old unconscious woman who required intubation and did not respond to naloxone infusion. The unconsciousness was initially thought to be due to hypoxic brain injury. However, a further review of brain imaging showed characteristic features of oxycodone-induced leukoencephalopathy. We describe the pathological and radiological features of this condition, and provide a concise review of the limited literature on this condition. Accurate diagnosis of this condition will be valuable to clinicians and patients in terms of their medium-term and long-term prognosis, and potential for rehabilitation.

KEYWORDS: Oxycodone leukoencephalopathy, cerebral white matter, toxic leukoencephalopathy, heroin, hypoxic brain injury

DOI: 10.7861/clinmed.2020-0650

Case presentation

A 57-year-old woman was found unresponsive at home. She had allegedly taken 14 tablets of 10 mg oxycodone. She had type 2 diabetes mellitus, depression and panic attacks. She was only on mirtazapine. Her Glasgow coma score was 5/15 (E1V1M3) with hypoxia. She had renal and liver dysfunction. Urine toxicology screen was positive for opiates. An initial computed tomography (CT) of the brain was reported as normal. With a diagnosis of oxycodone overdose, she was intubated and given a naloxone infusion over 48 hours. CT of the brain 2 days later raised the possibility of global hypoxic brain injury. Over the next 10 days, she did not need sedation while intubated and ventilated, and had no gag reflex. In view of possible global hypoxic brain injury, organ donation was considered and spiritual care offered with the

assumption that she was dying. Tracheostomy was performed 13 days later and she was stepped down to the stroke unit. Images reviewed by a neuroradiologist confirmed that findings were in keeping with oxycodone overdose. The initial CT showed low attenuation in both cerebellar white matter (WM) and globus pallidi (GPa). Subsequent imaging (Fig 1) showed progression of this low attenuation with pathologic mass effect resulting in tonsillar herniation and mechanical obstruction to cerebrospinal fluid outflow. An interval magnetic resonance imaging (MRI) of the brain showed appropriate evolution of the GPa and bi-cerebellar injury (Fig 2). The combination of cerebellar and GPa injury was suggestive of an acute oxycodone leukoencephalopathy rather than an inflammatory, metabolic or ischaemic insult. Electroencephalography was atypical for hypoxic ischaemic encephalopathy. She had a successful tracheostomy decannulation and percutaneous endoscopic gastrostomy insertion to maintain nutrition. Over the next 2 months she became more alert with significant neurological deficits and continues neurorehabilitation.

Cerebral white matter

The cerebral white matter (WM), with its myelinated axons arranged in tracts or fasciculi, occupies about half of an adult human brain volume with an estimated 100 billion neurones and 135,000 kilometres of axons, equivalent to running about thrice around the globe. With evolution, WM expanded disproportionately more than grey matter (GM) to transfer information rapidly between the distantly placed GM neuronal cell bodies.¹ It has also been recognised that WM is found within the GM of the cortical mantle and subcortical nuclei (thalamus and basal ganglia).

Toxic leukoencephalopathy

Toxins that disrupt myelin sheath and/or axons include drugs of abuse (heroin and opioids); environmental factors (carbon monoxide), occupational factors (paint) or therapeutics (anti-neoplastic, antimicrobial and immunosuppressives).^{2,3} Interhemispheric and intrahemispheric pathways that serve cognition and emotion (neurobehaviour) are predominantly involved. Hence the most important clinical feature includes a change in mental status.³

The spectrum of neurobehavioural symptoms and corresponding pathology include mild (confusion or inattention; patchy intramyelinic oedema with preservation of myelin), moderate

Authors: ^Afoundation year-2 doctor in stroke medicine, University Hospital Lewisham, Lewisham, UK; ^Bconsultant physician in geriatric and stroke medicine, University Hospital Lewisham, Lewisham, UK; ^Cfoundation year-1 doctor in stroke medicine, University Hospital Lewisham, Lewisham, UK; ^Dconsultant neuro-radiologist, University Hospital Lewisham, Lewisham, UK

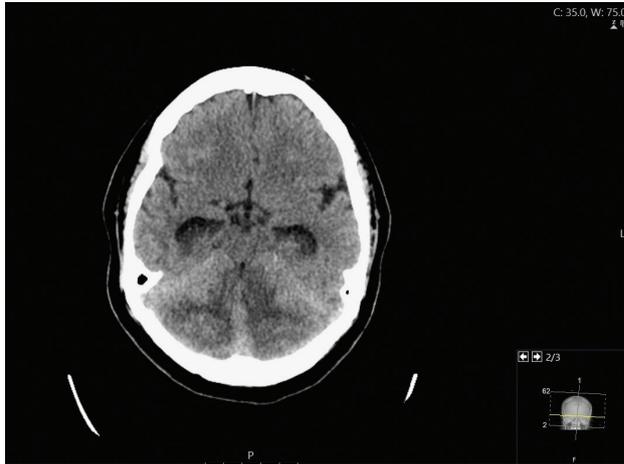


Fig 1. Computed tomography showing progression of low attenuation with pathologic mass effect resulting in tonsillar herniation and mechanical obstruction to cerebrospinal fluid outflow.

(apathy, somnolence or memory impairment; widespread oedema with demyelination but preserved axons) or severe (akinetic mutism, coma or death; axonal loss and oligodendrocyte

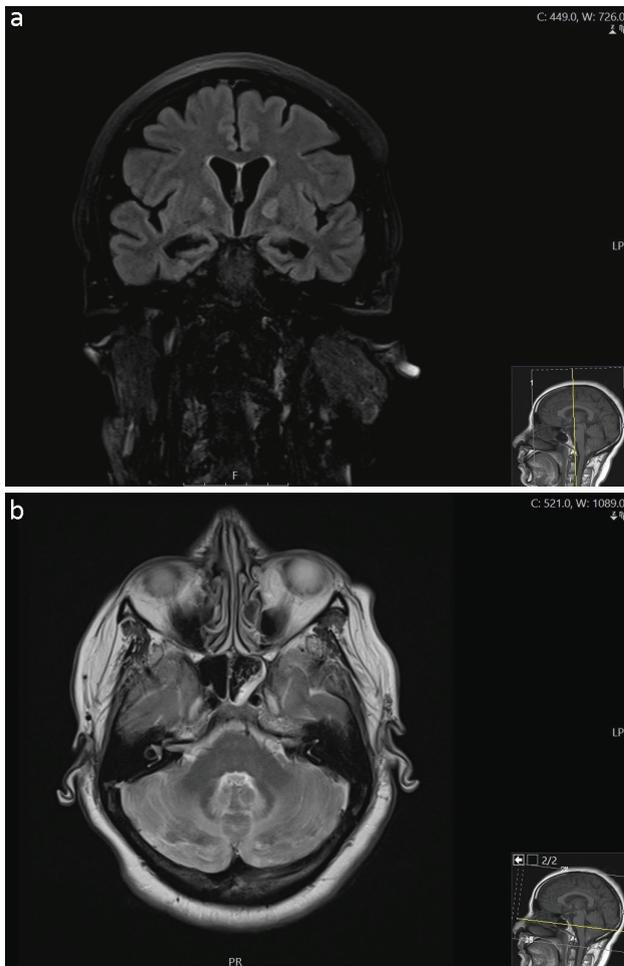


Fig 2. Interval magnetic resonance imaging of the brain showing appropriate evolution of the globus pallidi and bi-cerebellar injury.

destruction).³ Other clinical presentations include acute cerebellitis, seizures, ataxia, dysarthria, catatonic state².

Oxycodone leukoencephalopathy

Opioids are lipophilic and accumulate in the lipid-rich myelin sheath when taken in large doses. Oxycodone, a semi-synthetic strong prescription opioid, has an oral bioavailability of 87% (vs morphine at 30%) and attains a maximum plasma concentration under 1 hour with a plasma half-life of 3–4 hours.

The first case series (47 patients) of inhaled heroin pyrolysate-induced WM damage was described in 1982.⁴ These patients presented with cerebellar syndrome and CT revealed hypoattenuation in cerebral and cerebellar WM. There are further reports of, predominantly, children presenting unconscious or unresponsive with WM changes in the cerebrum or cerebellum after inadvertent exposure to heroin, morphine or methadone.² One Belgian case report was on a 65-year-old woman who had extensive, symmetrical cerebral WM changes after inadvertently ingesting a high dose of methadone.⁵

Oxycodone-associated neurotoxicity was first published in 2010. To the authors' knowledge, there are nine such cases reported in the literature (summarised in Table 1).^{2,6–11} These patients presented with varying symptoms. With opiate prescriptions on the rise, it is imperative to be aware of this clinical condition.

The hallmark of heroin-induced encephalopathy (along with morphine and methadone) is cerebellar involvement due to the affinity of heroin to 'μ' receptors that are heavily distributed in the cerebellum. Oxycodone, however, has a high affinity for 'κ' receptors that are heavily distributed in the basal ganglia and cerebellum.¹⁰

Magnetic resonance imaging

The WM involvement tends to be diffuse and symmetrical with characteristic vacuolisation and spongiform changes.³ Tormoehlen describes the classic MRI findings as symmetrical distribution in the cerebellar and posterior cerebral hemispheres, including the posterior limbs of the internal capsule.¹² Cerebellar dentate nuclei, subcortical 'U' fibres in the posterior cerebrum and anterior limbs of the internal capsule are relatively spared.

The feature that is common to oxycodone neurotoxicity is GPa injury (Table 1). The involvement of basal ganglia has also been noticed in other case reports with methadone use.^{13–15} The bilateral symmetry and involvement of two regions (cerebellum and GPa) are strongly suggestive of toxic damage.¹⁴ One has to be aware that GPa injury can also be seen in carbon monoxide poisoning and intravenous heroin abuse.¹⁶

A further analysis of MRI by Shrot and colleagues in three opioid-related acute brain injury cases showed bilateral symmetrical cerebral WM and cerebellar lesions with involvement of putamen in two of these cases.¹⁷

Conclusion

Acute neurological presentation in patients 'being down' after drug overdose can be incorrectly attributed to hypoxic brain injury. Toxic leukoencephalopathy should be considered in the differential diagnosis. Diagnosis is often achieved with careful consideration of the history, clinical features and imaging findings. There is paucity of case reports on oxycodone leukoencephalopathy, hence the authors felt the need for reporting this case. ■

Table 1. Case reports on oxycodone-induced leukoencephalopathy

Author (year)	Drug causing encephalopathy	Age and sex Presenting clinical feature	Brain structure(s) involved	Outcome at time of reporting
Morales Odia Y (2010) ⁶	Oxycodone 350 mg and oxycontin 400 mg	46 years M Respiratory depression and acute hydrocephalus	Cerebellum and GPa	Survived with residual disability
Beatty CW (2014) ⁷	Oxycodone 75 mg	14 years F Altered mental status and decreased respiration	GPa	Survived but with mild disability
Holyoak AL (2014) ⁸	Oxycodone and clonazepam	26 years M Unresponsiveness	GPa and periventricular WM	Tracheostomy; died of another cause soon after
Ramirez-Zamora A (2015) ⁹	Oxycodone	Adult Reduced sensorium	GPa and hippocampus	Persistent neurobehavioral symptoms
Middlebrooks EH (2017) ¹⁰	Oxycodone (nasal)	29 years F Acute confusion, bradykinesia and early hydrocephalus	Caudate, putamen, GPa, and internal and external capsule	Residual parkinsonism at discharge
		52 years F Coma, AKI and rhabdomyolysis	WM of supratentorial brain and right cerebellum	Died
		38 years M Unresponsiveness	Periventricular WM, and sparing of BG and posterior fossa	Persistent incoordination and weakness of all four limbs
Duran D (2017) ¹¹	Oxycodone	10 month F Unresponsiveness	Cerebellum and caudate nucleus	At 33 months had some neurological signs
Wheaton T (2019) ²	Oxycodone	4 years M Unresponsiveness	Cerebellar and cerebral WM lesions	Survived with residual disability

AKI = acute kidney injury; BG = basal ganglia; F = female; GPa = globus pallidi; M = male; WM = white matter.

Conflicts of interest

Dr Mehoor Patel is on the editorial board of *Clinical Medicine*.

References

- Zhang K, Sejnowski TJ. A universal scaling law between gray matter and white matter of cerebral cortex. *Proceedings of the National Academy of Sciences* 2000;97:5621–6.
- Wheaton T, Toll BJ, Breznak K *et al*. Opioid-induced toxic leukoencephalopathy: A case report and review of the literature. *Heliyon* 2019;5:e03005.
- Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med* 2001;345:425–32.
- Wolters EC, Stam FC, Lousberg RJ *et al*. Leucoencephalopathy after inhaling 'heroin' pyrolysate. *Lancet* 1982;320:1233–37.
- Salgado RA, Jorens PG, Baar I *et al*. Methadone-induced toxic leukoencephalopathy: MR imaging and MR proton spectroscopy findings. *AJNR Am J Neuroradiol* 2010;31:565–6.
- Morales Odia Y, Jinka M, Ziai MC. Severe leukoencephalopathy following acute oxycodone intoxication. *Neurocrit Care* 2010;13:93–7.
- Beatty CW, Ko PR, Nixon J, Gospe SM Jr. Delayed-onset movement disorder and encephalopathy after oxycodone ingestion. *Semin Pediatr Neurol* 2014;21:160–5.
- Holyoak AL, Trout MJ, White RP, Prematuranga S, Senthuran S. Toxic leukoencephalopathy in the intensive care unit. *Anaesth Intensive Care* 2014;42:782–8.
- Ramirez-Zamora A, Ramani H, Pastena G. Bilateral pallidal and medial temporal lobe ischaemic lesions after opioid overdose. *J Neurol Neurosurg Psychiatry* 2015;86:1383–4.
- Middlebrooks AH. Acute neurologic toxicity related to nasal insufflation of crushed oxycodone: A case series and review of the literature. *Neurographics* 2017;7:36–41.
- Duran D, Messina R, Beslow LA *et al*. Malignant cerebellar edema subsequent to accidental prescription opioid intoxication in children. *Front Neurol* 2017;8:362.
- Tormoehlen LM. Toxic leukoencephalopathies. *Neurol Clin* 2011;29:591–605.
- Corliss RF, Mandal R, Soriano BJ. Bilateral acute necrosis of the globi pallidi and rhabdomyolysis due to combined methadone and benzodiazepine toxicity. *Am J Forensic Med Pathol* 2013;34:1–4.
- Corré J, Pillot J, Hilbert G. Methadone-induced toxic brain damage. *Case Rep Radiol* 2013;2013:602981.
- Zanin A, Masiero S, Severino MS *et al*. A delayed methadone encephalopathy: clinical and neuroradiological findings. *J Child Neurol* 2010;25:748–51.
- Torres C, Zakhari N, Symons S, Nguyen TB. Imaging the unconscious 'found down' patient in the emergency department. *Neuroimaging Clin N Am* 2018;28:435–51.
- Shrot S, Poretti A, Tucker EW, Soares BP, Huisman TAGM. Acute brain injury following illicit drug abuse in adolescent and young adult patients: spectrum of neuroimaging findings. *Neuroradiol J* 2017;30:144–50.

Address for correspondence: Dr Udayaraj Umasankar, University Hospital Lewisham, Lewisham and Greenwich NHS Trust, High Street, Lewisham, London SE13 6LH, UK. Email: udayaraj.umasankar@nhs.net