Predictive Values of Serum Biochemical Markers and Apparent Diffusion Coefficient on Delayed Encephalopathy After Acute Carbon Monoxide Poisoning

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ABSTRACT

AIM: To explore the predictive values of serum biochemical markers and apparent diffusion coefficient (ADC) on delayed encephalopathy after acute carbon monoxide poisoning (DEACMP).

MATERIAL and METHODS: Seventy-nine patients were divided into two groups based on the onset of DEACMP 60 days after with acute carbon monoxide poisoning. The baseline data of ACMP patients were collected. Serum levels of cardiac troponin I (cTNI), lactic acid (Lac), carboxyhemoglobin (COHb), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), C-reactive protein (CRP), and neuron-specific enolase (NSE) were measured within 24 hours of ACMP onset. The ADC of globus pallidum, centrum semiovale, and periventricular white matter were recorded by diffusion-weighted magnetic resonance imaging (DW-MRI) within 48 hours of admission. Logistic regression analysis was performed to determine the risk factors for DEACMP.

RESULTS: The incidence of coma and duration of poisoning in the DEACMP group were significantly higher than those in the non-DEACMP group. The levels of Lac, CK, CK-MB, LDH, CRP and NSE in the DEACMP group were higher than those in the non-DEACMP group. The ADC value of globus pallidus in the DEACMP group was significantly higher than that in non-DEACMP group. The duration of poisoning, coma degree, CK, LDH, NES, and CRP were closely associated with the occurrence of DEACMP.

CONCLUSION: The duration of poisoning, coma degree, and serum levels of CK, LDH, CRP, and NSE were independent risk factors for DEACMP.

KEYWORDS: Carbon monoxide poisoning, Coma, Creatine kinase, Neuron-specific enolase, Magnetic resonance imaging

ABBREVIATIONS: ADC: Apparent diffusion coefficient, cTNI: Cardiac troponin I, Lac: Lactic acid, COHb: Carboxyhemoglobin, CK: Creatine kinase, CK-MB: Creatine kinase isoenzyme, LDH: Lactate dehydrogenase, CRP: C-reactive protein, NSE: Neuron-specific enolase

■ INTRODUCTION

Acute carbon monoxide poisoning (ACMP) is the most common type of fatal air poisoning, causing dysfunction of the cardiovascular and central nervous system (26). Delayed encephalopathy after ACMP (DEACMP) is one of its most serious complications (11). DEACMP is characterized by a series of neuropsychiatric symptoms such as extrapyramidal symptoms, dementia, and mental disorders (9,33). Patients with DEACMP have varying degrees of hypoxia and nerve cell damage (35). Sex, age, and degree of intoxication are significantly different among patients with DEACMP (47), thereby warranting efforts to explore new diagnostic methods for DEACMP.

Numerous studies have investigated the relationship between the values of serum biochemical factors and the incidence of late-onset disorder after ACMP. Wang et al. have reported that blood lactic acid (Lac) clearance rate in ACMP patients is negatively related to the incidence of DEACMP (39). Zhang et al. have found that the serum levels of creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH) are markedly increased in patients with ACMP (46). Cha et al. have shown that serum neuron-specific enolase (NSE) serves as an early predictor of delayed neuropsychiatric sequelae (DNS) in patients with ACMP (5). The diagnostic roles of these serum biochemical indexes, including Lac, CK-MB, LDH, and NSE on DEACMP need to be further investigated.

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a noninvasive medical diagnostic technique that provides high-quality three-dimensional or cross-sectional images of tissues or organs (8). The apparent diffusion coefficient (ADC) value determined by DW-MRI has been used for the diagnosis of ACMP complications. For instance, the ADC value measured by early DW-MRI has a predictive value for DNS in patients with ACMP (30). The ADC value of globus pallidus reflects the degree of brain injury in DEACMP patients on a microscopic scale (12). The diagnostic potential of DW-MRI for DEACMP needs to be further investigated.

In this study, we explored the predictive value of serum biochemical markers and ADC on DEACMP. Our research may discover promising biomarkers in the diagnosis of DEACMP.

■ MATERIAL and METHODS

Patients

A total of 79 ACMP patients were admitted at Zibo Municipal Hospital from June 2015 to March 2018. Based on DEACMP onset after 60 days, patients were divided into the DEACMP group and non-DEACMP group. The diagnostic criteria for DEACMP were in line with WHO recommendations. The clinical data of the ACMP patients were retrospectively analyzed, including their ages, genders, and whether they smoke and/or drink, previous coma cases, duration of poisoning, and the presence of other comorbidities such as hypertension, coronary heart disease, and diabetes. Informed consent was obtained from all patients before collection of samples. This study was approved by the Ethics Committee

of Zibo Municipal Hospital in accordance with the Declaration of Helsinki.

Serum Biochemical Indexes

Blood samples from the vein were taken from the patients within 24 hours of DEACMP onset. White blood cell (WBC) count was measured using an automatic blood cell analyzer (Sysmex, Kobe, Japan). The serum was separated by centrifugation at 2500 g for 15 min. The serum level of COHb was measured using a pulse co-oximeter (Masimo Rad-7, Masimo, Irvine, CA, USA), cTnI using a chemiluminescent immunoassay on Access 2 analyzer (Beckman Counter, Brea, California, USA), Lac using a Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany), CK by a colorimetric method using a creatine kinase activity assay kit (Abcam, Cambridge, MA, USA), CKMB isoenzyme using a Beckman CX3 automatic biochemistry analyzer (Hitachi, Tokyo, Japan), LDH using an AU 2700 automatic biochemistry analyzer (Olympus, Tokyo, Japan), NSE using a solid-phase immunoassay with double monoclonal antibodies with an Elecsys 2010 (Roche Diagnostics GmbH, Germany), and CRP using a turbidity method based on latex agglutination on a CRP-Latex (II) X2 reagent Hitachi 7020 analyzer (Hitachi, Tokyo, Japan).

Brain DW-MRI Techniques

A GE Signa HDxT 1.5T (MRI) (GE, Milwaukee, WI, USA) was used to examine craniocerebral MRI scans within 48 hours after onset of DEACMP. The radiographs were analyzed using an ADW4.4 workstation, and the apparent diffusion coefficient (ADC) values of the globus pallidus, centrum semiovale, and periventricular white matter were determined.

Statistical Analysis

Statistical analysis was performed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Measurement data were presented as means $\pm$ standard deviations (SD) and assessed using a Student's t-test. Enumeration data were presented as numbers (N) and assessed using a χ^2 test. Logistic regression analysis was performed to identify the independent risk factors for DEACMP. A p value < 0.05 was considered statistically significant.

■ RESULTS

Coma Cases and Duration of Poisoning were Increased in Patients with DEACMP

The coma cases and duration of poisoning in the DEACMP group were significantly higher than those in the non-DEACMP group ($p < 0.01$). Additionally, there was no significant difference based on sex, age, history of smoking and/or alcoholism, and the presence of comorbidities such as hypertension, coronary heart disease, and diabetes between the two groups ($p > 0.05$) (Table I).

Analysis of Serum Biochemical Values in DEACMP

Serum levels of COHb, Lac, cTnI, CK, CK-MB, LDH, NSE, CRP, and WBC counts were detected. The results showed

that serum levels of Lac, CK, CK-MB, LDH, CRP, and NSE were significantly higher in the DEACMP group than those in the non-DEACMP group ($p<0.01$). However, there was no difference in the serum levels of COHb and cTnI as well as WBC counts between the two groups ($p>0.05$) (Table II).

ADC Values of Different Brain Tissues in DEACMP

The ADC values of the globus pallidum, centrum semiovale, and periventricular white matter were determined by DW-MRI. The results found the ADC value of globus pallidum in the

DEACMP group to be lower than that in the non-DEACMP group ($p<0.01$). However, there was no statistical difference between these two groups in terms of ADC values of the centrum semiovale and periventricular white matter ($p>0.05$) (Table III).

Logistic Regression Analysis of Risk Factors for DEACMP

Logistic regression analysis showed that there was a significant correlation between DEACMP and the duration of poisoning ($p<0.05$), coma degree ($p<0.05$), CK ($p<0.001$), LDH ($p<0.05$),

Table I: Baseline Data for DEACMP and no-DEACMP Groups

Items	DEACMP group (n=34)	no-DEACMP group (n=45)	p
Gender (male/female)	21/13	26/19	0.721
Age (years old)	57.34 ± 17.34	52.43 ± 15.42	0.195
Smoke	14	24	0.284
Drink alcohol	16	24	0.581
Hypertension	15	25	0.314
Coronary heart disease	12	20	0.412
Diabetes	13	21	0.454
Coma	27 ^{***}	18	<0.001
Duration of poisoning (hour)	22.54 ± 10.25 ^{***}	13.41 ± 16.78	0.006

^{***} $p<0.01$ vs. no-DEACMP group.

Table II: Biochemical Values Between DEACMP and no-DEACMP Groups

Biochemical values	DEACMP group	No-DEACMP group	p	F value
COHb (%)	21.24 ± 18.11	24.01 ± 13.89	0.444	0.588
cTnI (mg/L)	1.62 ± 3.33	0.48 ± 1.76	0.053	0.279
WBC (/μL)	14287.23 ± 3786.46	13784.24 ± 8946.13	0.759	5.582
Lac (U/L)	6.11 ± 2.54 [*]	5.08 ± 1.63	0.032	0.412
CK (IU/L)	4231.18 ± 5346.17 ^{***}	721.34 ± 2332.14	0.0002	0.190
CK-MB (IU/L)	51.32 ± 33.12 [*]	36.72 ± 23.24	0.024	0.492
LDH (U/L)	384.67 ± 276.45 ^{***}	231.22 ± 108.64	0.001	0.154
CRP (mg/L)	30.34 ± 36.28 ^{***}	4.12 ± 2.57	<0.0001	0.005
NSE (U/mL)	18.73 ± 5.46 ^{***}	11.98 ± 4.16	<0.0001	0.580

^{*} $p<0.05$, ^{***} $p<0.01$ vs. no-DEACMP group.

Table III: ADC Values of Different Brain Tissues Between DEACMP and no-DEACMP Groups

Position (×10 ⁻³ mm ² /s)	DEACMP group	No-DEACMP group	p	F value
Globus pallidum	0.52 ± 0.07 ^{***}	0.76 ± 0.04	<0.0001	0.327
Semi-soft circle	0.67 ± 0.07	0.71 ± 0.16	0.177	5.224
Periventricular white matter	0.70 ± 0.06	0.72 ± 0.05	0.110	0.694

^{***} $p<0.01$ vs. no-DEACMP group.

Table IV: Logistic Regression Analysis of DEACMP Related Risk Factors

Items	β	SE	Wald	P value	Exp (β)
Coma degree	-0.096	0.057	0.624	0.008	0.872
Duration of poisoning	0.014	0.008	5.624	0.019	1.048
Lac	-0.412	0.204	3.683	0.056	0.672
NSE	-0.654	0.326	5.118	0.027	0.514
CK	0.064	0.026	12.859	< 0.0001	1.069
CK-MB	0.285	0.231	1.695	0.181	1.302
CRP	-0.145	0.057	9.215	0.002	0.826
LDH	1.313	0.564	4.625	0.026	3.326
ADC value of Globus pallidum	0.354	0.386	0.849	0.361	1.462

NES ($p < 0.05$), and CRP ($p < 0.01$) (Table IV). The above indices were possible independent risk factors for DEACMP with statistically significant differences.

DISCUSSION

DEACMP is a CO poisoning-induced disease with poor prognosis (15). CO poisoning causes both tissue hypoxia and direct cellular changes causing inflammatory or immunological injury (36,41). Prolonged exposure to CO leads to the development of neurologic sequelae, especially delayed encephalopathy (25,29). Song et al. have presented that approximately 10% to 30% patients who had CO poisoning develop DEACMP (32). Du et al. have shown that patients with DEACMP have a longer exposure to CO compared with those without DEACMP (9). In this study, the duration of exposure to CO in the DEACMP group was significantly higher than that in the non-DEACMP group. Our results are consistent with previous studies and illustrate that CO poisoning can cause DEACMP. Coma is one of the most obvious clinical manifestations of CO poisoning (27). Prolonged duration of coma after ACMP is also a risk factor for DEACMP (14,34). Pan et al. have shown that prolonged duration of coma for 11 hours may result in a markedly increased incidence rate of DEACMP (14). Taki and Nakajima have found that ACMP patients with coma have a higher incidence of DEACMP than ACMP patients without coma (34). In this study, the number of coma cases in the DEACMP group was also significantly higher than those in the non-DEACMP group, indicating that coma is closely related to the onset of DEACMP. Furthermore, upon logistic regression analysis, the duration of poisoning and coma degree were found to be independent risk factors for DEACMP. Therefore, special attention should be paid to the occurrence of DEACMP in ACMP patients with long duration of poisoning and high degree of coma.

Many serum biochemical markers which may be able to determine the degree of DEACMP have been studies, which include Lac (22), CK, CK-MB (20,31), and LDH (18). Lac is a product of anaerobic glycolysis under low oxygen supply that can act as an indicator for early CO poisoning (7). Moon

et al. have indicated that Lac is associated with short-term outcomes in patients with ACMP, as patients with high initial Lac level exhibit a high incidence of DEACMP (22). CK and CK-MB are intracellular enzymes predominantly located in skeletal muscle, myocardium, and the brain (3). High CK and CK-MB levels can be induced by CO-induced damage in multiple organs in patients with ACMP. Thus, serum CK and CK-MB levels can be used as predictors for ACMP-associated diseases (19,38). LDH is an important enzyme of the anaerobic metabolic pathway (10). Winburn et al. have found that exposure of human erythrocytes to exogenous CO moderately inhibited LDH activity (42). Kudo et al. have reported the levels of CK, CK-MB and LDH to be markedly increased in DEACMP patients (18). In this study, the serum levels of Lac, CK, CK-MB and LDH in the DEACMP group were significantly higher than those in the non-DEACMP group. Our results indicate that these serum biochemical markers are closely associated with the occurrence of DEACMP, which are consistent with previous studies. Furthermore, logistic regression analysis found increased serum levels of CK and LDH to be independent risk factors for DEACMP. These results indicate that CK and LDH may act as promising predictive factors of DEACMP in clinical practice.

CRP is a common acute phase protein that can be elevated by hypoxia, trauma and other stress states in human organisms (23,43). Sawiniec et al. have proved CRP levels to have diagnostic value for ACMP, with CRP levels in ACMP patients found to increase by over 33% (28). Song et al. have shown that serum CRP level is useful for the early diagnosis and prognostic assessment of DEACMP (32). NSE is a marker of the condition of the central nervous system, with elevations in its levels closely related to the degree of brain damage (4,44). Yildirim et al. have demonstrated that serum NSE level is an indicator for brain injury in CO poisoning patients (45). Cha et al. have also reported that serum NES acts as an early predictor of DNS in patients with ACMP (5). In this study, serum levels of CRP and NSE in the DEACMP group were significantly higher than those in the non-DEACMP group. In addition, logistic regression analysis showed that increased serum levels of CRP and NES were independent risk factors

for DEACMP. Our results illustrate that CK and LDH may be promising predictive factors of DEACMP.

MRI is an important diagnostic tool to identify ACMP patients who have developed chronic neurological symptoms (16). It can reveal neurological lesions resulting from DEACMP that are mainly located in the globus pallidus, subcortical white matter, and basal ganglia (40). The globus pallidus is a vulnerable structure in patients who had CO poisoning, including ACMP (6). Ischemic lesions in patients with ACMP are easily reflected in globus pallidus (24). Bleecker have reported that the globus pallidus was the most commonly affected area of the brain following CO poisoning (2). Hopkins et al. have observed bilateral lesions in the globus pallidus after CO exposure (13). ADC values measured by DWI is an effective indicator of brain dysfunction (17,37). Bang and Kim have reported the ADC values of the globus pallidus in DNS patients to be lower than that in non-DNS patients (1). Moon et al. have shown the ADC value of globus pallidus to be decreased in patients with ACMP (21). In this study, the ADC value of globus pallidus in the non-DEACMP group was significantly higher than that in the DEACMP group. This result is consistent with previous studies and indicates that the ADC value of globus pallidus can reflect the onset of DEACMP to some extent. However, logistic regression analysis showed that a decreased ADC value of the globus pallidus was not an independent risk factor for DEACMP, indicating that the predictive value of the ADC value of the globus pallidus for DEACMP is limited. Further studies on the predictive value of DW-MRI on DEACMP therefore need to be further investigated.

■ CONCLUSION

In conclusion, the serum levels of Lac, CK, CK-MB, LDH, CRP, and NSE in ACMP patients were positively related to DEACMP, while ADC value of the globus pallidus in ACMP patients was negatively related to DEACMP. Additionally, the duration of poisoning, coma degree, CK, LDH, NES, and CRP were independent risk factors for DEACMP.

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