Acetylcholinesterase inhibitor treatment alleviated cognitive impairment caused by delayed encephalopathy due to carbon monoxide poisoning

doi: 10.1097/MD.0000000000006125

Clinical Case Report

Medicine®

OPEN

Acetylcholinesterase inhibitor treatment alleviated cognitive impairment caused by delayed encephalopathy due to carbon monoxide poisoning

Two case reports and a review of the literature

Kumi Yanagiha, MD, Kazuhiro Ishii, MD, PhD*, Akira Tamaoka, MD, PhD

Abstract

Introduction: Delayed encephalopathy due to carbon monoxide (CO) poisoning can even occur in patients with mild symptoms of acute CO poisoning. Some cases taking conventional hyperbaric oxygen (HBO) therapy or steroid-pulse therapy may be insufficient, and AchEI may be effective.

Patient Concerns and Diagnoses: We report two cases of delayed encephalopathy after acute CO poisoning involving two women aged 69 (Case 1) and 60 years (Case 2) whose cognitive function improved with acetylcholinesterase inhibitor (AchEI) treatment. Delayed encephalopathy occurred 25 and 35 days after acute CO poisoning in Case 1 and Case 2, respectively. Both patients demonstrated cognitive impairment, apathy, and hypokinesia on admission.

Interventions and Outcomes: Although hyperbaric oxygen therapy did not yield any significant improvements, cognitive dysfunction improved substantially. This was evidenced by an improved Mini-Mental State Examination score ffom 9 to 28 points in Case 1 and an improved Hasegawa's dementia rating scale score from 4 to 25 points in Case 2 after administration of an AchEI. In Case 1, we administered galantamine hydrobromide, which was related with improved white matter lesions initially detected on brain magnetic resonance imaging. However, in Case 2 white matter lesions persisted despite AchEI treatment. AchEI treatment may result in improved cognitive and frontal lobe function by increasing low acetylcholine concentrations in the hippocampus and frontal lobe caused by decreased nicotinic acetylcholine receptor levels in delayed encephalopathy after CO poisoning.

Conclusion: Physicians should consider AchEIs for patients demonstrating delayed encephalopathy due to CO poisoning.

Abbreviations: AchEI = acetylcholinesterase inhibitor, CO = carbon monoxide, DWI = diffusion-weighted image, HBO = hyperbaric oxygen, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, T2WI = T2-weighted image.

Keywords: acute carbon monoxide poisoning, acetylcholinesterase inhibitor, carbon monoxide delayed encephalopathy, case report, donepezil hydrochloride, galantamine hydrobromide

1. Introduction

Neurological symptoms caused by carbon monoxide (CO) can be divided into immediate and delayed symptoms, with an intervening asymptomatic period (lucid interval). Immediate symptoms occur just after CO exposure, also known as acute CO poisoning. Delayed symptoms can occur following a 2 to 4-week lucid interval following clinical remission of acute CO poisoning. Such delayed encephalopathy due to CO poisoning is associated with frontal lobe dysfunction, including hypokinesia, cognitive impairment, and psychiatric symptoms.[1,2] Delayed encephalopathy due to CO poisoning can even occur in patients with mild symptoms of acute CO poisoning. This is possibly due to the hypoxia of brain tissues, the increased oxidative stress, or membranous lipid peroxide that results from mitochondrial dysfunction, rather than direct anoxic damage. However, the pathogenesis remains unclear.[1]

Hyperbaric oxygen (HBO) therapy and immune therapy are administered for the treatment or prevention of delayed encephalopathy after CO poisoning. However, a retrospective case study reports a half patient (23 of 46) of delayed encephalopathy after CO poisoning showed severe cognitive or physical sequelae in spite of HBO treatment was provided.[3] Therefore, a useful therapy is longed for this state. Recently, several studies have reported cognitive impairment due to delayed encephalopathy that occurred in patients with CO poisoning who demonstrated improvements after treatment with an acetylcholinesterase inhibitor (AchEI).[4,5] Here, we report 2 cases of delayed encephalopathy after acute CO poisoning in which cognitive impairment and movement disorder were dramatically improved following treatment with galantamine hydrobromide and donepezil hydrochloride.

Editor: Anser Azim.

The authors have no funding and conflicts of interest to disclose.

Department of Neurology, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan.

* Correspondence: Kazuhiro Ishii, Department of Neurology, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba-shi, Ibaraki 305-8575, Japan (e-mail: kazishii@md.tsukuba.ac.jp).

Medicine (2017) 96:8(e6125)

Received: 2 November 2016 / Received in final form: 30 December 2016 / Accepted: 20 January 2017

http://dx.doi.org/10.1097/MD.0000000000006125

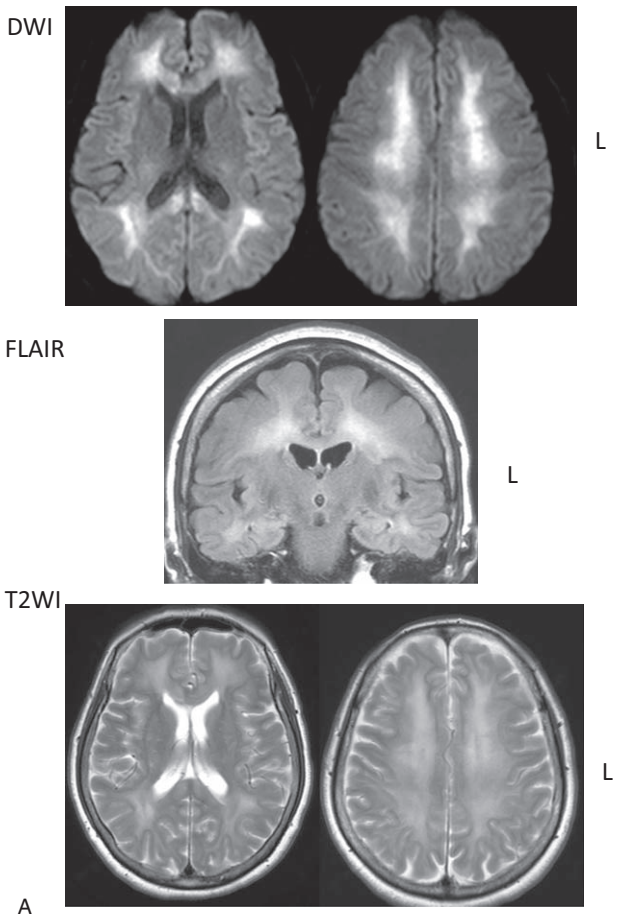

Figure 1. Brain MRI findings for case 1 at the onset (35 days after acute CO poisoning) of delayed encephalopathy (A) and 1 year later (B). (A) Axial view DWI showing bilateral, symmetrical high-intensity lesions in the white matter (upper). The white matter lesions demonstrate symmetrical high-intensity lesions on coronal FLAIR image (middle). Axial view T2WI showing a faint high-intensity lesion mainly located in the white matter (lower). (B) One year later, the white matter lesions previously observed disappeared completely. However, cerebral atrophy was observed on MRI. CO = carbon monoxide, DWI = diffusion-weighted image, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging, T2WI = T2-weighted image.

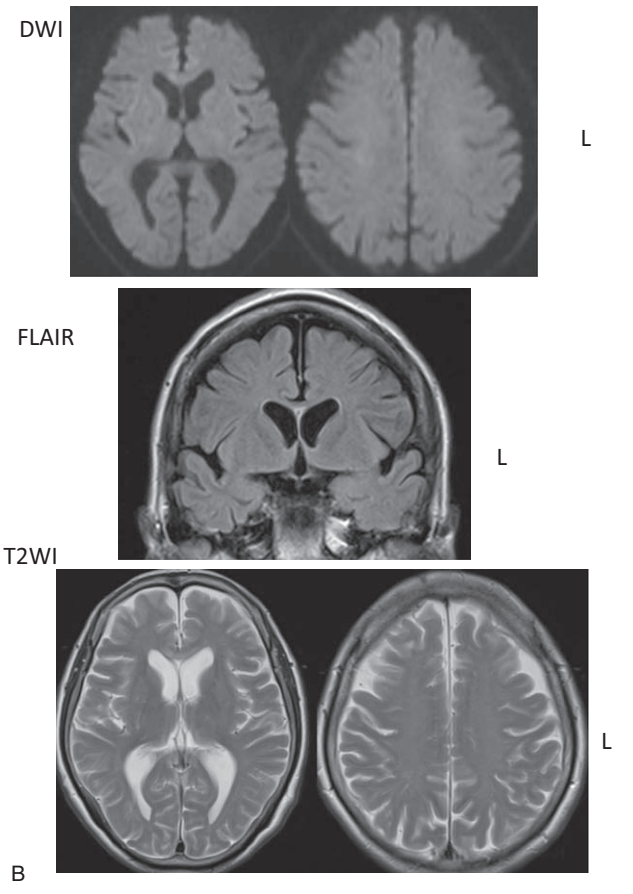

Figure 1. (Continued).

2. Case report

2.1. Case 1

A 69-year-old woman was admitted to the hospital 12 hours after attempting suicide using burning artificial coal. Upon admission, the patient was diagnosed with acute CO poisoning and treated with normobaric oxygen therapy. She was discharged 4 days later without any disturbance of consciousness or movement disorders. Twenty-five days after the acute CO poisoning, she began to experience amnesia, apathy, gait disturbance, and urinary incontinence, which worsened within a few days.

The patient was admitted to our hospital 35 days after the CO poisoning. On examination, she demonstrated an apathetic state and decreasing spontaneous speech ability. However, she could maintain a conversation and follow simple instructions. She had a Mini-Mental State Examination (MMSE) score of 9/30 and a Frontal Assessment Battery score of 3/18, which showed both cognitive and frontal lobe dysfunction severely. She exhibited hypokinesia, frozen gait, and a bilateral palmomental reflex. Sensory disturbance and cerebellar dysfunction were not detected. Hematological values, hepatic and renal function, clotting times, thyroid function, ammonia level, vitamin B1 level, vitamin B12 level, and tumor marker levels were all within the normal range, and antinuclear autoantibodies were not detectable. Examination of the cerebrospinal fluid showed cells (all monocytes: 6 cells/μL), a slightly elevated protein level (52 mg/dL; normal: 10–40 mg/dL), an elevated myelin basic protein level (422 pg/mL; normal: <102 pg/mL), and an oligoclonal band. Brain magnetic resonance imaging (MRI) showed high-intensity lesions in the white matter of the frontal, temporal, and parietal lobes on a T2-weighted image (T2WI) and a diffusion-weighted image (DWI; Fig. 1A). Decreased cerebral blood flow in the frontal lobes was observed on ^{123}I-IMP-single photon emission computed tomography. On electroencephalography, 5 to 7 Hz slow waves were observed in the basic rhythm, but paroxysmal discharges were not observed. Dopamine transporter scintigraphy demonstrated normal uptake in striatal areas, with a specific binding ratio of 6.33 for the right side and 5.74 for the left side (normal SBR range, mean ± 2SD: 5.25 ± 1.34). Taken together, the results of these examinations indicated delayed encephalopathy due to CO poisoning.

The patient was administered vitamins E, B1, and B12 35 days after acute CO poisoning. HBO therapy (2 atm abs, 120 minutes, every other day) was administered 40 days after acute CO poisoning and continued over 17 subsequent sessions. However, the treatment resulted in only mild or transient therapeutic effects. She was administered galantamine hydrobromide after an agreement for adequate informed consent without steroid

therapy. Then, 69 days after acute CO poisoning, the patient took galantamine hydrobromide at 8 mg/day as initial dose, and 28 days after the dose was increased to 16 mg/day as described in the instructions. She did not receive any other medicine except for galantamine hydrobromide after this point in time. Five days later, the patient demonstrated improvement of attention as recovery of spontaneous speech, and there were drastic improvements in disorientation and gait disturbance. The improvement in cognitive function 38 days after initiating galantamine hydrobromide treatment was remarkable, with an MMSE score of 28/30 and a Frontal Assessment Battery score of 18/18. ^{123}I-IMP-single photon emission computed tomography performed 38 days after the administration of galantamine hydrobromide showed increased cerebral blood flow throughout, especially in the frontal lobes. Thirty-nine days after initiating treatment with galantamine hydrobromide, and 74 days from the day of admission, the patient was discharged. At this point, she could perform activities of daily living almost independently. Brain MRI performed 1 year later showed disappearance of high-intensity areas on a DWI and only mild evidence of high-intensity lesions in the diffuse white matter on a T2WI (Fig. 1B). Symptomatic improvement and the related improvements seen on brain imaging have continued for the past 3 years with galantamine hydrobromide medication.

2.2. Case 2

A 60-year-old woman was admitted to a nearby hospital for acute CO poisoning due to attempted suicide using the exhaust gas of a car. She was discharged about a week later without any persisting symptoms. However, 35 days after acute CO poisoning, she began to experience hypokinesia, amnesia, and incommunicative behavior.

Subsequently, 43 days after acute CO poisoning, she visited a local hospital. On admission, there were no abnormal physical findings, but the patient demonstrated apathy, bradyphrenia, hypokinesia, paratonia in the upper extremities, forced gripping, and gait disturbance. She showed cognitive, especially memory dysfunction as Hasegawa dementia rating scale (HDS-R) score of 10/30. Blood tests including those for vitamins, tumor markers, autoantibodies, and hormone functions all yielded normal results. Brain MRI showed high-intensity areas in the cerebral white matter on a T2WI and a DWI (Fig. 2).

Fifty days after acute CO poisoning (and 15 days after the delayed encephalopathy) she was diagnosed with delayed encephalopathy due to CO poisoning and was immediately instructed to undergo 10 sessions of HBO treatment (2 atm abs, 120 minutes, every other day) without steroid therapy. Before and after HBO therapy, the HDS-R score was maintained at 4/30, indicating no improvement. Seventy four days after acute CO poisoning, the patient started to take donepezil hydrochloride at 3 mg/day under adequate informed consent, and the dose was increased to 5 mg in 34 days from starting donepezil hydrochloride. Six months after acute CO poisoning, her disorientation, apathy, and hypokinesia improved at outpatient consultation, and she could go shopping by herself on a bicycle and her HDS-R score improved to 25/30. Symptomatic improvement and related improvements on brain imaging have continued over the past 10 years without any adverse events.

3. Discussion

We have described 2 cases of delayed encephalopathy due to CO poisoning that manifested as cognitive impairment, apathy, hypokinesia, and gait disturbance, and that occurred approximately 4 weeks after clinical remission of acute CO poisoning. The patients were diagnosed with delayed encephalopathy due to CO poisoning based on the presence of high-intensity signals in brain white matter observed on T2WI, fluid-attenuated inversion recovery, and DWI.

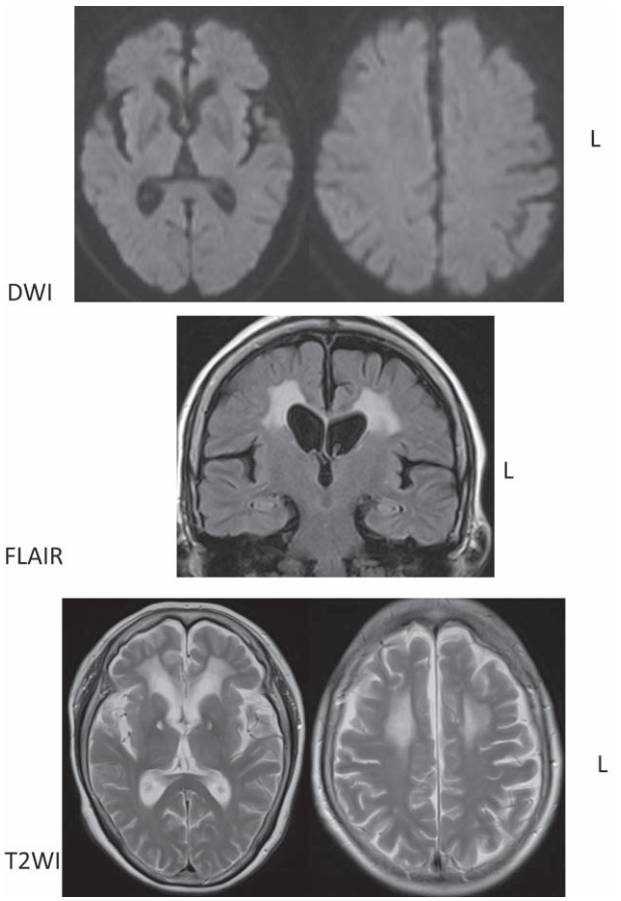

Figure 2. Brain MRI findings for case 2, 6 months after the onset. Unlike in case 1, the bilateral, high-intensity lesions in the cerebral white matter could still be detected on FLAIR image and the T2WI, but not on DWI. Additional characteristics of acute carbon monoxide poisoning, such as necrosis in the globus pallidi, was observed on the T2WI. DWI = diffusion-weighted image, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging, T2WI = T2-weighted image.

Delayed encephalopathy due to CO poisoning typically presents with slow and delayed neuronal cell death and demyelination after CO exposure. The mechanism of delayed encephalopathy due to CO poisoning is assumed to be related to oxygenation deficiency caused by carboxyhemoglobin and CO accumulation in brain tissue. This leads to lipid peroxidation via peroxidase activation and mitochondrial cytochrome c oxidase disorder, which slowly reduce mitochondrial energy production in neurons and oligodendrocytes.[1]

Little is known about cognitive impairment caused by delayed encephalopathy due to CO poisoning. However, studies of animals exposed to CO have reported demyelination and axonal degeneration in the hippocampus due to the degradation of myelin basic protein.[6] The latter results from decreasing neurons and nicotinic acetylcholine receptor levels,[7] and the reduction of acetylcholine levels in the frontal lobe.[8] A previous study also reported that an immunologic mechanism may be associated with

Table 1

Case reports of successful treatment of delayed encephalopathy due to carbon monoxide poisoning using an AchEI.

	Wang et al[4]	Song et al[5]	Case 1	Case 2
Age, year/sex	60/M	16/M	69/F	60/F
COHb level at admission	11.2%	17%	NA	NA
Consciousness disturbance	Present	Present	Present	Present
Treatment for CO poisoning	HBO	HBO	NBO/HBO	NBO/HBO
Onset of delayed symptoms, day	25	25	25	35
High-intensity regions on T2-MRI	NA	Cerebral white matter, basal ganglion	Cerebral white matter	White matter of the frontal lobe, basal ganglion
Type of AchEI administered	Donepezil, 10 mg	Donepezil, 5 mg	Galantamine, 16 mg	Donepezil, 5 mg
Improvement in cognitive function	MMSE 9 → 25	MMSE 8 → 26	MMSE 9 → 28 FAB 3 → 18	HDS-R 4 → 25

AchEI = acetylcholinesterase inhibitor, CO = carbon monoxide, COHb = carboxyhemoglobin, FAB = Frontal Assessment Battery, HBO = hyperbaric oxygen, HDS-R = Hasegawa dementia rating scale, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, NA = not available, NBO = normobaric oxygen.

cognitive dysfunction caused by delayed encephalopathy due to CO poisoning.[9]

Delayed encephalopathy due to CO poisoning is traditionally treated with HBO and steroid therapy, but the effects are often not adequate.[1] In our 2 cases, HBO treatment was the only traditional therapy we administered. Recently, a few studies have reported favorable outcomes for AchEI treatment for delayed encephalopathy due to CO poisoning.[4,5] Therefore, we administered AchEI, which resulted in some improvement in the delayed encephalopathy. As shown in Table 1, the MMSE score in case 1 improved from 9 to 28 and HDS-R score in case 2 improved from 4 to 25 following AchEI treatment.

The precise mechanism underlying improvements in clinical symptoms of delayed encephalopathy due to CO poisoning brought about by AchEI is poorly understood. However, it is thought that AchEI strengthens hippocampal acetylcholinergic neuron function such that delayed neuronal death by CO reactivation is prevented.[7] In addition, AchEIs demonstrate pleiotropic effects. They are known to act as neuroprotective agents by exerting antiapoptotic effects in cortical and hippocampal neurons, elevating Bcl-2 expression, stimulating nicotinic acetylcholine receptors, activating the PI-3K/Akt pathway, and suppressing glycogen synthase kinase-3.[4,5,10] The dysfunction of nicotinic acetylcholinergic neurons in the hippocampus was confirmed using an animal model of delayed encephalopathy due to CO poisoning.[7] Therefore, galantamine hydrobromide, which demonstrates allosteric[11] and protective[12] effects against nicotinic acetylcholinergic neuronal damage, has greater advantages than donepezil hydrochloride in terms of treating delayed encephalopathy.

In case 1, where galantamine hydrobromide was administered, most of the white matter lesions disappeared, and only mild cortical atrophy was observed on brain MRI. These findings indicate that galantamine hydrobromide affects not only neurons but also oligodendrocytes.

Of course, there are some limitations to consider in the presentation of these cases. For example, the efficacy of AchEI alone cannot be commented on as there may have been delayed effects of HBO therapy. Furthermore, the CO exposure conditions differed between the 2 cases, meaning we cannot draw direct comparisons. Indeed, additional data for cases of delayed encephalopathy due to CO poisoning need to be collected. In addition, future studies should compare the effects of galantamine hydrobromide and donepezil hydrochloride in large double-blind randomized controlled studies.

4. Conclusion

We reported 2 cases of improved cognitive and frontal lobe function following treatment of delayed encephalopathy due to CO poisoning with AchEIs (galantamine hydrobromide and donepezil hydrochloride). The pathogenesis of delayed encephalopathy due to CO poisoning is associated with the loss and dysfunction of hippocampal and frontal cortical neurons. Therefore, AchEIs are effective against hippocampal symptoms (cognitive dysfunction) and frontal lobe symptoms (apathy, hypokinesia, and gait disturbance). From the point of functional mechanism like allosteric and protective effects against nicotinic acetylcholinergic neuron, galantamine hydrobromide is predicted demonstrating a superior effect on nicotinic acetylcholinergic neurons compared with donepezil hydrochloride.

References

[1] Weaver LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med 2009;360:1217–25.

[2] Ernst A, Zibrak J. Carbon monoxide poisoning. N Engl J Med 1998; 339:1603–8.

[3] Hu H, Pan X, Wan Y, et al. Factors affecting the prognosis of patients with delayed encephalopathy after acute carbon monoxide poisoning. Am J Emerg Med 2011;29:261–4.

[4] Wang P, Zeng T, Chi ZF. Recovery of cognitive dysfunction in a case of delayed encephalopathy of carbon monoxide poisoning after treatment with donepezil hydrochloride. Neurol India 2009;57:481–2.

[5] Song IU, Cho HJ, Kim YD, et al. Improvement of cognitive impairment following delayed CO encephalopathy. Can J Neurol Sci 2011;38: 934–5.

[6] Watanabe S, Matsuo H, Kobayashi Y, et al. Transient degradation of myelin basic protein in the rat hippocampus following acute carbon monoxide poisoning. Neurosci Res 2010;68:232–40.

[7] Ochi S, Abe M, Li C, et al. The nicotinic cholinergic system is affected in rats with delayed carbon monoxide encephalopathy. Neurosci Lett 2014;569:33–7.

[8] Nabeshima T, Katoh A, Ishimaru H, et al. Carbon monoxide-induced delayed amnesia, delayed neuronal death and change in acetylcholine concentration in mice. J Pharmacol Exp Ther 1991;256:378–84.

[9] Thom SR, Bhopale VM, Fisher D, et al. Delayed neuropathology after carbon monoxide poisoning is immune-mediated. Proc Natl Acad Sci 2004;101:13660–5.

[10] Noh MY, Koh SH, Kim Y, et al. Neuroprotective effects of donepezil through inhibition of GSK-3 activity in amyloid-beta-induced neuronal cell death. J Neurochem 2009;108:1116–25.

[11] Dajas-Bailador FA, Heimala K, Wonnacott S. The allosteric potentiation of nicotinic acetylcholine receptors by galantamine is transduced into cellular responses in neurons: Ca2+ signals and neurotransmitter release. Mol Pharmacol 2003;64:1217–26.

[12] Geerts H. Indicators of neuroprotection with galantamine. Brain Res Bull 2005;64:519–24.