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Imaging of Subacute Blood–Brain Barrier Disruption After Methadone Overdose

Branko N. Huisa, MD, Charles Gasparovic, PhD, Saeid Taheri, PhD, Jillian L. Prestopnik, PhD, and Gary A. Rosenberg, MD

Departments of Neurology (BNH, ST, JLP), Neurosciences (CG, GAR), Cell Biology and Physiology (GAR), University of New Mexico, Health Sciences Center, Albuquerque, NM.

Abstract

BACKGROUND—Methadone intoxication can cause respiratory depression, leading to hypoxia with subsequent coma and death. Delayed postanoxic leukoencephalopathy (DAL) has been reported with intoxication by carbon monoxide, narcotics, and other toxins.

OBJECTIVE—To investigate the metabolic derangement of the white matter (WM) and blood–brain barrier (BBB) after DAL caused by methadone overdose.

DESIGN, SETTING, AND PATIENTS—Case report of 2 patients with DAL after a single dose of “diverted” methadone used for pain control.

RESULTS—In both cases brain magnetic resonance imaging (MRI) revealed initial extensive bilateral restricted diffusion lesions within the WM. Follow-up MRI using proton magnetic resonance spectroscopic imaging (¹H-MRSI) showed markedly lower N-acetylaspartate and higher choline within the WM. BBB permeability, calculated by Patlak graphical analysis of MRI T1 data obtained after contrast agent injection, showed disruption of the BBB within the WM lesions, which persisted longer than a year in 1 patient. Neuropsychological evaluation showed executive dysfunction in both patients. After 1 year, one patient recovered whereas the second remained impaired.

CONCLUSIONS—Methadone overdose can cause DAL with profound disturbances of neural metabolism and the BBB. The time course of these disturbances can be monitored with MR methods.

Keywords

Hypoxic ischemic injury; coma; MR spectroscopy; perfusion MRI; dynamic contrast enhanced MRI

Chronic use of methadone with gradual escalation of dose is generally well tolerated; however, overdose may lead to respiratory depression resulting in anoxia followed by coma or death.¹ Delayed postanoxic leukoencephalopathy (DAL) occurs days after recovery from

coma after severe hypoxic event of any cause, such as carbon monoxide intoxication and asphyxiation.²⁻⁷ It affects the white matter (WM), causing a broad range of clinical features such as inattention, forgetfulness, gait abnormalities, dementia, coma, and death.²⁻⁷ We report 2 patients who developed DAL after a single dose of “diverted” methadone used for pain control. Both patients provided written consent to obtain imaging and neuropsychological testing. They were studied by proton magnetic resonance spectroscopic imaging (¹H-MRSI); perfusion-weighted magnetic resonance imaging (MRI) by bolus tracking (PWI) and dynamic contrast-enhanced MRI (DCEMRI) for blood–brain barrier (BBB) permeability imaging.

Case 1

A 19-year-old male with no history of narcotic use was found on his bed with shallow breathing, unresponsive and pulseless. He medicated himself with 100 mg of methadone for abdominal pain. Urine toxicology screen was positive only for methadone. His initial brain MRI revealed extensive bilateral restricted-diffusion lesions throughout his WM (Fig 1). Electroencephalogram (EEG) was reactive, showing beta with superimposed delta rhythm, and non-epileptiform waves. On day 6 he was able to follow commands, talk, and eat, but remained confused. On day 7, he lapsed back into coma. On examination his brainstem reflexes were intact, he had spasticity, hyperreflexia, and bilateral extensor plantar responses; spontaneous and startle myoclonus was observed. He awoke from coma on day 16 and subsequently fully recovered.

Case 2

A 32-year-old male was found lying down unconscious after methadone overdose used for pain control. His first brain MRI was done a week later, and it showed bilateral WM hyperintensities in T2-weighted sequences. He improved and was discharged 10 days after his overdose. He was re-admitted 5 days later due to worsening confusion, insomnia, and hallucinations. On examination he was hyperalert, oriented to self only, nonfocal, his reflexes were increased, and he had mild spasticity with flexor plantar responses. His EEG was normal, with increased beta rhythm activity reflecting medication effects. He remained agitated and confused, requiring antipsychotic medications.

Neuropsychological evaluation at 90 days revealed severe executive dysfunction with mild memory deficits in both patients. Twenty months after his initial injury, case 1 showed significant improvement; he was able to return to his job and be fully independent. Case 2 had only a partial recovery and remained dependent with persistent cognitive deficits.

MRI Studies

Follow-up MRI studies were performed on a 1.5-Tesla whole-body scanner (Siemens AG, Erlangen, Germany) at 58 days after initial overdose in case 1, and after 112 days in case 2. DCEMRI was performed with a fast T1 mapping sequence after contrast injection (0.025 mmol/kg, Magnevist, Bayer Pharmaceuticals, Leverkusen, Germany). Pixel-by-pixel permeability maps were constructed using T1 time series data obtained by DCEMRI and compartmental modeling method previously described.⁸ Both patients showed reduced N-

acetylaspartate (NAA) and high choline levels in WM, and relatively normal gray matter (GM) NAA/Creatinine levels compared with age matched controls (Table 1). In both patients, DCEMRI showed disruption of the BBB within the WM, apparent diffusion coefficient showed normalization of signals, and PWI showed a relative decrease in cerebral blood flow within the WM. Case 1 had a third follow-up MRI study that showed partial normalization of metabolites and a decrease of BBB permeability (Table 1 and Fig 2).

Discussion

Using an MR-based method for evaluation of BBB permeability,⁸ we found that patients with DAL have an increased BBB permeability within WM during the subacute phase, with a persistence of the increased permeability months later after the initial hypoxic injury. BBB disruption is believed to be biphasic, with an early (24 hours) phase followed by a refractory period when the BBB is closed, and a delayed second opening.⁹ However, using DCEMRI, an animal model of cerebral ischemia has shown continuous BBB opening lasting up to 4–5 weeks.¹⁰ Disruption of the BBB within the WM is associated with a chronic inflammatory process, such as subcortical ischemic vascular disease (SIVD) and multiple sclerosis.⁸ Previous reports of patients with hypoxic injury have described similar DWI and ¹HMRSI abnormalities.^{2,4,7,11} NAA loss has been proposed to indicate metabolic dysfunction, neuron loss, axonal damage and myelin repair.¹² An increase of the choline signal in the subacute phase after the hypoxic event is compatible with the hypothesis that choline containing compounds increase during the breakdown or repair of myelin.¹² Both patients had a normal cortical NAA/Cr ratio, benign EEG patterns and no evidence of cortical involvement by brain MR. Postmortem pathological studies in patients with predominant anoxic brain injury have revealed edema and demyelination of WM with sparing of the cortex, which contrasts with an hypoxic/ischemic injury seen in cardiac arrest patients.^{3,4,6} It is possible that prior exposure to a long period of hypoxia, high doses of methadone or both may have “preconditioned the brain,” providing protection for selected vulnerable areas within the GM, whereas damage to the WM continues. Such a hypothesis is supported by studies on ischemic animal models in which pretreatment with morphine has shown preconditioning properties.¹³ Conversely, hypoxic preconditioning has been hypothesized as due to induction of hypoxia inducing factor-1 α (HIF-1 α) and endogenous erythropoietin (EPO).¹⁴ HIF-1 α induces transcription of many neuroprotective genes while, at the same time, it induces expression of prodeath genes involved in apoptosis.¹⁴ However, persistent HIF-1 α expression is associated with chronic damage of WM in patients with SIVD.¹⁵ Angiogenesis, chronic inflammation, and ongoing WM repair could explain the abnormalities observed within the WM of these patients. Still, the underlying mechanisms remain to be elucidated.

Prediction of outcome is problematic and it likely relates to length of hypoxic exposure, the different responses of human GM and WM after hypoxic injury and whether the expression of survival or death genes predominate. Thus, neither the extension of the WM lesions, the brain metabolites measured by spectroscopy, nor the degree of BBB leakage were found as predictors of long-term outcome in these two cases.

Acknowledgments

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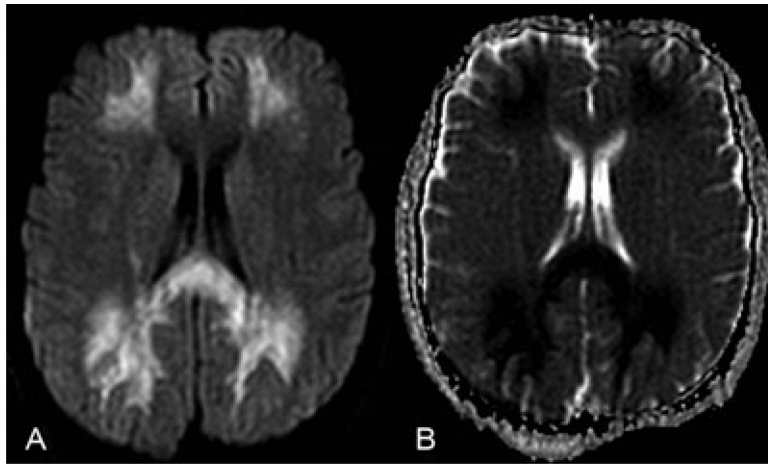


Fig 1. Initial brain MRI of case 1 depicts: (A) An abnormal hyperintense diffusion-weighted imaging (DWI). (B) Low abnormal signal in apparent diffusion coefficient (ADC) map. Initial T2 sequences were normal (not shown). Note mostly involvement of the white matter with sparing of cortex.

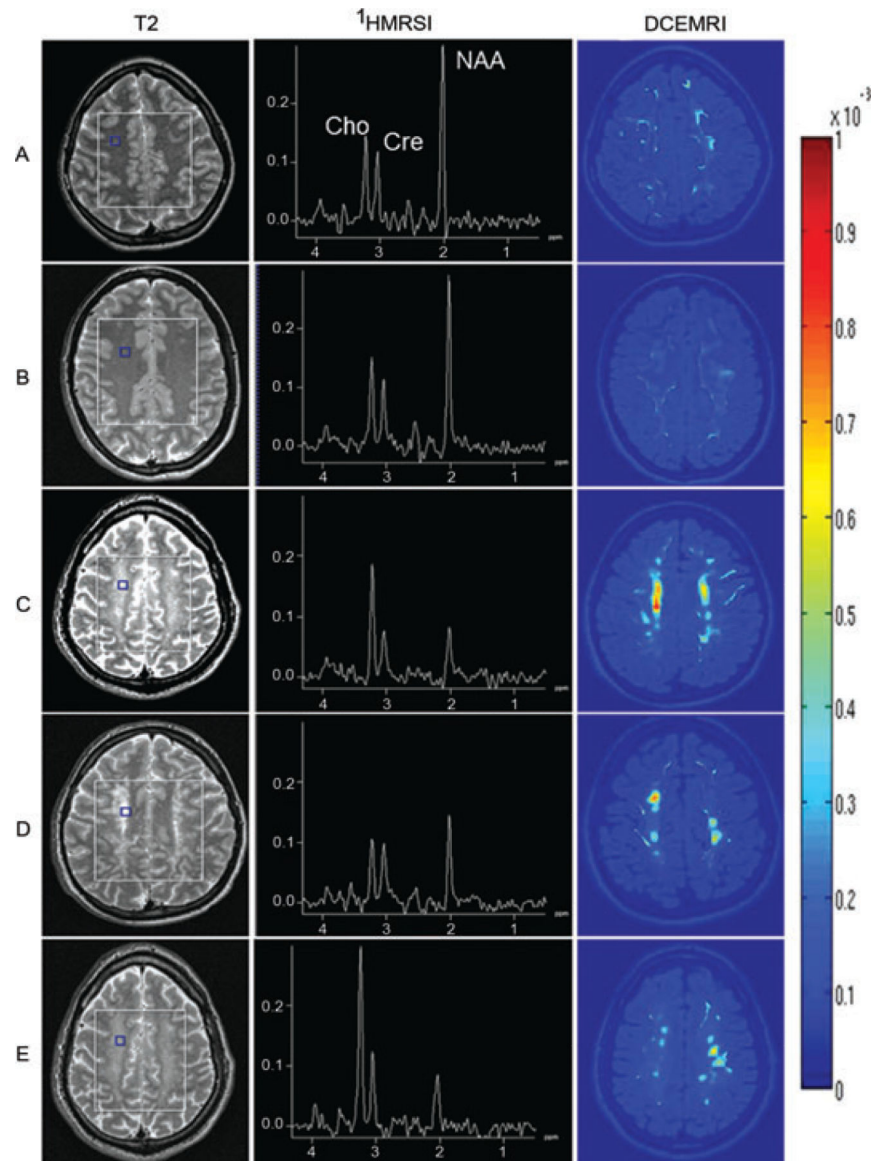


Fig 2. T2-weighted images (Left column), representative spectra analysis (second column), and parametric images—color coded—representing BBB permeability map in the WM (right column). Age-matched control subjects, on rows A and B, case 1 at row C (2nd MRI) and row D (3rd MRI), and case 2 at row E. Small square in each T2 image indicates WM spectroscopic image voxel from which the spectrum shown was obtained. Large square represents the spectroscopic regions of interest. Note lower NAA and higher choline levels in patients relative to controls and partial normalization in case 1 at second visit.

Table 1White Matter Permeability and ¹HMRSI Metabolites Values for Normal Controls and Cases 1 and 2

	Control #1	Control #2	Case 1 2 nd MRI *	Case 1 3 rd MRI *	Case 2 2 nd MRI *
Days postinitial injury	n/a	n/a	58	600	112
Age	22	22	20	21	32
Lesion fraction [†]	0	0	0.4	0.26	0.35
NAA WM mM	14.16	13.7	5.08	7.2	5.89
NAA/Cr WM	2.25	2.21	1.13	1.4	0.89
Choline WM mM	1.77	1.72	2.02	1.28	2.12
NAA/Cr GM	1.53	1.64	1.46	1.45	1.51
Total permeability in WM (mL/g-min)	0.21	0.47	1.29	1.35	1.04

mM = mmol/kg tissue water; WM = white matter; GM = gray matter; Cr = creatinine; NAA = N-acetylaspartate; ¹HMRSI = proton MR spectroscopy imaging; DCEMRI = dynamic contrast enhanced MRI; n/a = nonapplicable.

* First MRI (initial) was performed at the time of patient admission and did not include ¹HMRSI or DCEMRI studies.

[†] Ratio of WM hyperintensity to normal WM from the studied MRI slices.