

The Brain Lesion Responsible for Parkinsonism After Carbon Monoxide Poisoning

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Background: Parkinsonism is a common neurological sequela of carbon monoxide (CO) poisoning, but its pathophysiological mechanism has yet to be clarified.

Objectives: To describe a married couple who were both affected by CO poisoning, but only 1 of whom developed CO-induced parkinsonism, and to discuss the possible underlying pathophysiological mechanism of CO-induced parkinsonism by comparing the neuroimaging findings of these patients.

Design and Setting: Case report from a clinical neurology department.

Patients: A married couple experienced CO poisoning simultaneously. One month later, only the husband gradually developed delayed sequelae, including parkinsonism and intellectual impairment. On detailed neurological examination, the husband showed mild but definite rigidity and bradykinesia, while no parkinsonian signs were observed in the wife. Neuropsychological examination revealed impaired memory and attention in both

patients, but they were more severe in the husband than in the wife. Magnetic resonance imaging scans of the patients' brains disclosed diffuse high-intensity white matter signals in both patients and bilateral pallidal necrosis in the wife. Dopamine transporter imaging showed that the degree of dopamine neuronal loss was comparable between these patients. Magnetic resonance spectroscopy revealed more severe white matter damage in the husband than in the wife. Thirteen months later, neurological and neuropsychological examinations showed complete recovery from parkinsonism as well as intellectual impairment. Follow-up magnetic resonance spectroscopy also suggested remarkable improvements in white matter damage.

Conclusion: These results support the role of white matter damage in producing parkinsonism after CO poisoning and highlight the possible usefulness of magnetic resonance spectroscopy in predicting delayed sequelae in patients after CO poisoning.

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PARKINSONISM is a common neurological sequela of carbon monoxide (CO) poisoning.¹ The role of dopamine neuronal damage in producing CO-induced parkinsonism (COIP) has yet to be clarified, although the favorable effect of dopamine agonists has been reported.^{2,3} We describe a married couple who inhaled CO in the same place and for the same amount of time, but only the husband developed COIP. To investigate the underlying brain lesion responsible for parkinsonism in these similarly CO-poisoned patients, we performed detailed neurological and neuropsychological examinations, magnetic resonance imaging (MRI) of the brain, proton magnetic resonance spectroscopy (MRS), and [¹²³I]-N-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane ([¹²³I]-IPT) dopamine transporter

brain single photon emission computed tomography (SPECT).

REPORT OF CASES

CASE 1

A 56-year-old previously healthy right-handed man was admitted because of progressive memory impairment and slowness of movements. Approximately 1 month earlier, he had experienced acute CO poisoning due to a malfunctioning coal heating system and had remained unconscious for the following 2 days. After being discharged 7 days after the CO exposure, he had no disability and he returned to previous work, without any problem. About 2 weeks after discharge, however, the present symptoms developed and progressed.

The results of the physical examination were normal. On neurological exami-

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nation, the patient showed partial impairment in short-term memory. Parkinsonian features, including reduced facial expression, reduced arm swing, and mild-to-moderate bradykinesia and rigidity, more severe in the left extremities, were observed. Postural response was normal. Laboratory investigations, including a serum chemistry profile, complete blood cell count, urinalysis, and serological tests for syphilis, revealed no abnormalities. Neuropsychological tests showed that the patient's score on the Wechsler Adult Intelligence Scale (WAIS) was 92 but his score on the Memory scale was significantly reduced, at 48.5, with reduced attention. Brain MRI scans (1.5-T Signa; General Electric, Milwaukee, Wis) obtained on the third hospital day revealed diffuse high-signal intensities over the periventricular and supracallosal white matter on T2-weighted images (Figure 1, A). Magnetic resonance spectroscopy revealed an increased choline-containing compound (Cho)/creatine-phosphocreatine (Cr) ratio (1.85) with a decreased *N*-acetylaspartate (NAA)/Cr ratio (1.51) in the white matter (normal mean±SD control values: Cho/Cr, 1.30±0.23; NAA/Cr, 2.32±0.25), while those ratios in the cortex were within the normal range (1.24 and 2.06, respectively) (normal control values: Cho/Cr, 1.03±0.24; NAA/Cr, 2.24±0.31) (Figure 2, C and D). One month later, dopamine transporter brain SPECT (Triad 88; Trionix, Twinsburg, Ohio) was performed according to a previously described method.⁴ The basal ganglia–occipital cortex/occipital cortex ([BG-OCC]/OCC) uptake ratio was 2.65 in the right side and 2.97 in the left side (normal control value, 4.26±0.73). No dopaminergic medication, including levodopa, was given because the patient's parkinsonian symptoms were relatively mild.

About 2 months after discharge, his parkinsonian symptoms had improved enough that he could return to his previous work without any difficulty. However, a mild memory problem persisted until 4 months after discharge. Thirteen months after discharge, neurological examination revealed no parkinsonian symptoms or signs. Neuropsychological tests disclosed that, compared with previous test results, both the WAIS and the Memory scores were significantly improved to 107 and 101, respectively. Brain MRI scans showed remarkable improvements in white matter high-signal lesions (Figure 1, B). Follow-up MRS also showed remarkable improvements in the Cho/Cr ratio (1.51) as well as the NAA/Cr ratio (2.28) in the white matter, but those ratios in the cerebral cortex were unchanged (1.02 and 1.87, respectively) (Figure 2, E and F).

CASE 2

A 49-year-old previously healthy right-handed woman experienced acute CO poisoning and was found comatose next to her husband, patient 1, who was also unconscious. She was found, still unconscious, about 17 hours later. She and her husband remained unconscious for the following 2 days. However, in contrast to her husband, she did not complain of any neurological symptoms.

The results of her physical examination were normal. Detailed neurological examination failed to detect

any assessable parkinsonian symptoms or signs. Neuropsychological tests revealed that her WAIS score was 90, but her score on the Memory scale was reduced to 61.5, with borderline attention deficits. Brain MRI disclosed diffuse high-signal lesions in the periventricular and supracallosal white matter and focal hemorrhagic necrosis in the bilateral pallidum (Figure 1, C and D). Magnetic resonance spectroscopy revealed a slightly decreased NAA/Cr ratio (1.87) but a normal Cho/Cr ratio (1.18) in the white matter, while both ratios were normal in the cortex (2.23 and 1.17, respectively). The patient underwent [¹²³I]-IPT SPECT of the brain 1 month later, which revealed a reduced ([BG-OCC]/OCC) uptake ratio (2.51 on the right side and 2.71 on the left side).

Thirteen months later, repeated neuropsychological tests revealed that, compared with previous test results, the Wechsler Memory score was significantly improved to 93.5, while the WAIS score was unchanged (90). Brain MRI showed marked improvements in white matter high-signal lesions but no interval change in the bilateral pallidal necrosis (Figure 1, E, and F). Magnetic resonance spectroscopy showed a significant decrease in the Cho/Cr ratio in the white matter and cerebral cortex (0.75 and 0.76, respectively), but no change in the NAA/Cr ratio (1.68 and 2.14). The size (2×2 cm) and location of the voxels drawn for MRS studies were identical in both patients and between visits. The investigators analyzing the data of [¹²³I]-IPT SPECT (J.H.I) and MRS studies (H.S.K.) of the brain were blind to the patients' clinical status.

COMMENT

Clinical history and symptoms, including akinetic rigid parkinsonism with memory impairment in patient 1, strongly supported the diagnosis of COIP. Since our 2 patients were exposed to CO in the same place for the same period of time, and then remained unconscious for a similar duration thereafter, the amount of inhaled CO appeared to be similar in both patients. Thus, elucidating the differences in brain-damage patterns between them could provide an insight into the pathophysiological mechanism of COIP. There are 2 types of COIP: the progressive type and the delayed relapsing type.¹ The clinical features in case 1 seem to be compatible with the delayed relapsing type rather than the progressive type. Although the progressive type of COIP may have different clinical and neuroimaging features, case 1 represents the major form of COIP, because the delayed relapsing type is 3 times more frequently observed than the progressive type.¹

Brain MRI findings related to CO poisoning have included diffuse white matter hyperintensities and hemorrhagic necrosis of the pallidum.⁵ The former were observed in both patients, while the latter was only observed in patient 2. Dopamine transporter imaging including [¹²³I]-IPT SPECT of the brain has been a reliable method with which to quantitate the density of striatal dopamine neurons.⁶ By using [¹²³I]-IPT SPECT of the brain, a significant dopamine neuronal loss was observed in both patients, but the amount of loss was comparable between them. According to the report of Lee et al,⁴ who used the same machine and method for [¹²³I]-IPT SPECT

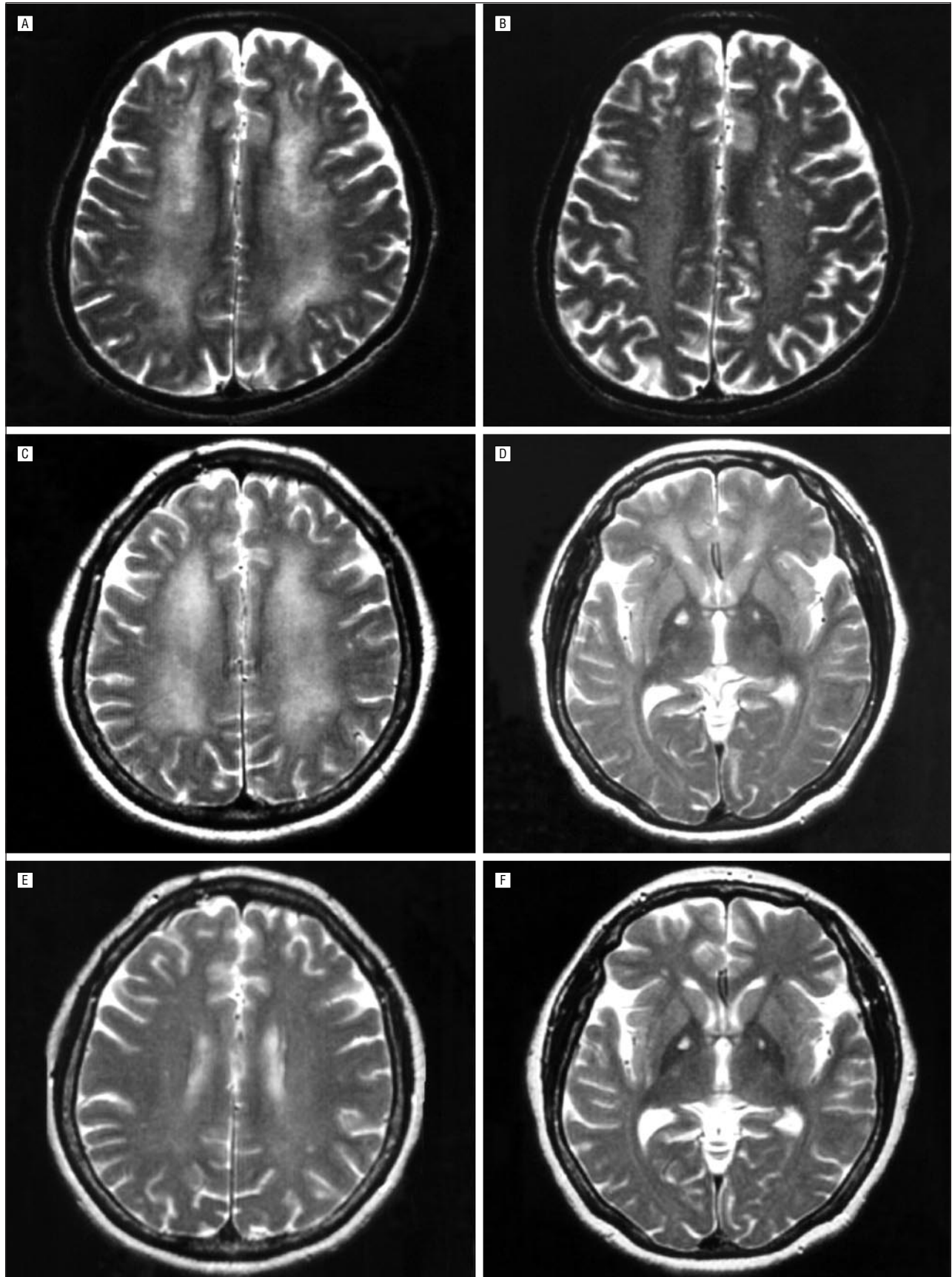


Figure 1. A, A T2-weighted magnetic resonance imaging (MRI) scan obtained 1 month after carbon monoxide poisoning shows diffuse high-signal lesions in the white matter in patient 1. B, Thirteen months later, a remarkable reduction in previously noted white matter lesions is shown. C and D, Diffuse high-signal changes in the white matter and bilateral pallidal necrosis in patient 2. E and F, Follow-up MRI scans obtained 14 months after onset show nearly complete disappearance of the white matter lesion, while pallidal necrosis persists.

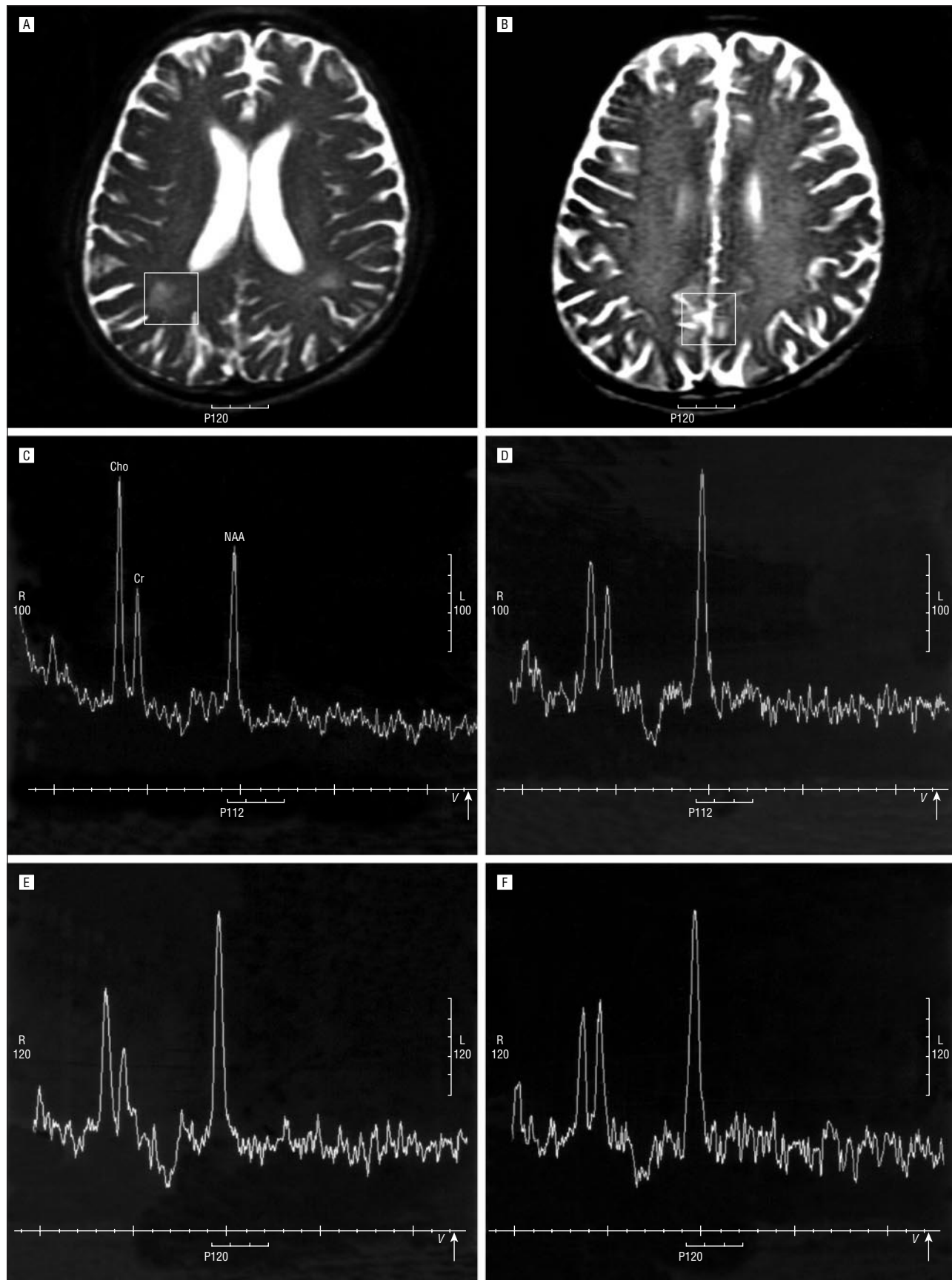


Figure 2. Patient 1. A and B, On T2-weighted magnetic resonance imaging scans, boxed areas indicate the location and size (2 × 2 cm) of voxels for magnetic resonance spectroscopy (MRS) of the white matter and cortex. C and D, Magnetic resonance spectroscopy of the brain performed on admission shows discrete peaks of choline-containing compounds (Cho), creatine-phosphocreatine (Cr), and N-acetylaspartate (NAA). E and F, Follow-up MRS performed 13 months later shows a reduction in the Cho/Cr ratio and an increase in the NAA/Cr ratio in the white matter, compared with initial MRS.

of the brain as we did, the ([BG-OCC]/OCC) uptake ratio in patients with early Parkinson disease was usually less than 2.5. Therefore, the reduction in the ([BG-OCC]/OCC) uptake ratio in our patients appeared to be insufficient to that producing Parkinson disease. These results indicate that neither the pallidal necrosis nor the loss of striatal dopaminergic neurons per se is sufficient to produce COIP. However, we were unable to exclude the possibility of the patients' differences in baseline susceptibility to developing parkinsonism with a similar degree of dopamine neuronal damage. Since pallidotomy can improve symptoms in Parkinson disease,⁷ pallidal necrosis in patient 2 may have had a protective effect against COIP. However, the fact that previously reported cases of COIP often showed bilateral pallidal necrosis¹ could exclude this possibility.

Magnetic resonance spectroscopy in vivo is a useful technique for the examination of brain metabolites. The major resonances of MRS are NAA, Cho, and Cr.⁸ N-acetylaspartate, since it is located primarily within neurons, is a specific neuronal and axonal marker, while Cho represents the membrane constituent phosphatidyl choline.⁸ Based on biochemical studies of demyelinating brains, Cho increases were attributed to an increase in phosphatidyl choline on demyelination or gliosis, while NAA decreases in the demyelinated white matter presumably represented axonal and neuronal loss.^{8,9} Compared with patient 2, patient 1 showed a significantly increased Cho/Cr ratio as well as a decreased NAA/Cr ratio in the white matter, but not in the cortex. This MRS result indicated that more severe white matter damage, including demyelination and axonal damage, as well as gliosis, had occurred in patient 1 than in patient 2.

Pathological findings in the brains of patients with CO poisoning include white matter changes and necrosis of the globus pallidus, but substantia nigra damage is rare.^{10,11} Among them, white matter changes are known to be related to the severity of COIP. Patients with delayed relapsing sequelae usually show pure demyelination, while those with severe symptoms and progressive deterioration often show additional damage to the axis cylinder.^{1,10,11} Initial MRI scans showed diffuse high-signal lesions in the periventricular and supracallosal white matter in both patients, but the recovery observed on follow-up MRI scans was superior in patient 2 compared with patient 1. These findings suggest that initial white matter damage was more severe in patient 1 than in patient 2. The difference in white matter damage between the patients was not distinguishable on MRI scans, but could be measured by MRS, which showed more severe demyelination, along with more axonal damage, in the white matter in patient 1 than in patient 2. These results provided in vivo evidence to support previous pathological observations of COIP.

Follow-up neurological and neuropsychological examinations revealed a complete recovery from parkinsonism in patient 1, as well as recovery of memory disturbances in both patients. Subsequent MRI scans of the brain in both patients showed remarkable improvements in high-signal lesions in the periventricular and supracallosal white matter. Follow-up MRS scans also revealed remarkable improvements in the Cho/Cr and NAA/Cr ratios in damaged white matter. This temporal relationship between clinical symptoms and the findings of MRI and MRS in the white matter suggests that the degree of white matter damage plays an important role in producing delayed sequelae after CO poisoning, including parkinsonism and intellectual impairment. Our observations also highlighted the possible usefulness of MRS in predicting the development of delayed sequelae after CO poisoning.

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