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Acute Brain Lesions on Magnetic Resonance Imaging and Delayed Neurological Sequelae in Carbon Monoxide Poisoning

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IMPORTANCE Preventing delayed neurological sequelae is a major goal of treating acute carbon monoxide poisoning, but to our knowledge there are no reliable tools for assessing the probability of these sequelae.

OBJECTIVES To determine whether acute brain lesions on diffusion-weighted imaging are related to subsequent development of delayed neurological sequelae after acute carbon monoxide poisoning.

DESIGN, SETTING, AND PARTICIPANTS This registry-based observational study was conducted at a university hospital in Seoul, Korea, between April 1, 2011, and December 31, 2015. Of 700 patients (aged ≥18 years) with acute carbon monoxide poisoning, 433 patients (61.9%) who underwent diffusion-weighted imaging at an emergency department were considered for the study. Patients who developed cardiac arrest before diffusion-weighted imaging (n = 3), had persistent neurological symptoms at discharge (n = 8), committed suicide soon after discharge (n = 1), and were lost to follow-up (n = 34) were excluded.

EXPOSURE The presence of unambiguous, high-signal-intensity, acute brain lesions on diffusion-weighted imaging (b = 1000 s/mm^2).

MAIN OUTCOMES AND MEASURES Development of delayed neurological sequelae defined as any neurological symptoms or signs that newly developed within 6 weeks of discharge.

RESULTS Of the 387 included patients (143 women [37.0%]; median age, 42.0 years [interquartile range, 32.0-56.0 years]), acute brain lesions on diffusion-weighted imaging were observed in 104 patients (26.9%). Among these, 77 patients (19.9%) had globus pallidus lesions, 13 (3.4%) had diffuse lesions, and 57 (14.7%) had focal lesions (37 patients [9.6%] had >1 pattern concurrently). Lesions were supratentorial and infratentorial in 101 and 23 patients, respectively. Delayed neurological sequelae occurred in 101 patients (26.1%). Multivariable logistic regression analysis indicated that the presence of acute brain lesions was independently associated with development of delayed neurological sequelae (adjusted odds ratio, 13.93; 95% CI, 7.16-27.11; P < .001). The sensitivity and specificity of acute brain lesions to assess the probability of delayed neurological sequelae were 75.2% (95% CI, 66.8%-83.7%) and 90.2% (95% CI, 86.8%-93.7%), respectively. In addition, the positive and negative predictive values were 73.1% (95% CI, 64.6%-81.6%) and 91.2% (95% CI, 87.9%-94.5%), respectively.

CONCLUSIONS AND RELEVANCE The presence of acute brain lesions was significantly associated with the development of delayed neurological sequelae. Diffusion-weighted imaging during the acute phase of carbon monoxide poisoning may therefore help identify patients at risk of developing these debilitating sequelae.

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Supplemental content

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Carbon monoxide (CO) poisoning, which causes hypoxic insults to the brain and other organs, is a leading cause of mortality and morbidity.[1-5] Neurological symptoms of CO poisoning can manifest not only immediately but also as late as 2 to 6 weeks after successful initial resuscitation as delayed neurological sequelae (DNS).[1,6] To date, no reliable methods of assessing the probability of DNS after acute CO poisoning have been developed.

Magnetic resonance imaging (MRI) has a pivotal role in assessing brain injury in CO poisoning. Previous studies on conventional MRI have shown that particularly vulnerable areas of the brain include the cerebral cortex, hippocampus, basal ganglia, and cerebellum and that lesions of the globus pallidus are typically seen in the chronic phase of CO poisoning.[7] However, little is known about these lesions during the acute phase of CO poisoning and how they may relate to subsequent findings. Diffusion-weighted imaging (DWI) is a sensitive modality that can elucidate acute lesions in various diseases of the brain.[8] Recent case series using DWI have indicated that it can also reveal acute brain lesions (ABLs) in CO poisoning; however, the prevalence and characteristics of these lesions are largely unknown.[9-11] Documenting acute lesions that can potentially indicate the subsequent development of DNS could give clinicians and researchers useful information for understanding the pathophysiology of DNS and targeting prevention. We aimed to investigate the prevalence and radiological characteristics of ABLs on DWI (which we termed *ABLDs*) and to determine whether the presence of ABLDs is related to the development of DNS in patients after acute CO poisoning.

Key Points

Question Can diffusion-weighted imaging detect acute brain lesions and assess the probability of delayed neurological sequelae after carbon monoxide poisoning?

Findings In this observational study of 387 patients with acute carbon monoxide poisoning, brain lesions on diffusion-weighted imaging were observed in 104 patients (26.9%) and delayed neurological sequelae occurred in 101 patients (26.1%). The presence of acute brain lesions was independently associated with the development of delayed neurological sequelae.

Meaning Diffusion-weighted imaging may be useful for identifying acute brain lesions in patients with acute carbon monoxide poisoning and patients at risk of developing delayed neurological sequelae.

Methods

Study Design and Population

This registry-based observational study was performed at Asan Medical Center, Seoul, Korea. Data were prospectively collected for all adult patients (aged ≥18 years) who presented to the emergency department (ED) with acute CO poisoning. In this study, we included consecutive patients who were admitted and underwent brain DWI. Patients were excluded if cardiac arrest developed before MRI, neurological deficits persisted at discharge from the ED, and information about DNS was not obtained. Patients presenting with neurological symptoms that resolved at discharge were not excluded. According to our management protocol, brain MRI was considered for all patients with acute CO poisoning. However, MRI was not performed when patients or their proxy did not consent or when a medical condition contraindicated an MRI scan. Patients were scheduled for MRI scans within hours of visiting the ED. The MRI scans were sometimes performed after hyperbaric oxygen therapy if this was critical to care or the MRI scanner was unavailable. This study was approved by the institutional review board of Asan Medical Center, and the need for written informed consent was waived because of the retrospective nature of this study.

Clinical and Laboratory Assessments

At the time of the ED visit, we collected the following data in our registry: demographic data, risk factors or medical comorbidities, level of consciousness at arrival (alert, voice, pain, unresponsive [AVPU] scale),[12] vital signs, and laboratory results. We also prospectively collected information about seizures, the presence of neurological symptoms and signs at discharge, survival status, and the development of DNS after discharge. Delayed neurological sequelae were defined as any neurological symptom or sign that newly developed within 6 weeks of discharge from the ED; these could include motor deficits, cognitive decline, dysphagia, dysarthria, dyspraxia, parkinsonism, seizures, psychosis, and mood disorders.[13,14] We evaluated DNS as follows. First, neurology consultations were routinely requested for the assessment of neurological signs before discharge. Second, patients were informed of DNS symptoms and our contact information. Third, patients were invited to regular follow-up visits in the neurology clinic after discharge. Fourth, we performed a telephone interview with either the patient or a surrogate using a structured questionnaire to evaluate DNS.[14] Fifth, neurologists evaluated DNS, but objective tools for documenting DNS were not used as dedicated tools to specify DNS were not available.

Medical Management

Every patient received 100% oxygen by facial mask or mechanical ventilator following endotracheal intubation. Hyperbaric oxygen therapy was delivered if patients manifested signs of serious poisoning (eg, unconsciousness, neurological signs, cardiovascular dysfunction, or severe acidosis) or had a carboxyhemoglobin level of 25% or higher (to convert carboxyhemoglobin to proportion of 1.0, multiply by 0.01). Hyperbaric oxygen therapy was applied in a monoplace chamber. The target pressure was 2.5 standard atmospheres and the total duration of hyperbaric oxygen therapy was 90 min/session.

Imaging Analysis

The MRI examination was performed with a 1.5-T MRI unit (Avanto; Siemens Healthcare) using a standard head coil. The MRI protocol consisted of DWI with or without fluid-attenuated inversion recovery imaging (FLAIR). The DWI parameters were as follows: repetition time, 6900 milliseconds; echo time, 87 milliseconds; matrix number, 192 × 192; field of

view, 250 mm; 2 *b* values of 0 and 1000 s/mm^2; slice thickness, 3 mm; and interslice gap, 3 mm. The FLAIR was obtained using a fast-spin echo sequence with a repetition time of 9000 milliseconds, an echo time of 100 milliseconds, an inversion time of 2500 milliseconds, and a matrix of 256 × 190.

The ABLDs were defined as unambiguous bright signal intensities on DWI (*b* = 1000 seconds/mm^2). Hyperintense lesions on DWI due to T2 shine-through effects from chronic lesions were not regarded as ABLDs. Equivocal signal changes and incidental findings related to underlying conditions, such as old infarction, leukoaraiosis, hydrocephalus, diffuse atrophy, encephalomalacia, arterial venous malformation, and chronic subdural hematoma, were also excluded. Because the size, shape, and distribution of ABLs varied, we categorized ABLDs into 3 patterns: globus pallidus lesions (GPLs) for lesions in the globus pallidus, diffuse lesions (DLs) for diffuse symmetric lesions, and focal lesions (FLs) for asymmetric focal lesions. We included GPLs with DLs and FLs because, although it is uncertain whether GPLs are caused by global hypoxia-ischemia or focal hypoxia-ischemia, they are a well-known characteristic of CO poisoning.[7,11] Focal lesions were further categorized into punctate (<10 mm in diameter), patchy (≥10 mm in diameter and not vascular), and territorial (≥10 mm in diameter and located in a specific vascular territory) lesions. The presence of ABLDs was also documented by location (cortex, white matter, deep nucleus, brainstem, and cerebellum) and region (frontal, parietal, temporal, occipital, insular, hippocampus, corpus callosum, splenium, internal capsule, centrum semiovale, periventricular white matter, globus pallidus, putamen, caudate, thalamus, midbrain, pons, medulla, and cerebellum). The signal intensities on apparent diffusion coefficient maps corresponding to each ABLD were classified into low-intensity signals and iso intense or high-intensity signals.

The severity of leukoaraiosis, assessed by FLAIR and DWI (*b* = 0 s/mm^2), was rated as none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3) using a visual rating scale for periventricular white matter and deep white matter.[15] A score of 2 or higher in either white matter was considered to indicate moderate-to-severe leukoaraiosis.[16]

All DWI and FLAIR sequences were interpreted jointly by 2 investigators (S.B.J. and C.W.S.) who were blinded to clinical data and outcomes. A third investigator (D.W.K.) was consulted in cases of disagreement.

Data Analysis

Data are presented as medians with interquartile ranges for continuous variables and as absolute numbers or relative frequencies for categorical variables. We compared each variable according to the presence of ABLDs and DNS. Pearson χ^2 test or Fisher exact test was used for categorical variables, and *t* test was used for continuous variables, as appropriate. Variables with a *P* value of <.20 by univariate analysis were included as candidate variables in the multivariable logistic regression model and removed by backward stepwise selection. We further performed all analysis using a forward selection procedure to confirm the final model. Adjusted odds ratios (ORs) with 95% confidence intervals were also calculated. A 2-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS, version 21 (IBM).

Results

In total, 700 patients with acute CO poisoning visited our ED. Of these, 313 were excluded for the following reasons: 267 did not undergo MRI, 3 developed cardiac arrest before their MRI scans, 8 had neurological deficits before discharge, 1 patient with intentional CO poisoning committed suicide after discharge, and 34 were lost to follow-up. Thus, 387 remaining patients were included (eFigure 1 in the Supplement).

Baseline characteristics, including demographic data, risk factors, clinical and laboratory findings at presentation, and the presence of ABLDs in patients included and excluded due to loss to follow-up, are shown in eTable 1 in the Supplement. Baseline characteristics of the final sample of 387 patients and the 313 excluded patients are presented in eTable 2 in the Supplement.

Of the patients who were included in the final sample, 244 (63.0%) were men, and the median (interquartile range) age was 42.0 (32.0-56.0) years. The median (interquartile range) time from the end of CO exposure to visiting the ED was 2.8 (1.6-4.4) hours. At presentation, 257 (66.4%) of the final sample had an altered mental status, but none of them had neurological deficits at discharge (**Table 1**).

Acute Brain Lesions on MRI

We observed ABLDs in 104 patients (26.9%) (**Figure** and eFigures 2 and 3 in the Supplement). The pattern, location, and region of ABLDs among the 104 patients are described in **Table 2**. Globus pallidus lesion was the most common pattern (GPL, 77 [19.9%]; DL, 13 [3.4%]; and FL, 57 [14.7%]), but 37 (35.6%) had multiple lesions: GPL + DL + FL patterns were observed in 6 patients; GPL + DL was observed in 3 patients; GPL + FL was observed in 26 patients; and DL + FL was observed in 2 patients. Thus, pure GPLs, pure DLs, and pure FLs were observed in 42, 2, and 23 patients, respectively. Focal lesions were seen in 57 patients (14.7%) (territorial lesion, 5 [1.3%]; patchy lesion, 38 [9.8%]; and punctate lesion, 50 [12.9%]), and distribution of FLs was intermixed in 35 patients: 1 had territorial, punctate, and patchy lesions; 1 had territorial and punctate lesions; 2 had territorial and patchy lesions; and 31 had patchy and punctate lesions. Thus, pure FLs were seen in 22 patients (pure territorial lesion, 1; pure patchy lesion, 4; and pure punctate lesion, 17).

Magnetic resonance angiography was additionally performed in 4 out 5 patients with territorial lesions, which revealed steno-occlusive lesions in the index arteries of all lesions. The ABLDs were supratentorial in 101 patients and infratentorial in 23, and as shown in Table 2, the most common region was the globus pallidus. Other commonly affected regions were the frontal, cerebellar, parietal, occipital, putamen, and temporal regions.

All 387 study patients underwent DWI, with FLAIR performed in an additional 350 patients. Among the 104 patients with ABLDs, 93 underwent both DWI and FLAIR. The ABLD signals were more prominent on DWI than on FLAIR in 48 patients (51.6%), more prominent on FLAIR than on DWI in 1 patient (1.1%), and comparable on both DWI and FLAIR in 44 patients (47.3%). Apparent diffusion coefficient signals were low in 94 patients (90.4%) and iso intense or high in 10 patients (9.6%).

Table 1. Baseline Characteristics

Characteristic	All Patients, No. (%) (N = 387)
Demographic	
Age, median (IQR), y	42.0 (32.0-56.0)
Male	244 (63.0)
Vascular risk factors	
Hypertension	75 (19.4)
Diabetes	45 (11.6)
Hypercholesterolemia	12 (3.1)
Cardiac disease	11 (2.8)
Smoking	164 (42.4)
Clinical findings and vital signs at presentation	
Mental status	
Alert	130 (33.6)
Response to voice	133 (34.4)
Response to pain	101 (26.1)
Unresponsive state	23 (5.9)
Seizure	7 (1.8)
Blood pressure, median (IQR), mm Hg	
Systolic	120 (108-135)
Diastolic	76 (65-87)
Body temperature, median (IQR), °C	36.5 (36.0-36.9)
Laboratory findings at presentation, median (IQR)	
Arterial oxygen saturation, %	100 (99-100)
Carboxyhemoglobin, %	32.5 (20.6-43.0)
Hemoglobin, g/dL	14.6 (13.0-15.8)
Lactate, mg/dL	18.9 (10.8-36.9)
White blood cell, $\times 10^3/\mu L$	11 900 (8400-16 500)
C-reactive protein, mg/dL	1.2 (1.0-4.7)
Time intervals	
Duration of exposure, median (IQR), h	3.8 (2.0-9.5)
From end of exposure to MRI scan, median (IQR), h	9.2 (5.1-20.8)
Hyperbaric oxygen therapy before MRI scan	137 (35.4)
MRI findings	
ABLD	104 (26.9)
Previous stroke lesion	35 (9.0)
Fazekas scale score, periventricular white matter	
0	249 (64.3)
1	87 (22.5)
2	39 (10.1)
3	12 (3.1)
Fazekas scale score, deep white matter	
0	236 (61.0)
1	116 (30.0)
2	18 (4.7)
3	17 (4.4)
Moderate-to-severe leukoaraiosis	57 (14.7)

Abbreviations: ABLD, acute brain lesion on diffusion-weighted imaging; IQR, interquartile range; MRI, magnetic resonance imaging.

SI conversion factors: To convert carboxyhemoglobin to proportion of 1.0, multiply by 0.01; hemoglobin to g/L, multiply by 10.1; lactate to mmol/L, multipy by 0.111; white blood cell to $\times 10^9$/L, multiply by 0.001; CRP to nmol/L, multiply by 9.524.

Delayed Neurological Sequelae

Delayed neurological sequelae occurred in 101 patients (26.1%). Symptoms and signs of DNS in our sample are described in eTable 3 in the Supplement. The pattern, region, and location of ABLDs were not different between patients who developed DNS and those who did not (Table 2). The following factors were associated with DNS: older age (odds ratio [OR] 1.02; 95% CI, 1.01-1.04; $P = .002$), hypertension (OR, 2.44; 95% CI, 1.43-4.14; $P = .001$), altered mental status (OR, 5.21; 95% CI, 2.73-9.95; $P < .001$), lower carboxyhemoglobin level (OR, 0.98; 95% CI, 0.96-0.99; $P = .005$), increased lactate level (OR, 1.10; 95% CI, 1.03-1.18; $P = .005$), leukocyte count (OR, 1.09; 95% CI, 1.05-1.13; $P < .001$), C-reactive protein level (OR, 1.42; 95% CI, 1.24-1.62; $P < .001$), duration of CO exposure (OR, 1.24; 95% CI, 1.18-1.31; $P < .001$), previous stroke lesion (OR, 2.65; 95% CI, 1.30-5.37; $P = .007$), moderate-to-severe leukoaraiosis (OR, 2.85; 95% CI, 1.59-5.10; $P < .001$), and the presence of ABLDs (OR, 28.01; 95% CI, 15.42-50.88; $P < .001$) (**Table 3** and eTable 4 in the Supplement).

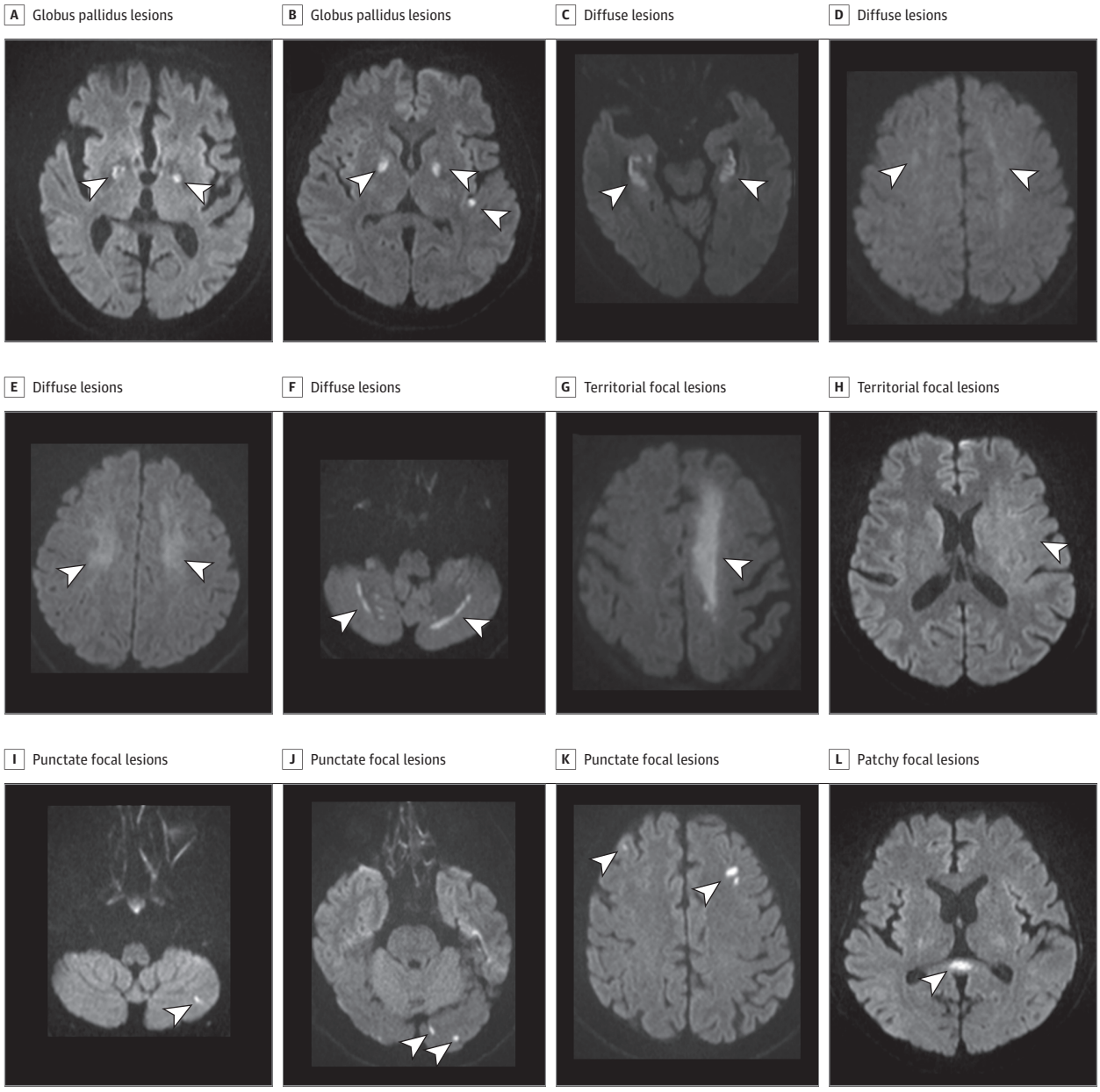
Multivariable analysis confirmed that altered mental status (OR, 2.10; 95% CI, 0.96-4.62; $P = .064$), longer duration of CO exposure (OR, 1.13; 95% CI, 1.07-1.20; $P < .001$), and the presence of ABLDs (OR, 13.93; 95% CI, 7.16-27.11; $P < .001$) were independently associated with the development of DNS. The sensitivity and specificity of the presence of ABLDs when assessing the probability of DNS were 75.2% (95% CI, 66.8%-83.7%) and 90.2% (95% CI, 86.8%-93.7%), respectively. In addition, the positive and negative predictive values were 73.1% (95% CI, 64.6%-81.6%) and 91.2% (95% CI, 87.9%-94.5%), respectively (eTable 5 and eTable 6 in the Supplement).

Discussion

In this registry-based study, we showed that 104 patients (26.9%) with acute CO poisoning developed ABLDs and that these appeared most commonly as GPLs followed by FLs and DLs, although 2 or more patterns coexisted in 37 patients (36%). In agreement with previous studies, DNS occurred in 26.1% of our patients.[14,17] Importantly, we showed that the presence of ABLDs during the acute phase of CO poisoning was significantly associated with a 14-fold higher risk of developing DNS in the future compared with those who did not have ABLDs. The sensitivity and positive predictive value of ABLDs to assess the probability of DNS was approximately 75%, and the specificity and negative predictive value were approximately 90%. Therefore, we concluded that DWI is a useful modality for detecting ABLs and assessing the probability of DNS in patients with CO poisoning.

The most common location of ABLDs in our cohort was the globus pallidus (19.9%). This result is broadly consistent with those of previous studies that used conventional imaging modalities.[6,18] However, our study revealed that ABLDs were variable in size, shape, and distribution and that 14.7% of patients with acute CO poisoning had FLs, including small punctate lesions, patchy lesions, and territorial lesions. Diffuse symmetric lesions exposing vulnerable regions (eg, the hippocampus) to hypoxia were seen in 13 patients (3.4%). Moreover, most ABLDs were supratentorial or cerebellar, whereas

Figure. Examples of Acute Brain Lesions on Diffusion-Weighted Imaging



Lesion distributions are variable but can be categorized into 3 patterns: globus pallidus (A and B), diffuse (C-F), and focal (G-L) lesions. Focal lesions can be further categorized into 3 types: territorial (G and H), punctate (I-K), and patchy (L) lesions. Two different patterns coexist in (B): both globus pallidus and focal punctate lesions. Arrowheads indicate acute brain lesions on diffusion-weighted imaging.

the brainstem and thalamus were only rarely involved in our population. The ABLDs in the splenium were present in 5 patients. Thus, ABLDs were prevalent in patients after acute CO poisoning, and the distributions of these ABLDs were diverse. Cellular mechanisms underlying the formation of ABLDs are unknown, but some hypotheses may be suggested based on our findings.[1,19] We propose 4 main possibilities.

First, it seems plausible that global hypoxia has a primary role. Indeed, the DL pattern was mostly distributed to the hippocampus, globus pallidus, cerebral cortex, and cerebellar folia, which are typically vulnerable to hypoxia.[20] The ABLDs with a DL pattern may therefore be caused by hypoxia. The association between arterial lactate levels and the presence of ABLDs in our patients supports this hypothesis because CO-bound hemoglobin will have inhibited the oxygen supply to neurons and lactate will have served as a surrogate of the resulting anaerobic metabolism.[19]

Second, it is also plausible that focal ischemic insults have important roles in the development of ABLDs. Small punctate lesions, especially when they are multiple in number and present in vascular territories, may represent embolic infarcts related to CO-induced cardiac dysfunction. This is because CO can cause

Table 2. Lesion Distribution According to the Development of DNS in Patients With Acute Brain Lesion on Diffusion-Weighted Imaging

Lesion Distribution	No. (%) Total (n = 104)	DNS Absent (n = 28)	DNS Present (n = 76)	*P* Value
Pattern				
Globus pallidus lesion pattern	77 (19.9)	22 (78.6)	55 (72.4)	.52
Diffuse lesion pattern	13 (3.4)	2 (7.1)	11 (14.5)	.51
Focal lesion pattern	57 (14.7)	15 (53.6)	42 (55.3)	>.99
Territorial lesion	5 (1.3)	0 (0)	5 (6.6)	.32
Patchy lesion	38 (9.8)	9 (32.1)	29 (38.2)	.65
Punctate lesion	50 (12.9)	14 (50.0)	36 (47.4)	.83
Region				
Frontal	24 (6.2)	5 (17.9)	19 (25.0)	.60
Parietal	18 (4.7)	4 (14.3)	14 (18.4)	.77
Temporal	11 (2.8)	1 (3.6)	10 (13.2)	.28
Occipital	14 (3.6)	2 (7.1)	12 (15.8)	.34
Insular	3 (0.8)	0 (0)	3 (3.9)	.56
Hippocampus	6 (1.6)	1 (3.6)	5 (6.6)	.68
Corpus callosum	1 (0.3)	0 (0)	1 (1.3)	>.99
Splenium	5 (1.3)	1 (3.6)	4 (5.3)	>.99
Internal capsule	7 (1.8)	2 (7.1)	5 (6.6)	>.99
Centrum semiovale	8 (2.1)	1 (3.6)	7 (9.2)	.44
Periventricular white matter	8 (2.1)	1 (3.6)	7 (9.2)	.44
Globus pallidus	77 (19.9)	22 (78.6)	55 (72.4)	.52
Putamen	13 (3.4)	4 (14.3)	9 (11.8)	>.99
Caudate	3 (0.8)	1 (3.6)	2 (2.6)	>.99
Thalamus	1 (0.3)	0 (0)	1 (1.3)	>.99
Midbrain	2 (0.5)	0 (0)	2 (2.6)	.60
Pons	0 (0)	0 (0)	0 (0)	
Medulla	0 (0)	0 (0)	0 (0)	
Cerebellum	21 (5.4)	4 (14.3)	17 (22.4)	.42
Location				
Cortex	36 (9.3)	9 (32.1)	27 (35.5)	.82
White matter	26 (6.7)	6 (21.4)	20 (26.3)	.80
Deep nucleus	83 (21.4)	23 (82.1)	60 (78.9)	.79
Brainstem	2 (0.5)	0 (0)	2 (2.6)	.60
Cerebellum	21 (5.4)	4 (14.3)	17 (22.4)	.42

Abbreviation: DNS, delayed neurological sequelae.

myocardial injury through non-hemoglobin-mediated impairment of oxidative phosphorylation at a mitochondrial level.[21,22] In addition, underlying stenotic lesions were observed in 4 patients with territorial lesions in index arteries, and platelet aggregations, hypercoagulable states, altered fibrinolytic pathways, and endothelial dysfunctions may have contributed to thrombus formation after CO poisoning.[23]

Third, cytotoxic edema, whether originating from hypoxia or ischemia, appeared to contribute to the development of ABLDs. In 90% of patients with ABLDs, the apparent diffusion coefficient map showed low signal intensities that suggested that cytotoxic edema rather than vasogenic edema underpinned the mechanism of ABLD formation.[8]

Fourth, a common pathologic process may coexist between ABLDs and DNS. The presence of ABLDs was an independent predictor of DNS in our study, and oxidative stress may have been behind this process. Reactive oxygen species caused and the interaction between CO-bound platelets and neutrophils can result in apoptosis and lipid peroxidation.[1] Furthermore, alterations in factors such as brain metabolism, the permeability of the blood-brain barrier, and the release of inflammatory cytokines may accelerate the development of DNS when triggered by ABLDs.[24,25] However, further studies are needed to understand the complex mechanisms underlying the formation of ABLDs and to confirm the link between ABLDs and DNS.

The results of our study may have important clinical implications. Previous studies have shown that DNS can develop in up to 45% of patients after acute CO poisoning.[13,26,27] Thus, special attention should be paid to patients with acute CO poisoning, even when they do not show neurological deficits at the time of presentation or discharge. Although this high rate has necessitated that screening be used for patients with a high risk of DNS, previous studies have failed to define meaningful screening measures for assessing the probability of DNS. For example, decreased consciousness levels, abnormal levels of key blood parameters (eg, carboxyhemoglobin, S100B, leukocytes, and copeptin), abnormal findings on electroencephalography, and abnormal imaging results (eg, on diffu-

Table 3. Factors Associated With the Development of DNS

Characteristics	Univariable Analysis		Multivariable Analysis	
	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Demographic				
Age, y	1.02 (1.01-1.04)	.002		
Male	1.08 (0.67-1.73)	.75		
Vascular risk factors				
Hypertension	2.44 (1.43-4.14)	.001		
Diabetes	1.67 (0.86-3.22)	.13		
Hypercholesterolemia	0.56 (0.12-2.59)	.46		
Cardiac disease	2.43 (0.73-8.15)	.15		
Smoking	1.33 (0.84-2.10)	.22		
Clinical findings and vital signs at presentation				
Altered mental status	5.21 (2.73-9.95)	<.001	2.10 (0.96-4.62)	.06
Seizure	1.14 (0.22-5.95)	.88		
Systolic blood pressure, mm Hg	1.00 (0.99-1.01)	.98		
Diastolic blood pressure, mm Hg	1.01 (1.00-1.03)	.07		
Body temperature, °C	1.59 (1.14-2.22)	.01		
Laboratory findings at presentation				
Arterial oxygen saturation, %	1.01 (0.94-1.08)	.80		
Carboxyhemoglobin, %	0.98 (0.96-0.99)	.005		
Hemoglobin, g/dL	1.06 (0.95-1.18)	.33		
Lactate, mmol/L	1.10 (1.03-1.18)	.005		
White blood cell, ×1000/μL	1.09 (1.05-1.13)	<.001		
C-reactive protein, mg/dL	1.42 (1.24-1.62)	<.001		
Time intervals				
Duration of exposure, h	1.24 (1.18-1.31)	<.001	1.13 (1.07-1.20)	<.001
From exposure to visiting ED, h	1.01 (0.97-1.05)	.71		
Hyperbaric oxygen therapy	0.85 (0.38-1.92)	.70		
MRI findings				
ABLD	28.01 (15.42-50.88)	<.001	13.93 (7.16-27.11)	<.001
Previous stroke lesion	2.65 (1.30-5.37)	.007		
Moderate-to-severe leukoaraiosis	2.85 (1.59-5.10)	<.001		

Abbreviations: ABLD, acute brain lesion on diffusion-weighted imaging; DNS, delayed neurological sequelae; ED, emergency department; MRI, magnetic resonance imaging; OR, odds ratio.

SI conversion factors: To convert carboxyhemoglobin to proportion of 1.0, multiply by 0.01; hemoglobin to g/L, multiply by 10.1; lactate to mmol/L, multipy by 0.111; white blood cell to $\times 10^9$/L, multiply by 0.001; CRP to nmol/L, multiply by 9.524.

sion tensor imaging, single-photon emission computed tomography, and computed tomography scanning) have all failed to reliably indicate the probability of DNS.[14,28-34] By contrast, we demonstrate that DWI may be a good screening tool for patients at high risk of DNS, with the presence of ABLDs being associated with DNS with high sensitivity (75.2%), high specificity (90.2%), a high positive predictive value (73.1%), and a high negative predictive value (91.2%). Based on these results, further prospective studies should be performed to validate our findings and investigate whether ABLDs may be suitable for use when deciding whether to apply preventive therapies, such as hyperbaric oxygen therapy.[35]

Limitations

Despite our findings, this study has some limitations. First, the retrospective nature of the study increases the potential risk for selection bias. The presence or absence of DNS was evaluated in person in a subset of the cohort and over the telephone in the remainder. This would further introduce reporting bias. However, a sensitivity analysis including only patients who underwent objective neurological assessments at follow-up complies with our results (eTable 6 in the Supplement). Second, this was a single-center study, which limits the generalizability of our findings. Countering this limitation is the fact that, to our knowledge, this is the largest imaging study to have been based on prospectively collected registry data of patients with CO poisoning. Third, small lesions could be missed, because our imaging protocol for DWI had 3 mm of interslice gap. This could negatively affect the detection of ABLDs. Fourth, because we did not routinely perform echocardiography or angiography, we cannot confirm whether FLs on DWI were caused by embolic disease or underlying atherosclerosis. However, regardless of the nature of such lesions, this study did show that ABLDs were prevalent in patients with acute CO poisoning and that the presence of ABLDs was significantly associated with the development of DNS.

Conclusions

The presence of ABLs was significantly associated with the development of DNS. Diffusion-weighted imaging during the acute phase of CO poisoning may therefore help identify patients at risk of developing these debilitating sequelae. Further studies are needed to validate our findings.

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