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Heterogeneous Diffusion Metrics Patterns in Delayed Encephalopathy After Acute Carbon Monoxide Poisoning: A Case Report

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HIGHLIGHTS

- We reported a case of delayed encephalopathy after acute carbon monoxide poisoning.
- We assessed the patient's brain structure with diffusion tensor imaging.
- Four distinct patterns were observed in the patient compared to age-matched controls.

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Heterogeneous Diffusion Metrics Patterns in Delayed Encephalopathy After Acute Carbon Monoxide Poisoning: A Case Report

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ABSTRACT

Delayed encephalopathy (DE) following acute carbon monoxide (CO) poisoning is characterized by a wide range of neurological symptoms, including akinetic mutism, cognitive impairment, and gait disturbances. Herein, we reported the case of a 61-year-old patient with DE after acute CO poisoning, who displayed heterogeneous patterns of cortical and subcortical structural integrity on diffusion tensor imaging (DTI). Four distinct patterns of diffusion tensor metrics (fractional anisotropy [FA] and mean diffusivity [MD]) were observed in the patient compared to age-matched controls (a decrease in FA and an increase in MD, a decrease in FA only, an increase in MD only, and an increase in FA and MD). This study revealed heterogeneous patterns of cortical and subcortical damage associated with DE after CO poisoning, contributing to a deeper understanding of the diverse clinical symptoms observed in this patient.

Keywords: Carbon Monoxide; Encephalopathy; Diffusion Tensor Imaging

INTRODUCTION

Carbon monoxide (CO) binds to hemoglobin, leading to tissue hypoxia. In cases of acute CO poisoning, individuals may experience either persistent neurological sequelae or delayed onset of neurological symptoms, referred to as delayed encephalopathy (DE) after CO poisoning [1]. Neurological symptoms associated with DE after CO poisoning can manifest in up to 50% of patients, with a lucid interval ranging from several to 240 days [2] after exposure. These symptoms may include akinetic mutism, cognitive impairment, gait disturbance, urinary or fecal incontinence, and involuntary movement disorders [3].

Recently, diffusion tensor imaging (DTI) has emerged as a valuable tool for characterizing microstructural changes in the white matter of patients with DE after acute CO poisoning and assessing disease severity. Studies have revealed that CO poisoning can impair axonal function and structural integrity of white matter, leading to a reduction of fractional anisotropy (FA) within the associated cortical regions [4,5]. However, the patterns of brain damage responsible for diverse neurological symptoms in DE are not yet fully understood.

Funding

None.

Conflict of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Lee J, Yoo WK; Data curation: Kim GJ, Lee E; Formal analysis: Ohn SH, Jung KI, Bashir S; Writing - original draft: Lee J; Writing - review & editing: Lee J, Yoo WK.

In this context, we aimed to investigate the changes in brain structures that result in diverse neurological symptoms by analyzing the DTI patterns in the patient with DE after acute CO poisoning. The patient has provided informed consent for the publication of this case.

CASE DESCRIPTION

A 61-year-old male with no underlying medical diseases was found unconscious after falling asleep while making a fire in a container box and was transferred to the emergency room of a nearby hospital. Diagnostic tests revealed elevated levels of creatine kinase and carboxyhemoglobin, leading to the diagnosis of acute CO intoxication, and the patient was admitted in the intensive care unit. The following day, he regained consciousness and was discharged from the hospital without any neurological sequelae. However, after 1 week of discharge, the patient began experiencing memory decline and was readmitted to the hospital. Despite receiving intravenous dexamethasone treatment, his symptoms worsened. He was subsequently transferred to our hospital one month after experiencing acute CO poisoning. Brain magnetic resonance imaging (MRI) revealed high-signal intensity lesions in the cerebral white matter on a T2-weighted image (T2WI), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted image (DWI) (**Fig. 1**). Upon neurological examination, the patient appeared apathetic and exhibited bradykinesia and mutism. While his motor strength remained intact, he had difficulty initiating and maintaining actions. He exhibited rigidity in both the upper and lower limbs, along with short-stepped and festinating gait patterns, often making him stumble forward. He displayed a loss of orientation while walking, occasionally moving in a different direction than instructed. He also faced difficulty in releasing objects once he grasped them. After undergoing 4 weeks of rehabilitation therapy, he was able to move eyes and focus on familiar individuals (his wife and friends) within a short period. His speed of initiating and ceasing actions improved. Due to the complete absence of verbal communication, his Mini-Mental State Examination score was 0 at both the initial and follow-up assessments. His Berg balance scale score improved from 8 to 18, and modified Barthel Index score improved from 2 to 10. He required minimal assistance to walk 10 m within 38 seconds but was able to walk independently within 22 seconds. His stride length and walking speed increased, and he did not experience falls when walking independently. We conducted DTI on the patient 2 months after acute CO poisoning. DTI was acquired

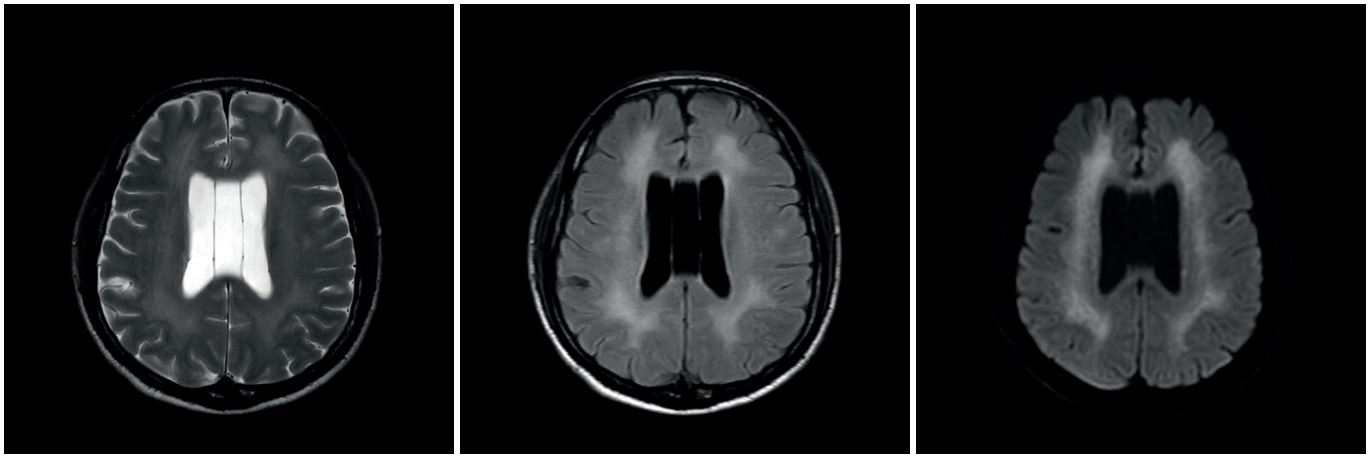

Fig. 1. T2WI, FLAIR, and DWI reveal symmetric confluent high-signal intensity lesions in both cerebral white matter, consistent with CO poisoning.
T2WI, T2-weighted image; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted image; CO, carbon monoxide.

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using a diffusion-weighted, echo-planar imaging sequence (repetition time [TR] = 5,000 ms; echo time [TE] = 100 ms; slice thickness = 2.2 mm; no gap; in-plane resolution = 2.4 × 2.4 mm^2, 32 independent diffusion gradient directions using b = 1,000 sec/mm^2). DTI data were analyzed using FMRIB's Diffusion Toolbox from the FMRIB Software Library (Oxford, UK). We selected the regions of interest (ROIs) based on the patient's symptoms. These ROIs included areas related to motor and sensory functions, such as the internal capsule (IC), red nucleus (RN), thalamus, and cerebellum. We also assessed ROIs specifically focused on gait performance, including the pedunculopontine nucleus (PPN), responsible for functioning as the mesencephalic locomotor center, and the subthalamic nucleus (STN), known for its role in movement regulation. Considering the patient's cognitive dysfunction, we included the frontal white matter (FWM) as an ROI for evaluation. We drew ROIs in each MNI coordinates of the IC (x = ± 16 [14 to 18], y = −7 [−5 to −9), z = 0), RN (x = ± 3 [2 to 4], y = −26 [−24 to −28], z = −17), thalamus (x = ± 10 [1 to 20], y = −15 [0 to 30], z = 5), middle cerebellar peduncle (MCP) of cerebellum (x = ± 20 [17 to 23], y = −37 [−31 to −43], z = −36 [−33 to −39]), PPN [6] (x = ± 7 [6 to 9], y = −32 [−30 to −35], z = −22 [−17 to −26]), STN [7] (x = ± 10, y = −17, z = −5), and FWM (x = ± 21 [21 to 22], y = 34 [34 to 35], z = 4) in standard space (**Supplementary Fig. 1**). All ROIs were projected to the individual space using the inverse transformation matrix. FA and MD were extracted from the ROIs. These diffusion metrics were compared with those of age-matched controls (5 controls, average age 61.8 ± 2.4, M:F = 3:2) using a modified t-test. It treats the control sample as a reference and establishes a confidence interval based on the deviation of scores from the norm [8,9]. Statistical analyses were conducted using the Singlims_ES.exe program. Significance was set at $p < 0.05$. This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB No. 2023-09-013).

Within each ROI, 4 distinct patterns were observed in the patient compared to age-matched controls. The first pattern exhibited lower FA and higher MD values than those of controls, and this pattern was observed in the RN and cerebellum. The second pattern exhibited lower FA values but no differences in MD values, corresponding to the PPN and FWM (**Fig. 2**). The

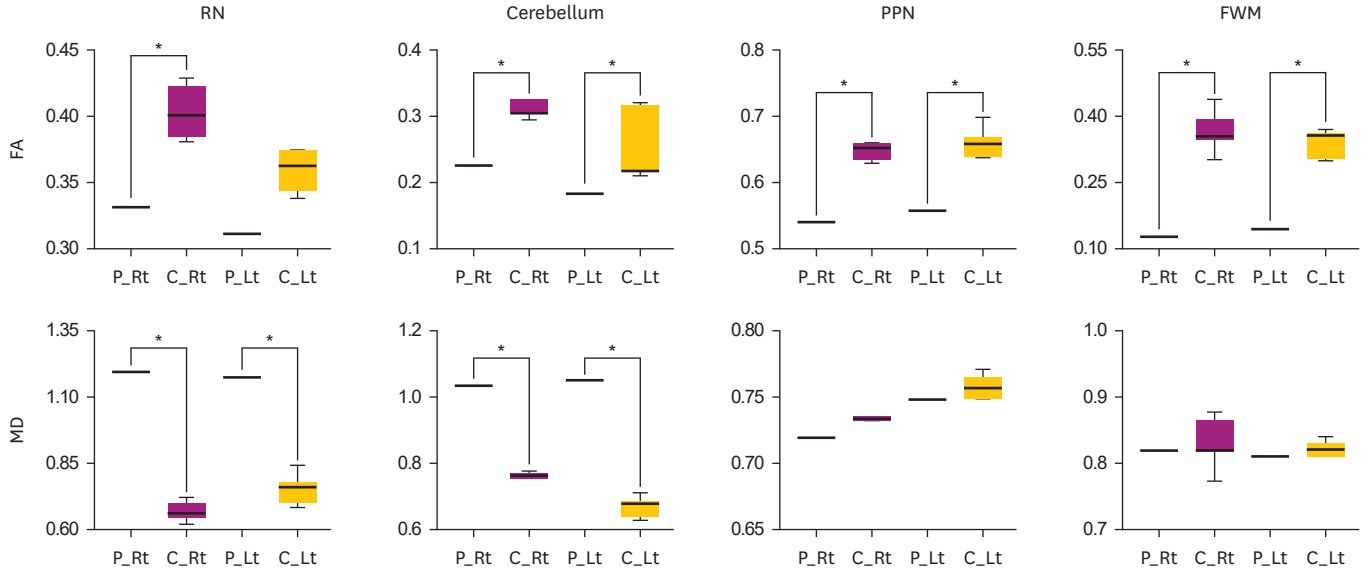

Fig. 2. Diffusion metrics of the RN, cerebellum, PPN, and FWM. Compared to controls, patient exhibits lower FA and higher MD values in the RN and cerebellum and lower FA values in the PPN and FWM.
RN, red nucleus; PPN, pedunculopontine nucleus; FWM, frontal white matter; FA, fractional anisotropy; MD, mean diffusivity; P, patient; C, control; Rt, right; Lt, left.
*$p < 0.05$.

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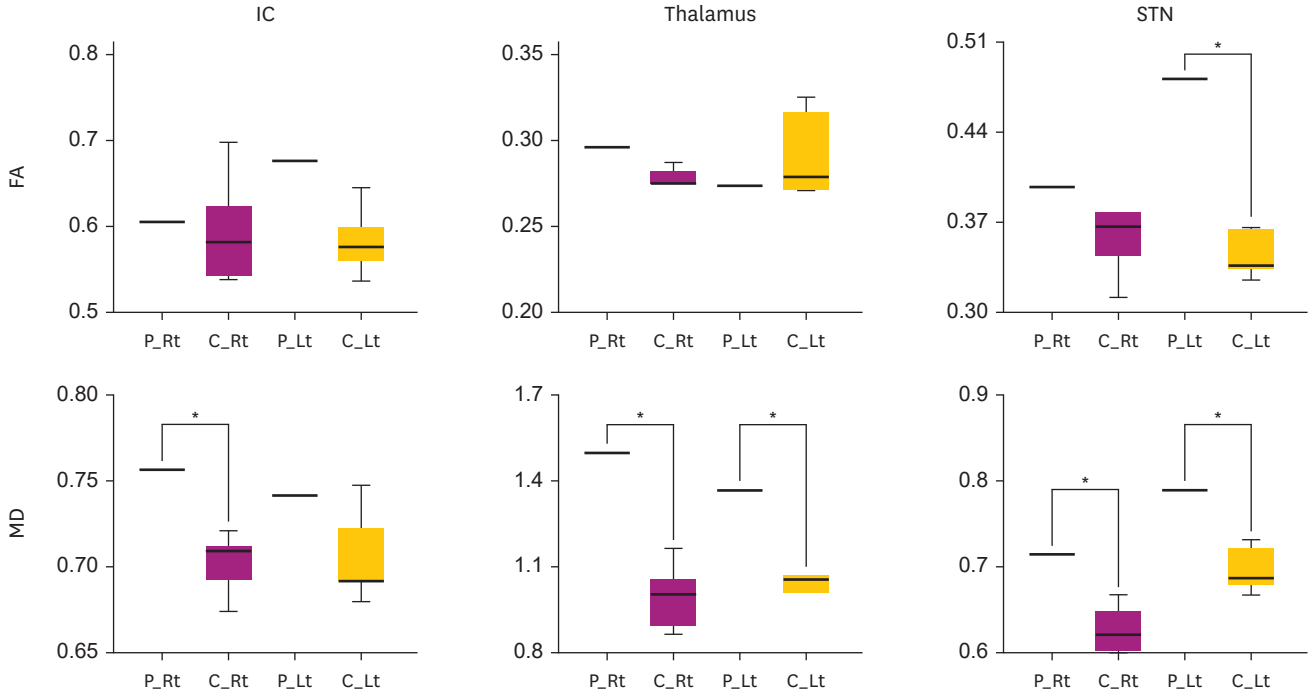

Fig. 3. Diffusion metrics of the IC, thalamus, and STN. Compared to controls, patient exhibits higher MD values in the IC and thalamus and higher FA and MD values in the STN.
IC, internal capsule; STN, subthalamic nucleus; MD, mean diffusivity; FA, fractional anisotropy; P, patient; C, control; Rt, right; Lt, left.
*$p < 0.05$.

third pattern exhibited higher MD values but no differences in FA values, corresponding to the IC and thalamus. The fourth pattern exhibited higher FA and MD values, primarily observed in the STN (**Fig. 3**).

DISCUSSION

Herein, we reported a case of a patient with DE after acute CO poisoning, where the patient exhibited symptoms including apathy, bradykinesia, mutism, cognitive impairment, and parkinsonism, corresponding to specific patterns of alteration in the diffusion metrics of cortical and subcortical structures. The exact mechanism underlying the development of DE after CO poisoning remains unclear; however, DE has been suggested to be attributed to demyelinating leukoencephalopathy caused by delayed pathogenic mechanisms involving apoptosis, lipid peroxidation, inhibition of the mitochondrial electron transfer enzyme system, mitochondrial oxidative stress, and adaptive immunological response [10-14].

Despite robust evidence of changes in diffusion metrics, such as decreased FA and increased MD in cortical white matter in cases of CO intoxication with DE [15,16], our findings of FWM in this case revealed significantly lower FA with no changes in MD, compared with that of controls. This could be interpreted as a loss of coherent fiber structures without associated tissue loss [17], indicating a type of dysfunctional condition that falls within a non-pathological boundary. A similar pattern was also observed in the PPN, which is the mesencephalic locomotor center located in the pontine area. The prognosis of gait function was expected to be positive in this case, unlike our previous case that displayed severe

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parkinsonian features with asymmetrical diffusion metrics between the right and left PPN, involving changes in both FA and MD [18]. In case of corticospinal tract measured using IC, a high MD value was observed without significant changes in FA. As MD indicates the extent of diffusion, a high MD may suggest the presence of cytotoxic edema with some degree of demyelination [19]. Since it is a pathological condition, better than both FA and MD changes, it is believed to represent relatively spared integrity and function, despite symptoms such as difficulty in initiating gait. A similar diffusion metric pattern was observed in the thalamus. Considering previous studies that reported decreased FA and increased MD in the acute (1 week) [20] and chronic (10 months) period [5], it is reasonable to speculate that our case demonstrated relatively better integrity in the thalamus. Together with some functional decline in FWM without the MD changes described above and mild pathological changes in the thalamus, it is reasonable to assume that the patient would experience a favorable cognitive outcome, aligning with the evidence demonstrating that maintained anterior thalamic connectivity is associated with improved cognitive function [21]. In contrast, the RN and cerebellum exhibited a typical pattern of low FA and high MD, indicating a certain level of tissue damage. The RN originates from the rubrospinal tract and is one of the extrapyramidal tracts that control muscle tone through interneurons of the spinal cord by segmental inhibition [22-24]. The cerebellum is also involved in controlling the muscle tone through signals from the muscle spindle, which can induce muscle hypertonia [25]. In the case of the STN, patient exhibited higher FA and MD values than those of controls. Notably, the increased FA and MD were unusual findings. Hyperactivity of the STN is known to be implicated in motor deficits in parkinsonism [26] and may be associated with clinical signs of akinesia [27,28].

Several DTI studies have been conducted to assess the severity of tissue injury in the affected areas and explain the clinical symptoms of DE following acute CO poisoning [5,15,29]. A common finding in these studies is the reduction in FA and an increase in MD in white matter regions [30-32]. Notably, a heterogeneous pattern of diffusion metrics is observed in the cortical and subcortical microstructures of the DE after acute CO poisoning, which has received limited attention in previous discussions.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

ROIs in standard brain. Only the ROIs on the right side were marked. Symmetric ROIs on the left side were also drawn in standard space.

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