CLINICAL CASE REPORT

Repetitive hyperbaric oxygen therapy for paroxysmal sympathetic hyperactivity after acute carbon monoxide poisoning

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ABSTRACT

Delayed neuropsychological sequelae (DNS) are relatively common complications of acute carbon monoxide (CO) poisoning, and usually develop within several days to weeks after the initial clinical recovery from acute CO poisoning. DNS can consist of various symptoms such as memory loss, confusion, ataxia, seizures, urinary incontinence, fecal incontinence, emotional lability, disorientation, hallucinations, mutism, cortical blindness, psychosis, parkinsonism, gait disturbances, rigidity, bradykinesia, and other motor disturbances.

Paroxysmal sympathetic hyperactivity (PSH) is a potentially life-threatening disease secondary to acute acquired brain injury. It is characterized by episodic and simultaneous paroxysmal increases in sympathetic and motor activities, not rare in patients with a severe traumatic brain injury. The term PSH is clinically more accurate than the previously used ones describing such conditions as non-stimulated tachycardia, hypertension, tachypnea, hyperthermia, external posturing, diaphoresis, and paroxysmal autonomic instability with dystonia. Development of PSH typically prolongs the length of hospital stay and potentially leads to a secondary brain injury or even death.

To date, the occurrence of PSH in the DNS after acute CO poisoning has not been reported in the literature. Potential mechanisms underlying the development of DNS in the deep white matter of the brain are immune-related inflammation and vasodilatation. Repetitive hyperbaric oxygen therapy, combined with methylprednisolone administration, may inhibit DNS progression by inducing cerebral oxygenation, inhibiting inflammation, and reducing cerebral edema. Herein, we report three cases in which the patients recovered from the PSH as DNS after CO poisoning after receiving repetitive hyperbaric oxygen therapy. ∎

KEYWORDS: carbon monoxide poisoning; complications; demyelinating disease; hyperbaric oxygenation

INTRODUCTION

Delayed neuropsychological sequelae (DNS) describes a relatively common complication of acute carbon monoxide (CO) poisoning [1-6]. DNS usually develops within several days to weeks after the initial clinical recovery from acute CO poisoning [3,7-12]. Individuals with this condition present with various signs and symptoms – e.g., memory loss, confusion, ataxia, seizures, urinary incontinence, fecal incontinence, emotional lability, disorientation, hallucinations, mutism, cortical blindness, psychosis, parkinsonism, gait disturbances, rigidity, bradykinesia, and other motor disturbances [7-12].

Paroxysmal sympathetic hyperactivity (PSH) is characterized by episodic and simultaneous paroxysmal increases in sympathetic and motor activities, not rare in patients with severe traumatic brain injury [13-15]. The term PSH is more accurate clinically than the ones previously used to describe such conditions: i.e., non-stimulated tachycardia, hypertension, tachypnea, hyperthermia, external posturing, and diaphoresis, and paroxysmal autonomic instability with dystonia [16-19]. The development of PSH typically prolongs the length of hospital stay and potentially leads to a secondary brain injury or even death [13,16,20]. To date, the occurrence of PSH as DNS after acute CO poisoning has not been reported in the literature.

Multiple approaches have been introduced for treating patients with DNS, including the administration of steroids, erythropoietin, allopurinol, glutathione, vitamin C, and targeted temperature management (TTM) [1,9, 21-27]. Still, a definitive treatment is currently unavailable for this potentially life-threatening disease.

Mechanisms under consideration underlying the development of DNS in the deep white matter (WM) are immune-related inflammation and vasodilatation [5,26,28].

Hyperbaric oxygen (HBO_2) therapy may inhibit DNS progression because treatment with HBO_2 induces cerebral hyperoxygenation, inhibits inflammation, and reduces cerebral edema [29-32]. HBO_2 is likely useful for treating this condition, even after the development of DNS. In this study, we report three cases in which patients received repetitive HBO_2 and steroids administration and recovered from the PSH as DNS after acute CO poisoning.

CASE SERIES

Three cases pertaining to PSH as DNS following acute CO poisoning are presented in this case series. This study was approved by the Ajou University Institutional Review Board (IRB), and an informed consent requirement was waived (AJIRB-MED-EXP-19-576).

Our hyperbaric center operated a monoplace chamber. Our chamber was manufactured in 1993 (HOT-101-0; Nambuk Medical Supply Industries, Inc., Yongin, Gyeonggi-do, Korea). Its internal dimensions were 70cm in diameter and 2m in length; its weight is about 900kg. The range of gas flow rates through the chamber was between 100 and 300 L/minute. Maximum operational pressure was 3.0 atmospheres absolute (ATA).

To treat acute CO poisoning we followed the protocol using a pressure of 2.8 ATA. In case 1, we started with 2.8 ATA but later reduced the pressure to 2.6 ATA due to a concern for oxygen toxicity. Thus, we chose 2.6 ATA for cases 2 and 3. The duration of the sessions was from door closing to door opening of the chamber, which was 90 minutes: at pressure (50 minutes), compression (20 minutes), and decompression (20 minutes). The investigators chose to not use air breaks.

Case 1

A 36-year-old man was transferred to our emergency department (ED) for treatment of acute carbon monoxide poisoning. The present illness is shown in Table 1. A brain computed tomography (CT) scan was performed, but nothing specific was found related to his condition. Laboratory exam results from ED admission are presented in Table 2. The patient was intubated so he could not undergo HBO_2 therapy. Instead he underwent target temperature management (TTM) at 33°C for 36 hours and was discharged on day 7 of hospitalization.

After discharge, he had received psychiatric consultation for four weeks regarding his depression. Beginning three or four days before his re-admission, he became unable to answer simple questions correctly and was seen taking small, shuffling steps. Additionally, he had urinary and fecal incontinence and progressive stiffness in his arms and legs. He was readmitted to our ED. His vital signs were: blood pressure 160/100 mmHg; heart rate 148 bpm; respiratory rate 26 cpm; body temperature 38.5C; and oxygen saturation 99%. His mental status demonstrated an acute confusional state characterized by mildly impaired consciousness, inattentiveness, and motor abnormalities in his arms and legs. His Glasgow Coma Scale (GCS) score was 10 (E4V4M2). The patient lost orientation to time, which occurred rather drastically, while his orientation to person and place was normal. There was no evidence for suspected infection.

Magnetic resonance imaging (MRI) of the brain was performed (Figure 1), and the patient was diagnosed with PSH as DNS based on the clinical evidence and MRI findings and his current health status.

We provided treatments for the PSH as DNS, which included repetitive HBO_2 therapy using a monoplace chamber and methylprednisolone administration, 1 g/day for three days. Repetitive HBO_2 therapy consisted of the patient breathing 100% oxygen at 2.8 ATA, 90 minutes/day, for 20 days. After 20 HBO_2 treatment sessions, the patient's physical and neurological symptoms of DNS resolved. Follow-up MRI was not conducted due to patient's financial constraints. He was discharged from the hospital on day 30, displaying no physical difficulties.

Case 2

A 31-year-old male was admitted to the ED unconscious and required immediate intubation. Specifics of his presentation are noted in Table 1. A brain CT was performed and is depicted in Figure 2. Upon physical exam, two burn bullae were noted on his left foot and at the back of his right hand, measured to be 5×5 cm^2 and 3×15.5 cm^2, respectively. Laboratory exam results from ED admission are presented in Table 2.

The patient could not undergo HBO_2 therapy because of his intubated state and unstable vital signs. Alternatively, he was treated with therapeutic hypothermia at 33°C for 90 hours. A follow-up brain MRI was performed on day four of hospitalization (Figure 2B). He was discharged on day 20 of hospitalization without neurologic abnormality.

He seemed to be living normally after the discharge, but then presented with abnormal behaviors such as urinating in the sink and talking to himself beginning about three weeks before rehospitalization (34 days after the initial CO exposure). Seven days prior to rehospitalization, the patient was confined to the bed because of the discomfort he experienced when mobile, was unable to converse

Table 1. Clinical features of each case

	CASE 1	CASE 2	CASE 3
Past medical history	History of adjustment disorder and depression. The patient has been having a hard time coping with recent financial problems.	Recently, the patient started having some psychiatric issues, and all he wanted to do was to continue sleeping.	No known history of diseases
Present illness	He was found unconscious on the bed in a motel room. There was no pill bottle or cases near him, but a fast-ignite honeycomb charcoal burner was found 50 cm from his feet, completely burnt.	He was found unconscious at home and lying on the floor. Several empty beer bottles and honeycomb briquettes that were completely burnt were next to the patient.	He was found unconscious in a motel room after he had lit a fast-ignite honeycomb charcoal. Empty pill bottles were found next to the patient. He was suspected of having taken 4 tablets of diphenhydramine 50 mg together with 4 tablets of aspirin 500 mg.
Duration from initial poisoning to development of PSH			
PSH features	tachycardia hypertension hyperthermia Unable to answer simple questions properly; Taking small, shuffling steps; Urinary and fecal incontinence; Progressive stiffness in his arms and legs	tachycardia hypertension hyperthermia Abnormal behaviors; urinating in the sink and talking to himself; Unable to converse with others; Spontaneous extremities stretching out as in an extensor posture; Severe diaphoresis and tremors	tachycardia hypertension hyperthermia Trouble in concentration; Awkward speech; Severe sweating and tremors
Treatments	Breathing 100% oxygen at 2.8 ATA, 90 min/day, for 20 days in a monoplace chamber and IV methylprednisolone, 1g/day for three days	Breathing 100% oxygen at 2.6 ATA, 90 min/day, for 20 days in a monoplace chamber and IV methylprednisolone, 1g/day for five days	Breathing 100% oxygen at 2.6 ATA, 90 min/day for 20 days in a monoplace chamber
Side effect of repetitive HBO_2 in a monoplace chamber	Not definitely identified	Not definitely identified	Not definitely identified

PSH=paroxysmal sympathetic hyperactivity; ATA=atmospheres absolute; IV=intravenous

with his family, and had a decreased appetite eating, small meals only. After three or four days in this condition, his mental status altered and he became acutely confused. He had moderately impaired consciousness; he was inattentive; his body temperature control became poor; his extremities stretched outward spontaneously, as in extensor posturing. Also, he had severe diaphoresis and tremors. He was hospitalized in another facility, where clinical evaluation and blood tests did not show any signs of infection. He was then transferred to our hospital, where a brain MRI was performed. Based on the MRI results, history of CO poisoning, and physical assessment findings (Figure 3A), the patient was diagnosed with PSH as DNS after acute CO poisoning. Subsequently, he underwent 20 sessions of HBO_2 therapy in a monoplace chamber and received intravenous methylprednisolone, 1 g/day for five days. Repetitive HBO_2 therapy consisted of breathing 100% oxygen at 2.6 ATA, 90 minutes/day for 20 days. On day 30 of rehospitalization, a follow-up brain MRI was performed (Figure 3B), and he was discharged from the hospital on day 54 of rehospitalization without physical difficulties.

Table 2. Laboratory results at ED admission

Laboratory results	CASE 1	CASE 2	CASE 3
V/S with mental status			
Blood pressure (mmHg)	140/70	164/110	120/61
Heart rate (bpm)	142	117	133
Respiratory rate (cpm)	28	22	25
Body temperature (°C)	37.5	37.0	37.4
Oxygen saturation (%)	99.8	100	99.8
Mental status	semi-comatose	comatose	stuporous
COHb concentration (%) (0.5~1.5)	26.2	10.8	36.1
Lactic acid (mmol/L) (0.70~2.00)	8.41	4.55	2.54
ABGA			
pH (7.35 ~ 7.45)	7.326	7.401	7.452
PCO_2 (mmHg) (35.0~48.0)	23.8	35.5	25.7
PO_2 (mmHg) (83.0~108.0)	335.8	275.2	315.9
BE (mmol/L) (-2.0~3.0)	-11.5	-2.5	-4.5
HCO_{3-} (mmol/L) (21.0~28.0)	12.2	21.5	17.5
Saturation (%) (95.0~98.0)	99.7	99.6	99.8%
BUN / Cr (mg/dL) (8.0~23.0 / 0.70~1.20)	17.2 / 1.6	27.8 / 1.3	14.2 / 1.03
AST / ALT (IU/L) (5~40 / 5~41)	43 / 45	226 / 721	26 / 15
Cardiac enzymes			
CK, (IU/L) (39~308)	207	53,843	142
CK-MB (IU/L) (0.0~5.0)	7.0	86.3	1.8
Tro-I (ng/mL) (0.000~0.04)	0.783	4.050	0.089
S100B protein (μg/L) (0.005~0.10)	0.260	0.579	0.074

V/S=vital sign; bp=beats per minute; cpm=cycles per minute; COH=carboxyhemoglobin; ABGA=arterial blood gas analysis; PCO_2=partial pressure of carbon dioxide; PO_2=partial pressure of oxygen; BE=base excess; HCO_{3-}=bicarbonate; BUN=blood urea nitrogen; Cr=creatinine; AST=aspartate aminotransferase; ALT=alanine aminotransferase; CK=creatine kinase; CK-MB=creatine kinase-MB

Case 3

A 36-year-old male presented to the ED in a stuporous state. Specifics related to this case are found in Table 1. His mental status progressed to semicomatose, requiring immediate endotracheal intubation and immediate brain CT depicted in Figure 4A. Lab exam results from ED admission are presented in Table 2. The patient was then admitted to the intensive care unit (ICU) but did not undergo HBO_2 treatment because he was intubated. He regained his consciousness on day two of hospitalization. After a brain MRI (Figure 4B) on day five the patient was discharged from the hospital without having any particular problem.

One month after discharge, his speech became awkward, and he had trouble concentrating. He also had severe sweating and tremors. Eventually he revisited our ED and was admitted to the ICU. While in the ICU he developed an acute onset of episodic tachycardia at a rate of 180 beats/minute, and hypertension, with systolic blood pressure up to 180 mmHg, increased respiratory rate in the 30s (cpm), and hyperthermia, with body temperature at 38.6°C. Despite this, clinical and laboratory evaluation failed to disclose signs of active infection.

A follow-up MRI was performed (Figure 5A), and the diagnosis of PSH as DNS was made based on his history of CO poisoning, current status, and brain MRI findings.

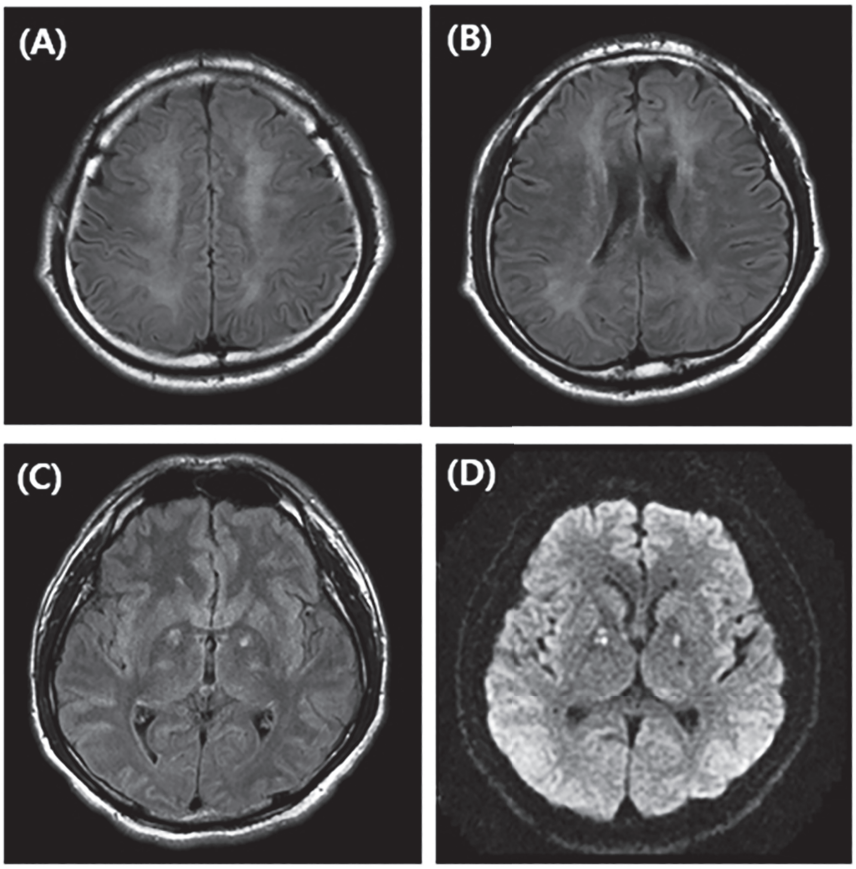

Figure 1. Brain magnetic resonance image upon readmission

Diffuse high signal intensities are observed at the (A) centrum ovale, (B) periventricular deep white matter, and (C) subcortical white matter on fluid-attenuated inversion recovery (FLAIR) images; at the (D) globus pallidus on diffusion-weighted images (DWI), which are concordant on DNS.

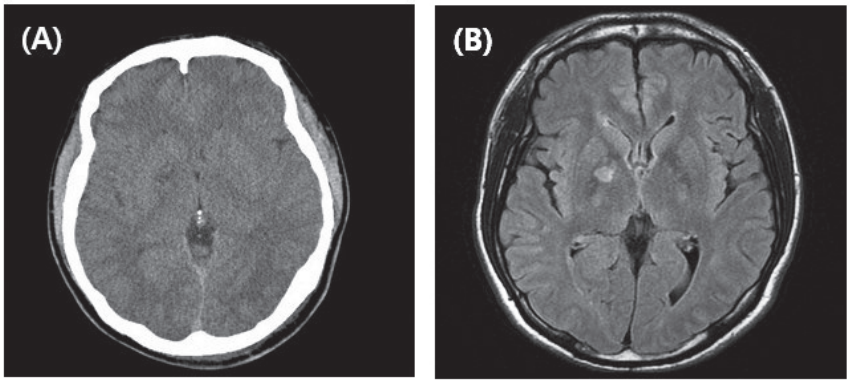

Figure 2. Scan images of (A) the initial brain computed tomography (CT) and (B) the brain MRI on day four of hospitalization

No definite abnormality is observed on the initial CT except a lesion with low Hounsfield unit at the right globus pallidus. High signal intensity is noted on the FLAIR image of the right globus pallidus on day four of hospitalization.

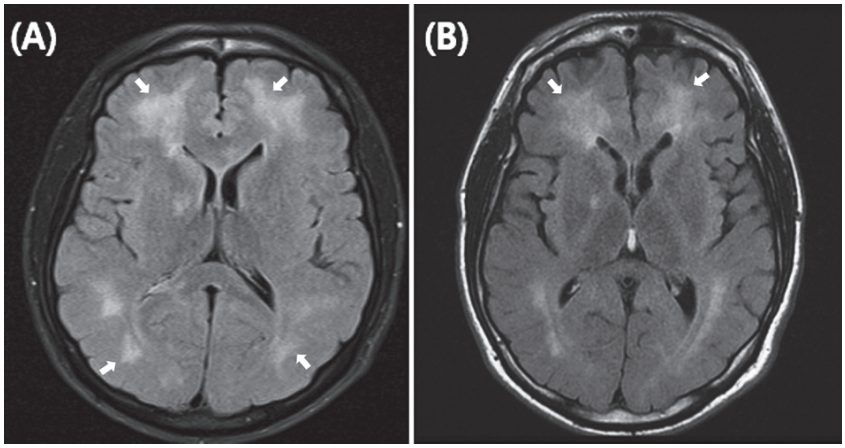

Figure 3. Brain MR images (A) before and (B) after repetitive hyperbaric oxygen therapy

Decreases in diffuse inflammation and demyelination are observed at the deep white matter for the FLAIR images after repetitive HBO_2 therapy.

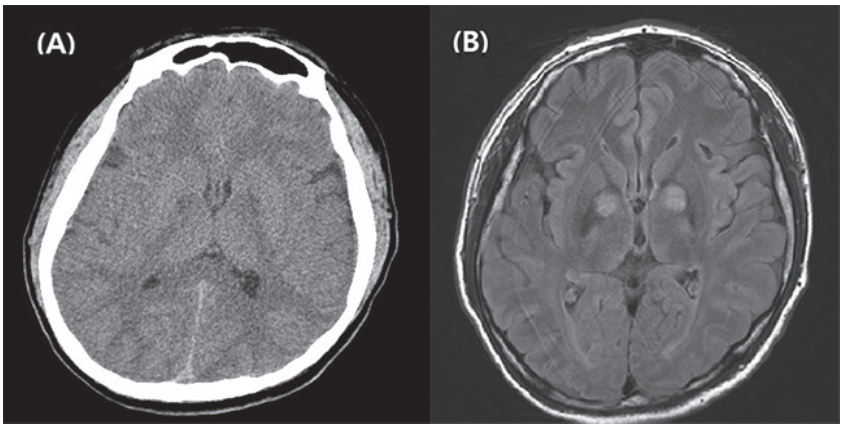

Figure 4. Images from (A) the brain CT upon ED admission and (B) the brain MRI on day five of hospitalization

The small lesions of low Hounsfield unit are shown on both globus pallidus on CT scan (A), whereas high signal intensities are remarkably noted on the MR FLAIR image (B) on both sides of the globus pallidus.

Consequently, he underwent 20 sessions of HBO_2 therapy in a monoplace chamber. Repetitive HBO_2 consisted of the patient breathing 100% oxygen at 2.6 ATA, 90 minutes/day, for 20 days. Following 20 HBO_2 treatment sessions, the patient's physical and neurological symptoms significantly decreased. Moreover, a follow-up MRI revealed mild improvement in demyelination and inflammation in the deep WM (Figure 5B).

DISCUSSION

In this case series we found that repetitive HBO_2 therapy may be a successful treatment method for the patients with PSH as DNS. Repetitive HBO_2 therapy may be useful for treating PSH as DNS after acute CO poisoning due to the relatively long recovery period associated with severe DNS, the lack of qualitative and effective treatments for DNS or PSH, and the short time to treatment following signs and symptoms of DNS, as experienced in our case series.

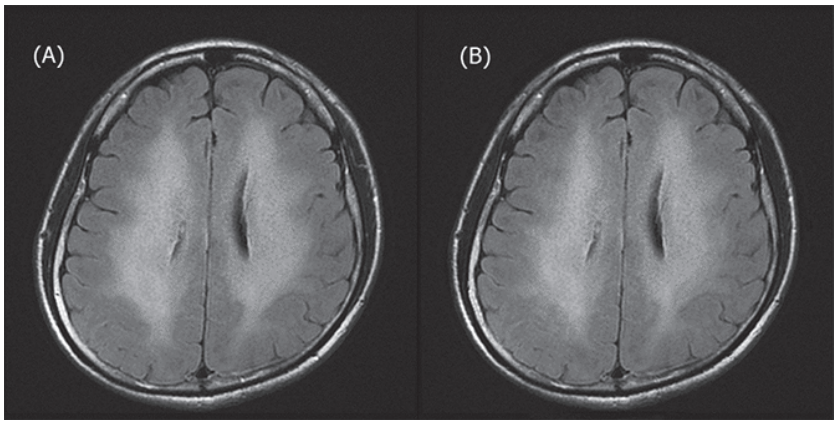

Figure 5. Brain MR images (A) before and (B) after repetitive hyperbaric oxygen therapy

The lesions in the semicentrum ovale are shown as confluent high signal intensities on FLAIR image (A), whereas high signal intensities in the periventricular deep white matter decreased slightly on FLAIR image (B).

The incidence rate of acute CO poisoning has rapidly increased in South Korea due to its use as a toxicological agent to commit suicide. The incidence of DNS may also be increasing due to these exposures in those surviving the attempted suicide. Suicide attempt is more prevalent for people in their 30s and 50s [33-36], thereby resulting in an extremely significant burden nationwide from injuries and related loss of labor force. Considering that a specific treatment is unavailable for DNS at this time, we believe that this case series should provide a significant contribution to the establishment of treatment strategies for DNS.

PSH has been receiving increasing attention relating to the clinical burdens resulting from it. This includes morbidity, weight loss, dehydration, infections, interrupted rehabilitation, and an increase in prolonged ICU admissions. Different sets of diagnostic criteria have been proposed, reflected in the fact that there are more than 30 terminologies: These include dysautonomia, sympathetic storm, and autonomic dysfunction syndrome), thereby leading to diagnostic confusion [15,16, 37]. The diagnosis is made by exclusion and using a substantial degree of suspicion, ruling out other potential diagnoses.

Outcomes correlate with the severity of signs and symptoms; the more severe, the worse the outcome. Therapeutic delays for PSH may have devastating consequences for the patient's recovery. Unfortunately, there is no specific treatment available for PSH, and pharmacological management of sympathetic hyperactivities is difficult because of limited evidence [38-40]. There is a need for future studies regarding the efficacy of repetitive HBO_2 therapy on PSH induced by causes other than acute CO poisoning.

The pathophysiology of DNS is not fully understood as yet. Previous studies demonstrated that the typical involvement of the WM in CO poisoning reflects a transient intramyelinic edema or inflammation associated with brain lipid peroxidation [1-3,5,8,26]. O'Donnell et al. [41] reported that the delayed neuropathology mediated by CO is likely related to the immunological response adapted to the chemical modification of myelin basic protein.

Regarding the treatment mechanisms, we make the following arguments. First, HBO_2 therapy has anti-inflammatory and anti-apoptotic effects [42-46]. Previous studies have shown that hyperbaric oxygenation has an anti-inflammatory effect on various diseases such as idiopathic sensorineural hearing loss, inflammatory bowel disease, chronic osteomyelitis, autism, and diabetic foot [47-55]. In addition, HBO_2 therapy can decrease the severity of ischemia-reperfusion (IR) injury; reduce leukocyte adherence on the endothelium of venules; decreases proinflammatory cytokine levels [43,44, 48,56,57]. Theoretically, HBO_2 therapy could lower serum glutathione levels and decreases activities of antioxidant enzymes according to the production of reactive oxygen species. This is mitigated by adaptive.

bodily mechanisms and immunomodulation responses such as the production of heme oxygenase-1, inducible heat shock proteins, catalase, and superoxide dismutase [43-49,51,54,58]. These adaptive mechanisms and responses to oxidative stress in HBO_2 therapy may explain the anti-inflammatory and anti-apoptotic effect on the above various diseases as well as central nervous system diseases by IR injury, perhaps leading to reduced lipid peroxidation in the IR injury of the central nervous system [1,42,43,48,54,56,57,59]. We also presume that additional anti-inflammatory effect could be achieved by co-administering HBO_2 therapy with steroids.

Second, HBO_2 therapy is effective in reducing tissue edema. Previous studies have shown that HBO_2 therapy can enhance arterial PaO_2 [60], increase oxygen levels [60], stabilize the blood-brain barrier (BBB) [61], decrease intracranial pressure, and relieve cerebral edema [29,30,62]. While repairing damaged BBB is delayed due to persistent vasodilation and cerebral edema, HBO_2 therapy is deemed effective due to the promotion of revascularization and recovery of nervous tissues.

In this case series, the patient's cerebral edema and inflammation were reduced after more than 20 sessions of repetitive HBO_2 therapy. Decreasing inflammation and edema should be a promising treatment because DNS is caused by inflammation in the deep WM. Based on the findings from the previous studies regarding the treatment of chronic inflammation, we had planned more than 30 sessions of HBO_2 therapy initially. Clinical symptoms began improving beginning on day 7 or 8 and had shown overall improvement by day 20 when we stopped the treatment to minimize side effects. Based on the investigators' experiences described in this case series, we believe that repetitive HBO_2 therapy might be an effective treatment for reducing inflammation and cerebral edema in DNS at the time of its progression. Further studies are necessary to clarify the efficacy of repetitive HBO_2 in treating DNS.

As the treatment progresses, improvement with MRI findings is not as notable as clinical improvements (Figures 3 and 5). Following HBO_2 treatments, patients demonstrated improvement of activity of daily living to a complete recovery. The progress was also evident with their cognitive improvement, but the imaging studies did not produce clear evidence. Future study is necessary for explaining this discrepancy.

HBO_2 is generally known to have few adverse effects that may become more prominent as the number of treatments progresses. Potential adverse effects of repetitive HBO_2 therapy are as follows [63,64]. First, high oxygen concentration may increase oxidative stress via the production of oxygen free radical species, influencing the cerebral blood flow negatively [65,66]; repetitive HBO_2 therapy may paradoxically worsen lesions caused by hypoxia [66]. Thus, estimation of a risk-to-benefit ratio should precede treatment decisions.

Second, the incidence rate of seizure associated with HBO_2 therapy is as low as 0.02% [63,64]. Still, it can happen, and one should monitor for it, as it is one of the most severe adversities in HBO_2 therapy [67].

Third, barotrauma is the most common adverse effect of HBO_2 therapy, but it usually has low clinical significance. According to Jokinen-Gordon et al. [64], the barotrauma incidence rate in patients undergoing HBO_2 therapy was merely 0.37%.

Fourth, claustrophobia is of a concern for patients with DNS undergoing HBO_2 therapy, according to the study by Anderson et al., in which 39% of the participants could not complete repetitive HBO_2 therapy [68].

The adverse effects of HBO_2 therapy are usually related to oxygen toxicity or pressure tissue damage. For the patient experiencing an altered level of consciousness, tympanostomy could be performed to help prevent pressure injuries. Treatment protocols must be strictly abided by to prevent the side effects associated with oxygen toxicity from developing.

To date, HBO_2 is used widely as the treatment for multiple clinical disorders, particularly hypoxia-induced disorders. Still, the promotion and application of HBO_2 treatment have been limited, explaining the slow progress of hyperbaric medicine because of its complex mechanisms, a therapeutic time window that is not known, undetermined dose, and potential side effects. We hope that this study provides further opportunity to expand and develop the use of HBO_2 for treating DNS.

CONCLUSION

In summary, providing approximately 20 HBO_2 sessions, using 100% oxygen at 2.6 to 2.8 ATA for 90 minutes daily in combination with steroid therapy may be a useful treatment to enhance recovery from paroxysmal sympathetic hyperactivity as delayed neuropsychological sequelae after acute CO poisoning.

Conflict of interest statement

The authors have declared no conflicts of interest.

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