Rapid Report

Evaluation of changes in magnetic resonance diffusion tensor imaging after treatment of delayed encephalopathy due to carbon monoxide poisoning

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Diffusion tensor imaging of the brain tissue microstructure was performed to predict or diagnose the pathophysiological mechanism underlying delayed encephalopathy after carbon monoxide poisoning and the treatment effect was analyzed. The changes in the diffusion parameters (average diffusion coefficient and fractional anisotropy) in adult patients after hyperbaric oxygen therapy of delayed encephalopathy after carbon monoxide poisoning were not significant differences of the two lateral ventricles or anterior or posterior limb of the internal capsule. In the group exposed to hyperbaric oxygen therapy, the fractional anisotropy values of the white matter in the ventricles of the brain and anterior and posterior limbs of the internal capsule were higher than those recorded before therapy, while the average diffusion coefficient values were significantly lower. These finding provide important monitoring indicators for clinicians.

Keywords

1. Introduction

Carbon monoxide (CO) poisoning causes severe tissue hypoxia by forming carboxyhemoglobin, which has a factor of 250 greater affinity for hemoglobin than for oxygen (de Pont et al., 2003). Delayed encephalopathy after carbon monoxide poisoning is difficult to cure and has a poor prognosis (Hu et al., 2011). The underlying mechanisms potentially include ischemia and hypoxia, cytotoxic damage, free radical damage in reperfusion injury, excitatory amino acid-induced neurotoxicity and apoptosis, abnormal blood rheology and abnormalities associated with neurotransmitters (Qin et al., 2017; Zhao et al., 2018). The main pathological changes in delayed encephalopathy after monoxide poisoning include extensive demyelination of the white matter of the brain, symmetrical softening of the globus pallidus, typical hemodynamic stagnation, and vascular paralysis, focal or lamellar degeneration and necrosis of the cerebral cortex and irreversible damage to the hippocampus and cerebellum.

Conventional magnetic resonance imaging (MRI) shows the pathological damage of the aforementioned brain tissues and the manifestations can be divided into three types. (1) White matter lesions resulting from reversible demylination are reduced both in extent and signal intensity with the improvement of clinical symptoms and can be used to guide the clinical detection of the treatment effect. (2) A mass observed in the cranial nerve nucleus, with the low signal intensity of iron deposition in the bilateral thalamus, nucleus shell and globus pallidus of some patients, is believed to be abnormal iron deposition. (3) Cortical involvement is observed. These manifestations are not isolated and patients with involvement of both the nerve nuclei and cerebral white matter or cortex have relatively severe clinical manifestations and worse prognosis. In late stages the ventricular system significantly expands and brain atrophy is mainly confined to the medulla.

Currently, diffusion tensor imaging (DTI) is the most effective functional imaging modality for the observation of protein fibers (Jones and Leemans, 2011). Under the physiological conditions of the human body the three-dimensional diffusion of water molecules is restricted as it is not only affected by cell characteristics but also by blockage of the free movement of water (the anisotropy of diffusion). Anisotropic diffusion occurs mainly in the white matter bundle and is greatest in the direction parallel to the fiber bundle. The use of DTI based on the average diffusion coefficient (ADC) and fractional anisotropy (FA) has therefore been proposed for quantitative analysis.

The ADC value represents the speed of the overall diffusion of water molecules in brain tissue, which is mainly associated with cytotoxic edema, vasogenic edema and cellular structural integrity. It provides information on the microstructure inside and outside of cells. The FA value reflects the directional anisotropy of the diffusion of water molecules in brain tissue. It is mainly associated with the integrity of the myelin sheath and provides information on the spatial orientation and integrity of myelin tissue. As FA most clearly shows the structure of the white matter fibers in the brain, it is the most widely used modality. The FA value reflects the proportional contribution of the anisotropic components of water to the whole-brain DTI. An FA value of 0.0-1.0 means that the diffusion is not limited and is isotropic. For example, the FA

value of cerebrospinal fluid is close to 0. For a regular directional movement within tissue the FA value is close to 1. For example, the FA value of the white matter bundle of the brain is close to 1 (Sohn et al., 2000).

Carbon monoxide poisoning presents with a series of neurological symptoms, including cognitive and memory dysfunctions, mental and conscious impairments, and pyramidal and extrapyramidal dysfunctions. Serious symptoms are associated with old age, high concentration of CO exposure, long duration of coma, and cardiovascular and respiratory diseases (Wang et al., 2016, 2017; Xiang et al., 2017a; Zhang et al., 2018). The detailed pathophysiological mechanism is unclear and poor clinical treatment effect and high cost of treatment seriously endanger the life of patients. The current clinical treatment method is hyperbaric oxygen and adjuvant therapy, which reduce craniocerebral hypertension, nourish brain cells, scavenge free radicals and improve microcirculation.

Hyperbaric oxygen therapy is widely accepted and used to treat delayed encephalopathy after carbon monoxide poisoning. Liu et al. (2017) report that treatment with nicotinic acid combined with hyperbaric oxygen is more effective than hyperbaric oxygen alone (Liu et al., 2017).

Xiang et al. (2017b) found that hyperbaric oxygen therapy has higher effectiveness than simple supportive treatment and Yu et al. (2002) found that hyperbaric oxygen therapy improves outcomes if performed early and has a higher effectiveness than high-flow oxygen therapy (Yu et al., 2002).

Terajima et al. (2008) reported a case study that included only two patients with delayed encephalopathy after carbon monoxide poisoning who were undergoing hyperbaric oxygen therapy, while only a few studies have reported the treatment outcomes of delayed encephalopathy after carbon monoxide poisoning with hyperbaric oxygen therapy (Yang et al., 2012).

DTI is used to diagnose delayed encephalopathy after carbon monoxide poisoning as it can non-invasively and quantitatively assess the integrity of white matter fibrosis and reflect minor structural changes in the brain tissue (Yang et al., 2012). The common parameters are ADC, FA, volume ratio, and relative anisotropy (Dubey et al., 2018) and FA and ADC values are always used in clinical settings and studies. FA shows any water molecules spread along the nerve fibers and ADC maps present measurement of the diffusion amplitude of water molecules that reflect the degree of diffusion of water molecules in the tissues.

Kuroda et al. (2012) reported a decrease in the FA value in the period of false recovery before the onset of symptoms of delayed encephalopathy after carbon monoxide poisoning and an association between the degrees of FA decline and damage to the nervous system (Kuroda et al., 2012). Simultaneously, the ADC value reduces in the period of false recovery and begins to increase before the rise in the FA value, representing the recovery of consciousness (Kuroda et al., 2012).

The FA value in the white matter was lower in patients with delayed encephalopathy after carbon monoxide poisoning than in healthy volunteers (Beppu, 2014; Hou et al., 2013). The white matter fiber repair takes less than six months (Hao et al., 2017) and demyelination of the white matter of the brain takes more than three months. After one month of clinical treatment changes are visi-

Table 1. MMSE in the two groups

Group	Number	MMSE score
Sick group	33	18
Follow-up group	33	33

Mini-Mental State Examination score (MMSE)

ble on MRI. However, damage to the white matter is irreversible (Chen et al., 2015; Lo et al., 2007; Otubo et al., 2007; Sahni et al., 2011; Terajima et al., 2008).

2. Materials and methods

2.1 Subjects

A total of 33 diagnosed subjects (18 males, 15 females, age: 16-71 years; average: 54.5 years), were enrolled from the Department of Neurology at the Third People's Hospital of Datong City from 2012 to 2016. Subjects were re-examined after six months of hyperbaric oxygen therapy. The detailed therapeutic schedule was as follows. Subjects absorbed hyperbaric oxygen after waking. There were 3-4 courses of treatment, with 10 days for each course and 2-3 days off between each course. Subjects were simultaneously administered auxiliary drugs, such as nutritional brain nerve agents, energy mixture and vitamins.

The inclusion criteria for subjects with delayed encephalopathy after carbon monoxide poisoning were: (1) a clear history of CO poisoning, (2) intermediate waking period and (3) clinical symptoms within seven days. The exclusion criteria were: (1) large intracranial cerebral infarction, hemorrhage, inflammatory diseases, or tumors and (2) unwillingness to join the follow-up group despite intracranial cerebral infarction, hemorrhage, or traumatic brain injury.

All subjects were scored for the Mini-Mental State Examination (MMSE) before MRI (Table 1). All subjects signed an informed consent form and the study was approved by the Ethics Committee of the Third People's Hospital of Datong City.

2.2 MRI Imaging

All subjects underwent MRI with a Philips Achieva 3.0T TX MRI scanner (Achieva TX, Philips Healthcare, NL), head and neck phased array coil and DTI. Eupnea was maintained for all subjects during the scanning procedure. The DTI scanning mode was single-shot spin echo-planar imaging (EPI), and scanning baseline positioning was consistent with the front and rear joints. Scanning parameters for EPI were 59, repetition time (7328 ms), echo time (83 ms), layer thickness (2 mm), interval-free scanning, field of view (224 mm), 15-direction, acquisition matrix (112×112), and a total of 60 levels. The b-values were 0 and 800 s/mm^2 and the acquisition time was 4 minutes 13 s.

2.3 Image analysis

DTI data were analyzed using Philips software. First, they were corrected, FA and ADC images were then generated (Fig. 1A, B). Two neuroimaging diagnosticians analyzed the images and marked the regions of interest (ROIs) to measure the FA and ADC values in the white matter of the lateral ventricles and anterior and posterior limbs of the internal capsule (values expressed as mean ±

Table 2. Region of interest on both sides in sick group

	Number	Ventricular level		Internal capsule forelimb		Posterior limb	
		FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)
Left	33	0.431 ± 0.121	0.736 ± 0.067	0.499 ± 0.108	0.695 ± 0.091	0.657 ± 0.097	0.718 ± 0.067
Right	33	0.412 ± 0.111	0.737 ± 0.089	0.464 ± 0.103	0.696 ± 0.080	0.655 ± 0.858	0.740 ± 0.047
T		1.973	0.007	1.166	0.029	0.077	1.296
P		0.057	0.995	0.262	0.977	0.939	0.215

Average diffusion coefficient (ADC), Fractional Anisotropy (FA).

Table 3. Region of interest on both sides in follow-up group

	Number	Ventricular level		Internal capsule forelimb		Posterior limb	
		FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)
Left	33	0.544 ± 0.128	0.817 ± 0.166	0.544 ± 0.160	0.747 ± 0.026	0.693 ± 0.113	0.760 ± 0.078
Right	33	0.501 ± 0.157	0.799 ± 0.133	0.523 ± 0.112	0.829 ± 0.180	0.686 ± 0.105	0.792 ± 0.071
T		1.905	0.866	0.561	1.523	0.509	1.871
P		0.066	0.393	0.583	0.148	0.618	0.081

Average diffusion coefficient (ADC), Fractional Anisotropy (FA).

standard deviation). The average ROI values were obtained from three measurement values. The anterior and posterior limbs of the internal capsule had a voxel size of two and the lateral ventricles had a voxel size of four (Fig. 1C, D).

2.4 Statistical analysis

All measurement data were expressed as mean ± standard deviation ($\bar{X}$ ± SD). A paired t-test was used to test for differences in FA and ADC values of the bilateral ventricles and anterior and pos-
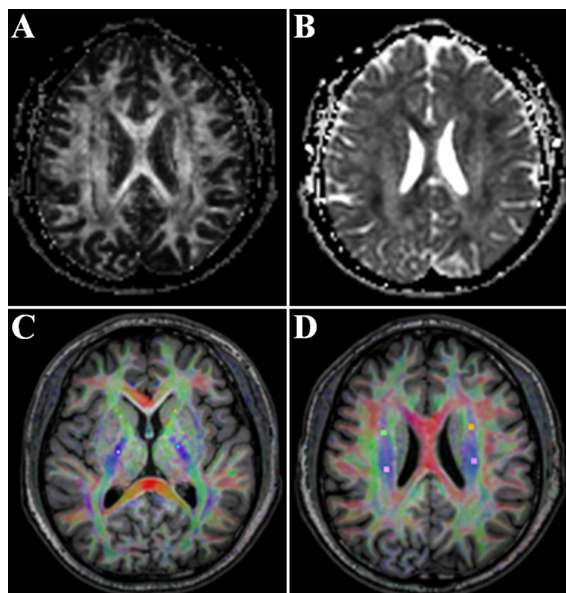

Figure 1. A. Image analysis of fractional anisotropy (FA). During carbon monoxide poisoning, FA in white matter is reduced. After hyperbaric oxygen therapy, the FA value is increased. (B): Average Diffusion Coefficient (ADC). During carbon monoxide poisoning, the ADC is increased. After treatment the ADC is reduced. (C): ROI in the white matter of the lateral ventricles. (D): ROI in the anterior and posterior limbs of the internal capsule.

terior limbs of the internal capsule between the sick and follow-up groups. All statistical analyses were performed using the Standard Package for the Social Sciences software version 19.0. P-values < 0.05 were considered statistically significant.

3. Results

MMSE scores were significantly improved after hyperbaric oxygen therapy and intelligence and mobility significantly recovered. The MMSE scores were compared between the sick and follow-up groups. Results showed they were higher in the follow-up group (value = 33) than in the sick group (value = 18) (Table 1).

FA and ADC values were also compared between the groups. No significant differences were found in the FA or ADC value of the two lateral ventricles or the anterior or posterior limb of the internal capsule in the sick group ($P > 0.05$, Table 2). Furthermore, there were no significant differences in the FA or ADC values of the two lateral ventricles or the anterior or posterior limb of the internal capsule in the follow-up group ($P > 0.05$, Table 3). The duration of the coma was 0.5-2.0 days and the intermediate waking period was 20-293 days.

The average FA and ADC values were obtained using a combination of values of the bilateral ventricles and the anterior and posterior limbs of the internal capsule in the sick and follow-up groups. The FA values of the bilateral ventricles and anterior and posterior limbs of the internal capsule were lower in the sick group than in the follow-up group. However, the ADC values of these four levels were higher in the sick group than in the follow-up group. Significant differences were detected in the FA and ADC values of the ventricles and anterior and posterior limbs of the internal capsule between the two groups ($P < 0.05$, Table 4).

4. Discussion

Before hyperbaric oxygen therapy, the values of ADC and FA in parietal white matter were significantly less than that of the normal white matter, suggesting pathological changes, such as cytotoxic edema and demyelination of the white matter. After hyper-

Table 4. Region of interest between the two groups

	Number	Ventricular level		Internal capsule forelimb		Posterior limb	
		FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)	FA value	ADC value (mm^2/s)
Sick group	33	0.422 ± 0.116	0.808 ± 0.149	0.482 ± 0.105	0.788 ± 0.151	0.650 ± 0.092	0.776 ± 0.075
Follow-up group	33	0.522 ± 0.144	0.736 ± 0.078	0.533 ± 0.137	0.695 ± 0.084	0.689 ± 0.107	0.729 ± 0.058
T		5.434	3.516	2.317	2.864	2.348	2.7
P		0	0.001	0.027	0.007	0.025	0.011

Average diffusion coefficient (ADC), Fractional Anisotropy (FA).

baric treatment, the ADC value gradually increased and exceeded the normal range, while the FA value was lower than that prior to treatment. The ADC value only gradually increased above the normal range after four months and returned to the normal range after five months. This suggests that restoration of the functional and structural integrity of the white matter surrounding an axon may take longer than expected. A decrease in the FA value may be associated with the loss of the lesioned axon and proliferation of glial cells. The highly ordered axon loss leads to increased diffusion, that is, an increased ADC value, but the degree of increased diffusion is limited by the simultaneous proliferation of glial cells. It is suggested that the progression of white matter lesions can be observed by monitoring the degree of these changes (Terajima et al., 2008). Furthermore, an ROI of only two voxels may be noisy, so the difference may be attributable to measurement error not actual changes in diffusion.

DTI of the brain tissue microstructure was performed to predict the pathophysiological mechanism underlying delayed encephalopathy after carbon monoxide poisoning. Results reported here show that the ADC value at the ventricular level, internal capsule forelimb and posterior limb were higher in the group before rather than after therapy. Significant differences were detected in the FA and ADC values of the ventricles and anterior and posterior limbs of the internal capsule between the two groups.

In this study, after treatment with hyperbaric oxygen therapy, subjects showed significant improvement and MMSE scores significantly increased. Two subjects were not cured, possibly attributable to old age and long-term diabetes and hypertension. Eight subjects improved, which may not be entirely due to the standardized treatment. No significant differences were demonstrated for FA or ADC values between the bilateral periventricular compartments or anterior or posterior limb of the internal capsule, implying that CO toxicity is the same for both cerebral hemispheres.

Furthermore, in the white matter of the periventricular compartment and anterior and posterior limbs of the internal capsule, FA and ADC values reduced after hyperbaric oxygen therapy. Potential reasons include: (1) angiogenic edema is relieved after hyperbaric oxygen therapy and water molecules are less active in all directions; (2) the number of water molecules in the extracellular space reduces from that measured before treatment; or (3) the myelin sheath increases the diffusion of water molecules using hyperbaric oxygen therapy for white matter myelin repair and increases brain tissue anisotropy.

Acknowledgment

Conflicts of interest

All authors declare no conflict of interest.

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