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ORIGINAL COMMUNICATION

^{1}H MR spectroscopy of gray and white matter in carbon monoxide poisoning

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Abstract Carbon monoxide (CO) intoxication leads to acute and chronic neurological deficits, but little is known about the specific noxious mechanisms. ^{1}H magnetic resonance spectroscopy (MRS) may allow insight into the pathophysiology of CO poisoning by monitoring neurochemical disturbances, yet only limited information is available to date on the use of this protocol in determining the neurological effects of CO poisoning. To further examine the short-term and long-term effects of CO on the central nervous system, we have studied seven patients with CO poisoning assessed by gray and white matter MRS, magnetic resonance imaging (MRI) and neuropsychological testing. Five patients suffered from acute high-dose CO intoxication and were in coma for 1–6 days. In these patients, MRI revealed hyperintensities of the white matter and globus pallidus and also showed increased choline (Cho) and decreased *N*-acetyl aspartate (NAA) ratios to creatine (Cr), predominantly in the white matter. Lactate peaks were detected in two patients during the early phase of high-dose CO poisoning. Two patients with chronic low-dose CO exposure and without loss of consciousness had normal MRI and MRS scans. On follow-up. five of our seven patients had long-lasting intellectual impairment, including one individual with low-dose CO exposure. The MRS results showed persisting biochemical alterations despite the MRI scan showing normalization of morphological changes. In conclusion, the MRS was normal in patients suffering from chronic low-dose CO exposure; in contrast, patients with high-dose exposure showed abnormal gray and white matter levels of NAA/Cr, Cho/Cr and lactate, as detected by ^{1}H MRS, suggesting disturbances of neuronal function, membrane metabolism and anaerobic energy metabolism, respectively. Early increases in Cho/Cr and decreases of NAA/Cr may be related to a poor long-term outcome, but confirmation by future studies is needed.

Keywords CO intoxication · Choline · Magnetic resonance imaging · *N*-acetyl aspartate · Neuropsychology · Outcome

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Introduction

Carbon monoxide (CO), alone or in combination with smoke intoxication, is one of the major causes of poisoning injury and death worldwide [3, 21]. However, CO intoxication is often overlooked because CO is an odorless gas and induces various non-specific symptoms [19]. The first of these to appear are often headache, fatigue, nausea and concentration difficulties. Acute low-dose CO exposure may result in substantial but reversible neuropsychological impairment [2].The brain and heart are particularly vulnerable to CO and, consequently, high-dose exposure may

lead to myocardial ischemia and arrhythmia and to neurological disturbances, including coma, seizures and focal signs. Carbon monoxide can also evoke chronic neurological deficits despite normalized carboxyhemoglobin (COHb) levels at the time of hospital admission. Two syndromes occur after acute CO poisoning: persistent neurological sequelae and the interval form of CO poisoning. The latter may occur in 15–40% of survivors following acute CO poisoning [19]. In patients with the interval form of CO poisoning, neurological impairment occurs days to weeks after a lucid period [7, 27, 29]. In both syndromes, deficits usually include motor and neuropsychiatric symptoms. The monitoring of neurochemical disturbances by ^{1}H magnetic resonance spectroscopy (MRS) may enable the clinician to estimate the risk of chronic deficits after acute CO poisoning [6], but the body of information currently available on the potential of MRS as a diagnostic tool in CO poisoning is still limited. To date, fewer than 30 cases have been described [9, 10, 12–15, 18, 22, 24, 26, 28], with most of these studies involving only a single voxel ^{1}H MRS in the white matter (WM). Information on gray matter (GM) metabolism remains scarce. To provide additional information on the short-term and long-term effects of CO on the central nervous system, we describe here seven patients with CO poisoning assessed by GM and WM ^{1}H MRS, magnetic resonance imaging (MRI) and neuropsychological testing.

Methods

Between 1999 and 2007, seven patients (mean age 38 ± 15 years) with neurological symptoms due to prolonged low-dose or acute high-dose CO poisoning were evaluated using neuropsychological testing assessment, MRI and MRS. Patients 2, 4, 5, 6 and 7 were assessed repeatedly. In addition, patients 2, 3, 5, 6 and 7 were examined by single proton emission computed tomography (SPECT) and patient 5 by dopamine active transport (DAT) scan. All patients except patient 1 were treated with hyperbaric oxygen (HBO). A neuropsychological examination was performed in patients 1, 2, 3, 5, 6 and 7, including an assessment of concentration, verbal and nonverbal learning and retention, visuospatial construction and abstraction. All diagnostic procedures and data acquisition were performed according to the 1964 Declaration of Helsinki.

The MRI was performed using a 1.5T (patients 1–7) or 3T magnet (follow-up MRI in patients 2 and 7) and included spin-echo T_1- and T_2-, gradient-echo T_2- and diffusion-weighted imaging. Two volumes of interest (VOI) were examined by ^{1}H-MRS, as described earlier [5] using STEAM, TE 20 ms, TM-interval 30 ms, TR 3000 ms, 86 averages: (1) occipitoparietal VOI ($25 \times 25 \times 20$ mm^3), mainly containing WM, and (2) midoccipital VOI ($21 \times 27 \times 20$ mm^3), mainly containing GM. Post-processing of the spectra for display purposes included eddy-current correction, zero filling, Gaussian apodization, fast Fourier transform, phase correction and filtration of the residual water signal. Quantization was achieved using the LCModel [20]. The basis set used in the LCModel fitting consisted of spectra for alanine, aspartate, creatine, gamma-aminobutyric acid (GABA), glucose, glutamine, glutamate, glycerophosphocholine, phosphocholine, myo-inositol (ml), lactate, *N*-acetyl aspartate (NAA), *N*-acetyl aspartylglutamate, myo-inositol and taurine. Estimates for the sums of glutamine and glutamate, glycerophosphocholine and phosphocholine, and NAA and *N*-acetyl aspartylglutamate were also included in the analysis. ^{1}H MRS data from GM and WM using the identical protocol in 21 healthy adults (mean age 32 ± 8 years) served as a normal reference. Signals from creatine (Cr), total choline (Cho), glutamate + glutamine (Glx), lactate, lipids, ml and NAA were analyzed using the full standard basis set as provided by the LCModel software package. Results were expressed as metabolite ratios relative to Cr, which are less sensitive to minor movement artifacts that are often unavoidable during acute CO intoxication. Values within two standard deviations of the average in healthy subjects were regarded as normal. The inter-individual coefficients of variance for NAA/Cr, Cho/Cr, Glx/Cr and mI/Cr in GM were 7, 9 15 and 10%, respectively, and in WM, 8, 13 13 and 12%, respectively. Schirmer et al. [23] have shown that the intra-individual coefficients of variance for metabolites measured by MRS are about half the inter-individual coefficients of variance. Thus, the day-to-day variance for NAA/Cr, for example, is less than 4% in any one particular patient.

Case reports

The salient clinical and radiological findings are summarized in Tables 1 and 2. Patients 1 and 2 suffered from chronic low-dose CO exposure, and patients 3–7 from acute high-dose exposure.

Low-dose exposure without loss of consciousness

Patient 1

A 32-year-old man was referred with a 4-week history of mild headache, dizziness and abnormal tiredness. Five family members had expressed similar complaints. However, their symptoms had resolved upon relocation into a hotel 5 days earlier when CO exposure due to a

Table 1 Clinical and radiological data from patients with carbon monoxide poisoning

	Neurological examination			Neuropsychological deficits			Magnetic resonance imaging			^{1}H magnetic resonance spectroscopy (see Table 2 for further details)		
	Days	Months	Years	Days	Months	Years	Days	Months	Years	Days	Months	Years
Low-dose CO exposure												
Patient 1: male 32 years	Normal	Normal	–	None	None	–	Normal	–	–	Normal	–	–
Patient 2: female 42 years	Normal	Normal	Normal	Mild to moderate	Mild to moderate	Mild to moderate	Normal	Normal	Normal	Normal	Normal	Normal
High-dose CO exposure												
Patient 3: male 26 years	Coma (<24 h), chorea, visual impairment	Mild chorea	Mild chorea	Mild to moderate	Mild to moderate	Mild to moderate	Infarcts of pallidum, occipital laminar necrosis	–	–	GM: NAA/Cr↓	–	–
Patient 4: male 41 years	Coma (48–72 h), decorticate posturing	Normal	–	Clinical depression	–	–	Pallidum infarcts	Hemorrhagic pallidum infarcts	–	WM: NAA/Cr↓ Cho/Cr↑	WM: NAA/Cr↓ Cho/Cr↑↑	–
Patient 5: male 56 years	Coma (<24 h)	Apraxia, paranoid psychosis	Normal	–	Moderate to severe	Minimal	–	Hyperintense WM signals, pallidum hemorrhage	Normalizing WM, pallidum necrosis	–	WM: NAA/Cr↓↓ Cho/Cr↑↑ mI/Cr↑ GM: NAA/Cr↓	WM/GM: NAA/Cr↓ WM: mI/Cr↑
Patient 6: female 53 years	Coma (120–144 h), amnesia, apraxia	Parkinsonism	–	Severe	Mild to moderate, clinical depression	–	Hyperintense signals WM, thalamus, substantia nigra	Progressive signal changes, cerebral atrophy	–	WM: lactacte↑ WM/GM: NAA/Cr↓ Cho/Cr↑	WM/GM: NAA/Cr↓↓	–
Patient 7: female 15 years	Coma (120 h inclusive sedation), decerebrate posturing	Minimal hemiparesis	Normal	Moderate	Mild	Mild	Hyperintense signals in WM and pallidum	Decreasing hyperintense signal intensity	Normal	WM: lactacte↑ NAA/Cr↓ GM: Cho/Cr↑	WM: NAA/Cr↓	WM: NAA/Cr↓ mI/Cr↑

WM White matter, *GM* gray matter, *NAA* *N*-acetyl aspartate, *Cho* choline, *mI* myo-inositol, *Cr* creatine, – no data

Table 2 ^{1}H magnetic resonance spectroscopy in patients with high-dose carbon monoxide poisoning

Patient	Days post insult	WM				GM			
		NAA/Cr (%)	Cho/Cr (%)	mI/Cr (%)	Lactate (%)	NAA/Cr (%)	Cho/Cr (%)	mI/Cr (%)	Lactate
Patient 3	13	ns	ns	ns	nd	−13	ns	ns	nd
Patient 4	4	−15	+13	ns	nd	ns	ns	ns	nd
	30	−18	+40	ns	nd	ns	+15	ns	nd
Patient 5	52	−46	+57	+43	nd	ns	ns	+21	nd
	121	−20	+33	+84	nd	ns	ns	+36	nd
	418	ns	+27	+68	nd	ns	ns	+32	nd
Patient 6	2	−15	+40	ns	lac ++	−15	+33	ns	nd
	50	−35	+15	ns	nd	−25	ns	ns	nd
Patient 7	3	ns	+47	ns	lac +	ns	+41	ns	nd
	9	−18	ns	ns	nd	ns	ns	ns	nd
	323	−20	ns	+49	nd	ns	ns	ns	nd
	542	−17	ns	+21	nd	ns	ns	ns	nd

Results are given as differences from healthy subjects. See text for further details

ns Not significant, *nd* no lactate detected, *lac* + lactate detected

malfunctioning coal heating system had been discovered in the flat. At admission the patient, a non-smoker, had a blood carbon monoxide (COHb) level of 3.2%. Results from the neurological examination and neuropsychological assessment were normal. The MRI and MRS 8 days following the last exposure to CO revealed no abnormal findings. All symptoms had vanished completely at 2-month follow-up.

Patient 2

A 42-year-old woman developed headache, nausea, intermittent vomiting and mild impairment of memory and concentration. Four family members had similar complaints. Symptoms vanished during a 1-week vacation but reappeared upon arrival back home. Four months later CO poisoning caused by a faulty domestic gas stove was diagnosed. Upon admission, the COHb level in this non-smoking patient was 8.4%. Results from the neurological examination were normal. The patient was given 15 treatment sessions with HBO during the following month. The findings from the MRI and MRS examinations were normal, but SPECT disclosed a mild left-sided parietal hypoperfusion of uncertain significance. Neuropsychological testing revealed mild to moderate impairment in concentration, learning, verbal fluency, visuospatial orientation and executive function. Eight months after the last CO exposure, the findings from a repeated examination with MRI, ^{1}H-MRS and SPECT were normal. Neuropsychological testing showed unchanged cognitive deficits. Two of the patient's three children had a similar persisting cognitive impairment.

High-dose exposure with loss of consciousness

Patient 3

A 26-year-old man started a fire in his flat. The next day he was found in the smoke-filled flat breathing, but unconscious and covered by soot. His blood pressure was 75/45 mmHg, and he had tachycardia (145 bpm). He was intubated and sedated. Oxygen was administered, the blood pressure stabilized and metabolic acidosis corrected. Five hours after having been rescued, this patient, a non-smoker, had a COHb level of 2.8%. He was extubated the following day and transferred to our hospital. At admission he was somnolent, but orientated. Examination revealed no focal signs except visual impairment consistent with occipital laminar necrosis revealed a few days later by MRI. The SPECT and CT of the brain were normal. During the next 10 days he received 20 HBO treatment sessions. Although he recovered well in the beginning, after 5 days he developed choreoathetotic movements of the extremities and the head. He was cooperative and orientated with respect to his personal data and place, but not to time, and he showed emotional lability. Visual acuity was improving; the rest of the neurological examination was normal. The MRI 13 days after CO poisoning showed bilateral infarction of the pallidum and parietooccipital cortex, and small lacunar hypodensities of the cerebellum. The ^{1}H-MRS revealed normal WM metabolism. A 13% decrease in the NAA/Cr was found in the GM. A neuropsychological interview 2 weeks later was consistent with mild retrograde amnesia, but structured testing was not performed. The emotional lability had resolved.

Neuropsychological testing 6 weeks after CO intoxication showed disturbed visual perception, impairment of learning and retention for verbal and visual material as well as reduced short-term memory and memory span. Tetrabenazine 150 mg three times daily was prescribed for chorea, with good effect as evidenced on the 2-month follow-up. Five years after discharge he still suffered from reduced central vision, concentration difficulties and tiredness. Cognitive rehabilitation had only limited effect. He remained unable to read a book and worked part-time at a sheltered workshop. A period of major depression was successfully treated, but he was still dependant on tetrabenazine and pimozide to suppress chorea.

Patient 4

A 41-year-old man suffered from repeated episodes of depression. He was found unconscious, but breathing, in the garage in his car with running engines. On admission he was intubated, unresponsive and restless with spontaneous movements in his left side and decorticate posturing of the right extremities on pain stimulation. There was mild increase of tonus, and both plantar reflexes were extensor. Urine and blood toxicology screening was negative. The blood COHb level was 46%. He had mild cherry-red discoloration of the skin. Bilateral globus pallidus lucencies were noticed on computed tomography (CT) scan of the brain. Hyperbaric oxygen therapy was initiated, and a total of 12 treatments were given. The patient regained consciousness 3 days after admission. The results of the neurological examination were unremarkable except for selective amnesia for the suicide attempt and mild right-sided dysdiadochokinesia. T_2-weighted MRI the following day showed bilateral symmetric hyperintensities of the globus pallidus but normal WM signals. The ^{1}H-MRS revealed reduced NAA/Cr in the WM and increased Cho/Cr in both the WM and GM. Thirty days after CO intoxication, neurological examination was normal. A second MRI demonstrated bilateral hemorrhagic infarction of the globus pallidus. The WM MRI signals remained unremarkable. However, the MRS scan revealed progression of the WM abnormalities, with a further increase of Cho/Cr to 40% above normal and an 18% decrease of NAA/Cr, suggesting disturbed myelin metabolism and neuronal injury. Further follow-up was not available.

Patient 5

A 56-year-old man traveled to Asia where he and 50 other hotel guests sustained CO poisoning due to gas leakage from the air conditioning system. He regained consciousness the day after the exposure and received four treatments of HBO. The mild headache had resolved completely on discharge from hospital 5 days later. Back home in Europe he returned to work without any difficulties. However, 6 weeks later he developed confusion, memory disturbances, apraxia and paranoid hallucinations; The neurological examination revealed no other abnormal results, and a CT scan of the brain was normal. Neuropsychological testing revealed moderate to severe dysfunction in all cognitive domains. The SPECT showed bilaterally decreased frontal cerebral blood flow (CBF). T_2-weighted MRI 8 weeks after CO poisoning disclosed bilateral periventricular WM hyperintensities and hemorrhage in the globus pallidus. The ^{1}H-MRS of WM was consistent with demyelination and gliosis, showing 57% increased Cho/Cr, 46% reduced NAA/Cr and 43% increased mI/Cr. Signals from lipids and macromolecules were seen, but not from lactate. The GM ^{1}H-MRS was unremarkable except for lipid signals and a 21% increase in mI/Cr. A DAT scan showed a 40% decrease of transmitter binding in the striatum bilaterally. Neuropsychological retesting 3 months after CO exposure revealed significant cognitive improvement, although a moderate impairment of processing speed, executive function, verbal fluency and learning remained. The patient appeared to be hypomimic. The other results from the neurological examination were normal. One month later SPECT revealed improved CBF with residual hypoperfusion in the left frontal lobe only. Unchanged bilateral WM hyperintensities were seen on T_2-weighted MRI scans, but hypodense signals from the globus pallidus were less pronounced on the T_1-weighted images. The ^{1}H-MRS scan showed normalizing WM Cho/Cr (33% above normal) and NAA/Cr (20% below normal), but the mI/Cr had increased 84%, consistent with gliosis. The GM MRS scan showed a further increase of mI/Cr to 36% above normal. Neuropsychological follow-up showed further improvement. The patient returned to work. A slight impairment of foreign language skills did not prevent him from performing on a highly professional level. Fourteen months after CO intoxication, the DAT scan transmitter binding was near normal. The MRI revealed persisting changes in the globus pallidus, but there was a regression of WM abnormalities. The ^{1}H-MRS scan showed further regression of the abnormalities. Neuropsychological testing revealed continuing improvement. Two years after the CO poisoning event only a minimal decrease of psychomotoric processing speed and attention span remained.

Patient 6

A 53-year-old woman had repeated episodes of depression and suffered from CO poisoning when she attempted suicide by leading automobile exhaust into her motor vehicle. She was found unconscious in the car the next day, where she had a normal blood pressure and was breathing.

Supplemental oxygen was administered. On admission 3 h later, the blood COHb was 2.8%. Toxicology screening in the blood and urine was negative. The patient was unresponsive but withdrew all extremities symmetrically to painful stimuli. There was a bilateral increase in muscle tonus, and both plantar reflexes were extensor. An electroencephalogram (EEG) revealed diffuse 2- to 4-Hz activity at a low frequency in both hemispheres. During the following 2 days, she received six treatments with HBO. Two days after admission bilateral hyperintensities were observed on the T_2- and diffusion-weighted MR images, and low apparent diffusion coefficients (ADC) were noticed in the WM, substantia nigra and thalamus. The ^{1}H-MRS showed 40% increased Cho/Cr and 15% decreased NAA/Cr in the WM and comparable abnormalities in the GM (Fig. 1). A lactate peak was seen in the WM spectrum, likely due to a minor VOI overlap with WM that appeared hyperintense on the diffusion-weighted MR scan, suggesting contamination by cytotoxic edema of a small part of the MRS volume. Six days after admission the patient gradually regained consciousness. Neurological examination was normal except for cognitive impairment: she scored 13 out of 30 points on the Mini Mental State Examination. The patient needed help in nearly every activity of daily living. Neuropsychological assessment demonstrated anterograde and retrograde amnesia, apraxia, visuospatial impairment, decreased attention span and confabulation. During the following weeks she developed mild Parkinsonism with staggering gait, hypokinesia and slight rigidity in both arms. Six weeks after the suicide attempt, the SPECT showed decreased CBF periventricularly and in the frontal lobes. Although ^{1}H-MRS revealed that the Cho/Cr was near normal again and that there was no dectable lactate, MRI of the brain revealed a progression of periventricular and subcortical hyperintensities. The NAA/Cr was further reduced in the GM to 25% and in the WM to 35% below normal, which is consistent with diffuse neuronal injury on MRI. However, 3 months after CO poisoning, her cognitive capabilities had improved and she became independent in her activities of daily living. Neuropsychological retesting confirmed normalization of all cognitive domains except for stress intolerance and increased reaction time.

Patient 7

A 15-year-old girl was found unconscious in a car with running engine in a garage. Another individual was found dead next to her. The patient's initial Glasgow Coma Scale score was three. On admission, the blood COHb was 25%. The patient was intubated and sedated. The blood and urine toxicology screens were negative. She reacted to painful stimuli with decerebrate posturing in the upper extremities, and there was bilateral Babinski sign. The CT brain scan showed cerebral edema, although intracranial pressure monitoring revealed normal values. The EEG recorded 1–2 Hz activity in both hemispheres. The patient received ten HBO treatments during the following week. Four days after the CO poisoning event, diffusion weighted MRI and T_2-weighted MRI images showed symmetric hyperintense signals in the WM and the globus pallidus, and a corresponding low ADC was seen on the MRI scan. There was also a slight herniation of the cerebellar tonsils. The ^{1}H-MRS image showed normal NAA/Cr in the GM and that the Cho/Cr had increased by 41% in the GM. In the WM, similar abnormalities were revealed, with 47% increased Cho/Cr together with a small lactate resonance. The patient was extubated and regained consciousness during the following 2 days. She was fully orientated and had no focal deficit apart from mild right sided hemiparesis. Neuropsychological testing revealed disturbances in psychomotor tempo, concentration, learning, visual perception and verbal fluency. A second MRI 9 days after the accident showed hyperintensities of the central WM, the corpus callosum and brain stem. Cerebellar herniation was no longer seen. Despite progressive hyperintense signal changes on the MRI images, the MRS scan was normal except for an 18% decrease in WM NAA/Cr. Eleven months after the initial incident the patient had returned to school. She passed all tests, although with poorer grades. She complained of cognitive impairment, constant moderate headache and tiredness. Although the neurological examination revealed no motor weakness, the right leg would sometimes give away and there was right-sided hyperreflexia. Neuropsychological retesting showed normalization of psychomotor speed and abstract reasoning but persisting difficulties regarding verbal and visual learning and concentration. There was a slight hypoperfusion of the CBF in the temporal lobes, as evidenced on SPECT. Regression of WM hyperintensities was seen on the MRI. In the WM, the NAA/Cr was decreased by 20% and the mI/Cr was increased by 49%, suggesting persisting neuro-axonal loss, i.e. gliosis. The ^{1}H-MRS scan of the GM was normal. Eighteen months after CO intoxication repeated neuropsychological assessment and SPECT revealed unchanged results. However, the MRS scan showed partial normalization, and MRI, including T_2- and diffusion weighted images, was now normal.

Discussion

Magnetic resonance spectroscopy enables a serial non-invasive monitoring of neurochemical disturbances in the diseased brain. The most striking finding in our case series was that NAA/Cr decreased and the Cho/Cr increased, particularly in WM, in all patients suffering from high-dose CO exposure. In contrast, although patient 2 had persisting

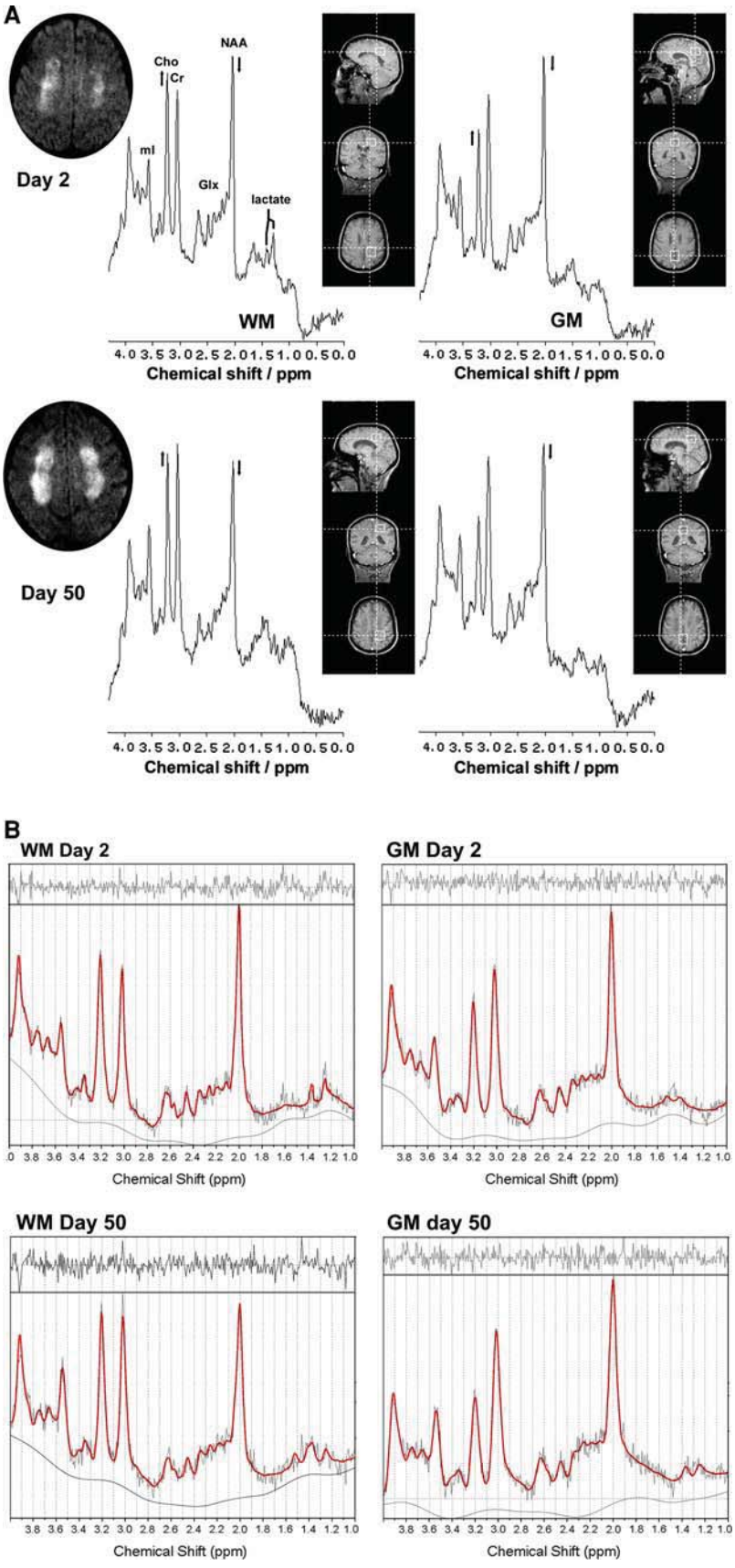

Fig. 1 **a** Two and fifty days after the suicide attempt of patient 6 by CO poisoning, ^{1}H magnetic resonance spectroscopy (^{1}H MRS) of the occipitoparietal white matter (*WM*) and occipital gray matter (*GM*) revealed metabolic disturbances with decreased *N*-acetyl aspartate (*NAA*/*Cr*) and increased choline (*Cho/Cr*). On day 2, a lactate (*lac*) *peak* was seen in the WM. Whereas the MRS showed a progression of NAA/Cr disturbances on day 50, Cho/Cr was near normal at this time. *Insets* show corresponding diffusion weighted MRIs with characteristic high signal changes in WM. **b** The corresponding LCModel fits

neuropsychological deficits, the MRI and MRS scans did not reveal abnormalities following low-dose CO exposure. It must be borne in mind, of course, that metabolites are measured in relatively small VOIs (and not in the entire white and gray matter of the brain); consequently, the MRS data should always be interpreted with caution.

N-acetyl aspartate

N-acetyl aspartate is primarily located in neuroaxonal tissue and, therefore, decreased amounts of NAA indicate neuronal damage or dysfunction [4]. The NAA/Cr was reduced in the WM (patients 4–7) and GM (patient 3 and 6). Although the changes in the GM were mild in patient 3, the absence of WM alterations in this patient suggests that CO may also lead to neuronal impairment in the cortex alone. *N*-acetyl aspartate decays after neuronal death, with a half life of approximately 48 h [4]. Patient 3 had a 13% decrease of NAA/Cr in the GM on day 13 post-injury, but a follow-up was lacking. Patient 6 had a progressive decrease in the NAA/Cr in the GM and WM from day 2 to day 50. In contrast, decreased values of WM NAA/Cr in patient 5 normalized with follow-up examinations (days 52–418), and the minor decreases in the WM NAA/Cr in patients 4 and 7 did not progress during the follow-up (days 30–542). Patients 4 and 7 had normal NAA/Cr in the GM, both initially and at follow-up, as opposed to patient 6, possibly indicating that progression is more likely with an early decrease of NAA/Cr in GM. In WM, the MRS showed an overall pattern of decaying NAA/Cr, which stabilized or normalized in the patients with better outcomes. This finding is in agreement with previous case reports [9, 10, 14, 26].

Total choline

Increase of the membrane constituent Cho indicates altered membrane synthesis and degradation, such as in demyelination, in which the previously bound Cho is released [4]. Magnetic resonance spectroscopy has revealed increases in WM Cho/Cr in several toxic encephalopathies, such as secondary to drug overdose [11]. Patients 6 and 7 had transiently increased Cho/Cr in the GM. The WM Cho/Cr increased in patients 4, 5, 6 and 7, and there was a tendency towards normalization of values on long-term follow-up, which is in agreement with previous reports [9, 10, 14, 26]. An early increase in Cho/Cr may be related to poorer long-term outcome, as seen in patients 6 and 7, but this must be conformed by future studies.

Myo-inositol

Myo-inositol has been suggested as a marker for astrocytes and, consequently, increased amounts of mI seem to be consistent with gliosis [4]. High mI/Cr was seen in the WM at the long-term follow-up in patients 5 (days 52–418) and 7 (days 323–542). Whether this is a biochemical marker reflecting chronic neuropsychological sequelae in these patients or whether it is just a loose association remains unclear. Normal values were seen on day 50 in patient 6, either because gliosis was yet not detectable or because of its absence. Patients 3 and 4 had their last MRS on days 13 and 30, which was too early to expect elevated mI/Cr as a reflection of gliosis.

Lactate

Lactate resonances point towards a conversion of aerobic metabolism to anaerobic energy production, but whether this is due to mitochondrial impairment secondary to hypoxia, to macrophage invasion or to a direct consequence of CO-induced neurotoxicity is not clear [4]. Lactate was detected only in the acute period of CO poisoning in WM in patients 6 and 7. In these MRS studies, WM VOIs partially overlapped with regions that were hyperintense on diffusion-weighted MRI, suggesting temporary compromise of aerobic metabolism due to cytotoxic or vasogenic edema. A similar transient occurrence of lactate combined with hyperintense signal on diffusion-weighted MRI has also been found in pericontusional edematous brain regions after mild head injury [25].

Glutamate and glutamine

The Glx/Cr was within ± 2 SD from normal in all patients, implying that glutamatergic metabolism is largely unaffected by CO poisoning. However, MRS is a relatively insensitive technique, and there might have been effects on glutamate metabolism below the detection threshold.

MRS in comparison to MRI and other imaging modalities

Magnetic resonance spectroscopy provides valuable information on GM and WM function in CO poisoning, including information on brain injuries that can or cannot be seen on MR images. For example, MRS revealed disturbances in VOIs of WM (patients 4 and 5) and GM (patients 4–7) despite a normal MRI signal. Therefore, MRS complements MRI, but data from the former should never be interpreted alone. As an example, patient 3 had a normal WM MRS and only a slight reduction of GM NAA/Cr, yet he had focal neurological deficits reflected by findings on MR images, i.e. visual impairment due to occipital laminar necrosis. The MRI also revealed the focal lesions responsible for Parkinsonism (hyperintensities in substantia nigra and white matter; patient 6) and chorea

(pallidum hyperintensities; patient 3). Pallidum necrosis, however, did not necessarily lead to motor deficits, as seen in patients 4 and 5. In line with this, decreased striatal dopamine binding was detected on a DAT scan of patient 5 who had no motor symptoms except mild hypomimia. Further, SPECT showed decreased CBF variably affecting the frontal, temporal and parietal lobes in four of the five patients, although in patient 5, the CBF normalized in parallel with clinical improvement; consequently, the additional information provided by SPECT seems rather modest.

The prediction of long-term outcome after acute CO poisoning is probably impossible on clinical grounds alone. Although only four of five patients with high-dose intoxication had an MRS during the acute phase, it seems that early metabolic disturbances in the GM and WM, in particular abnormalities of NAA/Cr and Cho/Cr, are associated with progressive disease, a longer recovery and persisting deficits. It should be remembered that absence of MRS abnormalities does not necessarily predict good outcome, as focal lesions revealed by MRI, such as basal ganglia infarcts, may be the decisive factor. The prediction of which patient develops the interval form of CO poisoning seems even more difficult. In the present series only patient 5 suffered clearly from the interval form. Patients 3 and 6 never had a truly lucid period, but they developed chorea and Parkinsonism, respectively, several weeks after the CO intoxication event and partial recovery. It may thus be argued that patients 3 and 6 nevertheless had developed an interval form of CO poisoning. The relapse of symptoms in the interval form normally occurs after a lucid period ranging from a few days to several weeks [7, 27] and, as discussed below, the mechanisms may differ accordingly. Unfortunately, neither patient 3 nor patient 5 had an MRI and/or MRS prior to the relapse. Future studies are needed to determine whether MRS can predict some of the cases with the interval form of CO poisoning.

Effect of HBO treatment and clinical outcome

Despite repeated HBO treatment, three of our five patients with high-dose CO exposure developed new neurological deficits after a variable period of days and weeks, which is consistent with the interval form of CO poisoning in at least one of them. Up to half of all individuals with CO poisoning will develop chronic cognitive defects [6]. In our study, at least four of seven patients were left with various degrees of intellectual impairment. It is also possible that chronic low-dose CO exposure can lead to long-term neuropsychological disturbances, as seen in patient 2. The mechanisms by which acute high-dose or chronic low-dose CO exposure causes neurological sequelae are complex and cannot be explained by hypoxia alone [27]. The most sensitive regions to hypoxic injury are the cerebral cortex and hippocampus; yet with CO poisoning, the most pronounced changes on MRI are seen in WM and globus pallidus [16]. Thus, various other mechanisms have been proposed, including peroxidation of brain lipids [30], neuronal apoptosis [17], dysfunction of the mitochondrial respiratory chain [1] and autoimmune response to chemically modified myelin basic protein [27]. Since the duration of CO exposure is frequently unknown and oxygen administration in the ambulance increases CO elimination fivefold [8], COHb blood levels on admission do not always allow reliable estimation of the CO burden. Patients 3 and 6 serve as examples of this. The diagnosis of CO poisoning therefore depends mainly on the history of exposure and the clinical findings in the acute phase [7].

Conclusion

Although the results of our case series must be interpreted with caution due to the low patient number, some conclusions may be drawn. All patients with acute high-dose CO exposure had morphological changes that were visible in the WM and/or globus pallidus on the MR images. The WM hyperintensities were reversible in patients 5 and 7. Cortical occipital laminar necrosis was seen in patient 3 who was hypotensive at hospital admission. All patients with high-dose CO poisoning had abnormalities visible on the MRS scans, usually as decreased NAA/Cr and increased Cho/Cr in the WM but also often in the GM. In two of these patients, the MRS scans remained abnormal despite normalization of the MRI findings. No abnormalities were seen on the MRI and MRS scans of those patients with low-dose CO exposure, despite neuropsychological sequelae in one of them. Thus, whereas its role in chronic low-dose CO exposure appears uncertain, ^{1}H MRS provides the clinician with valuable information on patients with acute high-dose CO intoxication. Whether the early biochemical alterations that are evident on MRS scans of patients with high-dose CO poisoning predict long-term outcome must be addressed in further studies.

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