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Callosal damage and cognitive deficits in chronic carbon monoxide intoxication: A diffusion tensor imaging study

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ABSTRACT

Purpose: To evaluate the correlation between microstructural damage in the corpus callosum (CC) and the cognitive performance of patients with or without delayed encephalopathy (DE) after carbon monoxide (CO) intoxication in the chronic stage.
Methods: Diffusion tensor imaging (DTI) was performed more than 6 months after CO intoxication for 10 patients with DE and 10 patients without DE recruited from out-patient clinics, as well as for 15 normal controls (NCs). Using a probabilistic tractography method to parcel the CC based on fiber projections to cortical connectivity patterns, the DTI indices were calculated in the CC subregions and further correlated with cognitive performance.
Results: The DE group exhibited significantly lower fractional anisotropy (FA) and higher radial diffusivity (RD) values in the prefrontal, premotor, primary motor, primary sensory, parietal, and occipital CC subregions than did the NCs. The DE group also exhibited significantly lower FA values in the prefrontal and premotor subregions than did the non-DE group. Lower FA and higher RD values in the CC subregions were associated with poorer scores on the symbol search test.
Conclusions: CO intoxication may cause lower FA and higher RD in the CC subregions, with subsequent cognitive impairment. This finding suggests that selective CC damage after CO intoxication is more profound in patients with DE.

1. Introduction

Carbon monoxide (CO) intoxication is the most commonly occurring form of lethal gas intoxication, and can also result in extensive brain injury and subsequent cognitive impairment in non-lethal cases [1]. After CO intoxication, two common types of clinical presentation may develop: (1) acute consciousness deterioration which occurs immediately after CO exposure, and (2) delayed encephalopathy (DE), which occurs in approximately 0.06–40% of survivors after CO intoxication and presents with rapid neurologic deterioration and a broad spectrum of neuropsychiatric symptoms after a lucid interval [2]. The latter syndrome is clinically characterized by a recurrence of neurologic or psychiatric symptoms that include dementia, disorientation, Parkinsonism, psychiatric syndrome, and akinetic mutism or apallic states [3].

Evidence has shown that lesions in the white matter (WM) of the brain, especially the peri-ventricular WM and centrum semiovale, occur as a result of CO intoxication and that these lesions might contribute to DE. Such lesions have been associated with diffuse demyelination of the cerebral WM [4–7], including the corpus callosum (CC) [5–7]. Damage to different portions of CC fibers may contribute to distinct behavioral and cognitive symptoms. However, little is known about how microstructure damage to the CC occurs after CO intoxication. In addition, there is a paucity of information regarding the nature of the damage to different portions of fibers in the CC after CO intoxication, both in patients with and without DE.

Abbreviations: CO, carbon monoxide; DE, delayed encephalopathy; WM, white matter; CC, corpus callosum; DTI, diffusion tensor imaging; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; NC, normal control; NP, neuropsychological.

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Recently, non-invasive MRI techniques, such as diffusion tensor imaging (DTI), have been shown to be capable of providing information about the white matter pathways in the human brain by detecting the water molecular diffusion in the local microstructure at a given voxel [8]. Among the DTI indices, the MD (average diffusion coefficient, $[(\lambda1 + \lambda2 + \lambda3) / 3]$) is viewed as a measurement of isotropic diffusion in the context of free movement of water. Axial diffusivity (AD) (which is the principal diffusion component and is denoted mathematically as $\lambda1$) is the diffusion coefficient along the direction of maximal "apparent" diffusion. The second and third eigenvalues in the DTI can be averaged and presented as radial diffusivity (RD) (which is the transverse diffusion component and is denoted mathematically as $[(\lambda2 + \lambda3) / 2]$). Lastly, the fractional anisotropy (FA) representing the integrity of white matter fibers is the relative ratio of the axial to radial diffusivities [9,10]. However, there have only been a limited number of neuro-imaging studies that have focused on the condition of the CC and its correlation with cognitive declines in CO patients through the use of multiple diffusion indices.

In the present study, we measured all the aforementioned diffusivity indices to comprehensively explore the different types of diffusion characteristics in the CC in patients with CO. The parcellation of the CC was estimated by probability tractography, with the CC being divided into seven subregions based on projections to specific cortical areas. Our goal was to investigate the subregional callosal damage in patients with and without DE after CO intoxication. Microstructure differences in the CC subregions and cognitive performance were determined for all the patient subjects.

2. Materials and methods

2.1. Participants

Using cross-sectional data from 2008 to 2010, patients with CO intoxication in the chronic stage (which was defined as the follow-up period occurring more than 6 months after the acute CO intoxication episode) who were treated at Kaohsiung Chang Gung Memorial Hospital were evaluated as candidates for the present study via chart review, telephone interview, or in-person clinical interview. Initially, twenty-five patients with CO intoxication were found to fully fit the criteria. Finally, twenty patients with CO intoxication in the chronic phase (>6 months) were enrolled in the study (four of the aforementioned patients were not willing to participate, and one patient was excluded due to an imaging artifact). For comparison, fifteen age- and sex-matched normal controls (NCs) were also recruited. The subjects' demographic and clinical data are listed in Table 1. All of the subjects underwent MRI studies and neuro-psychological tests in the chronic stage (for the CO intoxication subjects) or, in the case of the NCs, at the time of enrollment.

A clear history of acute CO intoxication was defined as an episode of past exposure to burning charcoal or gas in an enclosed space and/or an elevated COHb level [11]. Those with a history of neurologic or psychiatric illness, developmental disorders, or head injuries that could affect the results of the neuropsychiatric or neuroimaging surveys, as well as those who used medication for unrelated conditions, were excluded. The enrolled CO patients either sought first aid at our hospital's emergency room during the acute CO intoxication and received follow-up treatment at our out-patient clinic ($n = 15$) or sought first aid at another hospital's emergency room and then visited our out-patient clinic following the development of new symptoms after the acute CO intoxication ($n = 5$). All of them awoke within 24 h of their acute CO intoxication episode and underwent hyperbaric oxygen therapy for several days. During the acute stage, all of the patients underwent conventional MRI.

The CO intoxicated patients were determined to belong to one of two subgroups based on the presence or absence in their disease course of delayed encephalopathy (DE), which is characterized clinically by recurring neurologic or psychiatric symptoms punctuated by temporary asymptomatic periods (lucid intervals) of varying durations [6]. For our 20 patients, there were 10 patients in the non-DE group and 10 patients in the DE group according to the above definition.

Chang Gung Memorial Hospital's Institutional Review Committee on Human Research approved the study, and all the participants provided written informed consent.

2.2. Neuropsychological (NP) testing

All the subjects underwent neuropsychological testing and MR imaging on the same day. The neuropsychological testing included the Wechsler Adult Intelligence Scale. The Wechsler Adult Intelligence Scale, a family of tests created by David Wechsler to measure cognitive domains that contribute to intelligence, is commonly used to assess a wide range of cognitive abilities and impairments [12]. This study used the full scale intelligence quotient measure from the Taiwanese version of the Wechsler Adult Intelligence Scale — III [13,14], which was based on the combined verbal comprehension index, perceptual organization index, working memory index, and processing speed index scores [15]. All of the participants finished the picture completion and matrix reasoning tasks, the sub-tests that comprise the perceptual

Table 1
Demographic and clinical characteristics of the DE, non-DE, and normal control groups.

	Patients with chronic COI		Normal control	F or X^2	P value
	DE group	Non-DE group			
Definition	With DE	Without DE	Healthy control		
Number of cases	10	10	15	–	–
Gender (n = male/female)	7/3	7/3	8/7	1.020	0.601
Age (years)	40.4 (9.0)	39.4 (9.1)	39.33 (9.36)	0.046	0.955
Duration of follow-up (months)	23.1 (17.54)	29.9 (12.2)	–	2.359	0.328
COHb% during the acute stage	15.88 (8.92)	11.58 (13.34)	–	1.716	0.529
WAIS					
Picture completion	13.14 (6.31)	13.8 (3.77)	11.53 (1.77)	1.185	0.32
Digit symbol	59 (16.67)[§]	65.6 (20.1)[#]	12.33 (2.32)	55.365	<**0.001**
Symbol search	21.57 (14.81)[§]	28.3 (6.94)	36.2 (8.39)	5.796	<**0.001**
Matrix reasoning	11.71 (4.42)	14 (4.62)	15.73 (5.89)	1.433	0.255
Digit span	22.4 (3.9)[§]	20.44 (4.1)[#]	13.07 (2.74)	20.975	<**0.001**

Data are presented as mean (standard deviation). Boldfaced P-values indicate significant differences ($P < 0.05$) in appropriate statistical tests.
Results of post-hoc ANCOVA test in neuropsychological tests were corrected for multiple comparisons using Tukey's correction (adjusted for age and sex).
Abbreviations: WAIS, Wechsler Adult Intelligence Scale; DE, delayed encephalopathy.
[#] $P < 0.05$ in post-hoc comparison with normal control and non-DE groups.
[§] $P < 0.05$ in post-hoc comparison with normal control and DE groups.