Hyperbaric oxygen ameliorates delayed neuropsychiatric syndrome of carbon monoxide poisoning

D.C. CHANG¹, J.T. LEE², C.P. LO³, Y.M. FAN ⁴, K.L. HUANG⁵, B.H. KANG⁵, H.L. HSIEH⁷, S.Y. CHEN⁵,6

¹Department of Neurology, Chu Shang Show Chwan Hospital, Nantou, Taiwan, Republic of China; ²Department of Neurology, Tri-Service General Hospital, Taipei, Taiwan, Republic of China; ³Department of Radiology, Buddhist Tzu Chi General Hospital, Taichung Branch, Taichung County, Taiwan, Republic of China; ⁴Department of Nuclear Medicine, Cardinal Tien Hospital, Taipei, Taiwan, Republic of China; ⁵Department of Undersea and Hyperbaric Medicine, Tri-Service General Hospital, Taipei, Taiwan, Republic of China; ⁶Department of Hyperbaric Medicine and Department of Neurology, Cardinal Tien Hospital, Taipei, Taiwan, Republic of China; ⁷Department of Urology, Chu Shang Show Chwan Hospital, Nantou, Taiwan, Republic of China

ABSTRACT

Objectives: Delayed neuropsychiatric syndrome (DNS) is characterized by mental impairment, motor dysfunction, dementia, or psychosis that develops between a few days and weeks after acute carbon monoxide (CO) poisoning. One possible mechanism responsible for CO-mediated encephalopathy involves oxidative stress, such as lipid peroxidation, caused by the cellular uptake of CO and which leads to an inflammatory cascade. There is no current effective treatment for DNS. We applied 8-40 sessions of hyperbaric oxygen therapy (HBO₂) to patients with DNS and evaluated its effectiveness.

Methods: After admission, all patients were administered piracetam or bromocriptine, or both, and received HBO₂. Neuropsychiatric tests included EEG, mini-mental status examination (MMSE), brain MRI, event-related potential (ERP), and brain perfusion scan (brain SPECT). Results of these tests were compared before and after HBO₂, and the clinical features were monitored during this period.

Results: The symptoms of DNS for all patients improved significantly after HBOT. Although white matter changes remained evident in the brain MRI scans, other examinations such as EEG, MMSE, ERP, and ⁹⁹ᵐTc-ECD brain SPECT were nearly normal after HBOT.

Conclusion: Our results suggest that HBO₂ decreases the severity of impairment in patients with DNS. Although a large randomized trial is required to address the efficacy of this therapy, therapeutic application of HBO₂ may be recommended in patients with DNS after CO poisoning.

INTRODUCTION

Exposure to carbon monoxide (CO) can cause various clinical symptoms and signs including headache, nausea, dizziness, malaise, blurred vision, severe seizure, coma, and death. Providing the patient with supplemental oxygen can accelerate the dissociation of CO from hemoglobin and help improve the oxygenation of hypoxic tissues. Hyperbaric oxygen therapy (HBO₂) given within 24 hours after acute CO poisoning reduces the risk of cognitive sequelae (1). However, there is no effective therapy for the delayed neuropsychiatric syndrome (DNS) after acute CO poisoning.

DNS after acute CO poisoning is characterized by impairment of neurological functions such as concentration, attention, language, learning, memory, and motor function, as well as psychiatric functions such as depression, dementia and psychosis, which develop between two and 28 days after poisoning.
The typical MRI findings of DNS show bilateral high-signal intensity in the periventricular white matter and centrum semiovale on T2-weighted images (2). Although the pathogenesis of and risk factors for DNS remain unclear, basic studies have implicated oxidative stress as a possible mechanism that may result from the cellular uptake of CO, toxic effects of excessive release of excitatory amino acid neurotransmitters and a cascade of inflammatory changes (3-4). However, lipid peroxidation induced by oxidative stress may be the most important pathophysiology based on the findings of an animal study and a human study showing white matter demyelination of T2-weighted MRI in DNS patients (5-6). HBO₂ can improve tissue salvage in different oxidative injuries (e.g., thermal burns, tissue flaps and ischemia-reperfusion injury) and can decrease lipid peroxidation (7-10).

The purpose of this study was to investigate the effects of HBO₂ on DNS. From 2004 to 2005, we used HBO₂ to treat 9 patients who developed DNS after acute CO poisoning. After diagnosis by neurologists and hyperbaric physicians, the patients were admitted to the hospital for further management.

In addition to medication such as piracetam or bromocriptine, or both, patients received continuous HBO₂. Several neuropsychiatric tests — including EEG, mini-mental status examination (MMSE), brain MRI, event-related potential (ERP) and brain perfusion scan (brain SPECT) — were administered before and after HBO₂. All the experiments and treatments followed the regulation of Taiwan Medical Research Ethics Foundation and the principles of the Declaration of Helsinki.

**EEG protocol**

EEG signals were recorded during a state of relaxed wakefulness (initial background, two to three minutes in duration), during intermittent photic stimulation of various frequencies and during wakefulness between stimulations at different frequencies. The subjects’ eyes were closed throughout the experiment. Each presentation of a fixed frequency lasted 20-30 seconds, and the period was constant between stimulations. One series of stimulations consisted of the following flicker frequencies: 3, 4, 5, 6, 8, 10, 12, 15, 18, 21 and 24 Hz.

The EEG was recorded with an 18-channel Nihon Kohden polygraph (Nihon Kohden, Tokyo, Japan) (EEG-4418), at 14 scalp points, according to the International 10/20 System, with unilateral references to the corresponding earlobes. These points were located over the following areas of the left (odd index) and right (even index) hemispheres: occipital (O1, O2), parietal (P3, P4), central (C3, C4), frontal (F3, F4), posterior temporal (T5, T6), mid-temporal (T3, T4) and anterior temporal (F7, F8).

The recording characteristics were: 0.3 seconds time constant, 70 Hz high frequency filter, and 15 μV/mm sensitivity. The EEG signals were recorded on magnetic tape with a TEAC XR-7000 tape recorder (Tokyo, Japan), with simultaneous paper recording, after digitalization with an A/D converter (12-bit precision) at a sampling frequency
of 256 Hz. The instants of stimulation were also acquired to be used as a reference when applying the signal processing techniques. To avoid the possible short post-stimulation effect (27), the first five s after each stimulation was excluded from analysis.

**MMSE**

The MMSE is used to systematically and thoroughly assess mental status and comprises an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30; a score of 26 or lower is indicative of cognitive impairment. The MMSE takes only 5-10 minutes to administer and is therefore practical to use repeatedly and routinely. The validity and reliability of the MMSE to assess the cognitive aspects of mental function have been established.

In addition to its diagnostic value, the MMSE can be used for serial measurement of disease progression. Scores can range from 0 to 30, with scores ≥24 indicating very mild dementia, 20-23 mild dementia, 10-19 moderate dementia, and 0-9 severe dementia.

**MRI protocol**

MRI was performed using a 1.5-T unit (Magnetom vision Plus; Siemens, Erlangen, Germany). Conventional MRI images were obtained with axial T2-weighted fast spin-echo (TR/TE 4000/98), axial fluid-attenuated inversion recovery (FLAIR) (TR/TE/TI, 9000/110/220), and sagittal T1-weighted spin-echo (500/20) sequences.

**ERP and P300**

Ag/AgCl electrodes were used to record EEG activity. They were placed at 21 sites of the 10-20 electrode system including Fpz (midpoint between Fp1 and Fp2) and Oz (midpoint between O1 and O2). Linked ear electrodes were used as the reference. To record the ERP, two kinds of brief tone (2000 and 1000 Hz), each with a duration of 100 ms, were generated by an automatic stimulator and were presented to the patients through an earphone at the intensity of 60 dB (normal hearing level).

The 1000 Hz (frequent) tone was presented at 80% incidence and the 2000 Hz (rare) tone at 20% incidence. The presentation order of tones was randomized. The interstimulus interval was also randomized within the range of 1.0-3.0 seconds (mean 2.0 seconds).

The patient was placed in an electrically shielded and sound-attenuated laboratory and was exposed to the sound stimulation. The patient was told to respond to the rare stimuli (target) by pressing a button attached to the palm of his or her right hand with the thumb (oddball paradigm). The button-press response was converted to an electrical signal that was monitored and recorded with other data on an FM data recorder. The amplitude and latency of P300 was measured at Pz on the scalp. The amplitude of P300 varied substantially between blocks of the same period. However, the latencies of P300 obtained from blocks of the same period were relatively stable. Therefore, only P300 latency was evaluated as an index of brain activity.

**99mTc-ethyl cysteinate dimer (ECD) brain SPECT**

99mTc-ECD was prepared according to the instructions given with a commercial vial (Neurolite Dupont, N. Billerica, Massachusetts, USA). The radiochemical purity of the 99mTc-ECD complex was measured by thin-layer chromatography on Whatman MKC 18 plates developed with acetone and 0.5 M ammonium acetate (60:40 v/v). The radiochemical purity was calculated by comparing the peak for the 99mTc-ECD complex to the sum of all other peaks on the plate. The radiochemical purity of 99mTc-ECD was >97%. 99mTc-ECD (740 MBq) was intravenously injected in a dark and quiet room. The position of the patient’s head was fixed and maintained during SPECT imaging using a hemicylindrical plastic head shoulder with a radiolucent plastic neck-contoured headrest. Fifteen to 45 minutes after intravenous 99mTc-ECD injection, SPECT data were obtained using a dual-headed gamma camera equipped with fan-beam collimators (GE Medical Systems, Milwaukee, Wis., USA). Data were collected from 120 projections per three angular samples in the 140 keV photo-peak over 360° (180° for each
head) in $128 \times 128$ matrices, with an acquisition time of 30 seconds per projection in a step-and-shoot mode. A zoom factor of 1.46 was used. After data acquisition, the data were normalized for the decay of $^{99}$mTc from the first to last frame. The counts within each frame of SPECT were the same.

For SPECT images, the transaxial, coronal and sagittal slices were reconstructed. To identify areas of abnormal perfusion, agreement was required by at least two of three independent, experienced observers based on their visual interpretation of the SPECT images from each patient, observed in random order along with images from healthy controls. The expert observers were unaware that the images were from a cohort of patients with CO poisoning and were blind to other clinical information. Normal $^{99m}$Tc-ECD brain SPECT findings were defined as homogenous regional cerebral blood flow (rCBF) in the gray matter of brain cortex and basal ganglia without hypoperfusion lesions or visible asymmetry. Abnormal findings included heterogeneous rCBF with hypoperfusion lesions or visible asymmetry on at least two consecutive slices.

**RESULTS**

**DNS after acute CO poisoning**

Before the HBO$_2$, all patients had symptoms of cognitive impairment and motor dysfunction. Six patients had parkinsonian features such as bradykinesia, rigidity of limbs, or resting tremor. The abnormalities of neuropsychiatric tests are shown in Table 1 (Page 32). The brain MRI scans revealed generalized diffused white matter demyelination in all patients. Abnormal or borderline EEG with poor sustained alpha background was found in nine patients. The patients displayed mild to moderate dementia as tested by the MMSE, except the one patient with decorticate posture.

**No significant interval changes for white matter lesions on conventional MRI images before and after HBO$_2$**

T2-weighted and FLAIR images showed bilateral areas of confluent high signal intensity in the periventricular white matter and centrum semiovale in all patients (Figures 1A and 1B, facing page), although the hyperintensity varied from slight to severe. Six patients had necrosis of the bilateral globus pallidi in brain MRI scans (Figure 1E). The MRI scan of the brain was repeated as the symptoms of DNS improved after serial sessions of HBO$_2$.

Compared with the prior MRI scan, no interval improvement was found for the signal intensity of the white matter of T2-weighted and FLAIR images (Figures 1C and 1D). In patients with previous necrotic globus pallidi, this became partially collapsed on the following MRI scan (Figure 1F).

**Changes in P300 wave form and latency after HBO$_2$**

The ERP is used as a psychological marker of various cognitive functions to examine psychiatric and neurological disorders. In particular, the P300 potential of the ERP is used widely because of the ease of its observation in a simple discriminative task. We recorded the ERP over time during HBO$_2$ and evaluated the changes in the P300 potential. Before HBO$_2$, the ERPs showed poor waveform with late response latency and less accuracy. The ERPs recorded after HBO$_2$ showed significant improvement of response accuracy, latency and waveform, although the latency was still delayed compared with the normal pattern (Figure 2, Page 28).

**Changes in $^{99m}$Tc-ECD brain SPECT**

All DNS patients had hypoperfusion brain lesions on $^{99m}$Tc-ECD brain SPECT. Perfusion increased after serial sessions of HBO$_2$ (Table 2, Page 33) in the frontal, temporal, and occipital lobes and in the basal ganglia, although the extent of increase differed between areas (Figure 3, Page 29).

**Functional improvement of DNS patients after HBO$_2$**

All patients were able to care for themselves and walk without support after 8-40 sessions of HBO$_2$. Functional neurological tests including ERP, EEG, MMSE, and brain perfusion scans showed improvements that were compatible with their
FIGURE 1

**A, B and E:** T2-weighted images show bilateral, symmetric and confluent areas of high-signal intensity in the centrum semiovale (A) and periventricular white matter (B). The high intensity also appears in the bilateral globus pallidi of some patients (E).

**C, D and F:** T2-weighted images show similar high-signal intensity in the centrum semiovale (C), periventricular white matter (D), and the bilateral globus pallidi (E).
FIGURE 2

<table>
<thead>
<tr>
<th>Response latency</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before HBO₂</td>
<td>0.537</td>
</tr>
<tr>
<td>After HBO₂</td>
<td>0.469</td>
</tr>
<tr>
<td>Normal</td>
<td>0.25</td>
</tr>
</tbody>
</table>

FIGURE 2: ERP P300 in DNS patients before HBO₂ (green line) and after HBO₂ (red line) differed significantly from that in the normal control (blue dotted line). The table shows the shortened response latency and increased response accuracy after HBO₂ compared with condition before HBO₂. Response latency was still delayed after HBO₂ compared with the normal control.

clinical presentation (Table 2, Page 33). The most severe patient was able to remove his nasogastric tube and walk by himself after 30 sessions of HBO₂. However, the findings of conventional MRI scans of the brain remained unchanged while the patients’ symptoms improved.

Discussion

The benefit of HBO₂ after acute CO poisoning has been debated for decades (11-13). Although studies showing positive results indicate that early HBO₂ can reduce the risk of cognitive sequelae and the incidence of DNS after acute CO poisoning (1, 11), a certain percent of patients still develop DNS between periods of lucid intervals (14-15). In our study, half of the DNS patients had received 3-10 sessions of HBO₂ for acute CO intoxication; however, the symptoms of DNS still developed 30-60 days later. Our patients had a longer interval than those in other reports (usually within 30 days) because their families did not feel that anything was wrong until the patients developed serious symptoms, such as dementia, psychosis, rigidity of limbs, and urinary incontinence, in addition to
the initial mild depressive mood (all had attempted suicide through CO poisoning). In addition to these clinical features, all patients showed bilateral symmetric hyperintensity of the periventricular white matter and centrum semiovale on FLAIR and T2-weighted images of MRi scans. These lesions were consistent with the most obvious characteristic of delayed encephalopathy with CO intoxication or the biphasic myelinopathy of Ginker (16).

Demyelination of the white matter is the most common and specific imaging finding for DNS (16-17), and this indicates necrosis of the globus pallidi. However, only some of our DNS patients showed this finding, which had been detected in the acute stage. We found no interval changes in the conventional brain MRI scans as the symptoms improved after HBO2. Diffusion tensor imaging has been proposed to evaluate the magnitude and the directionality of water diffusion in tissue. Normal myelinated white matter tracts have higher degree of fractional anisotropy (FA) because they are highly directional. If the myelination or axonal integrity is disrupted, the FA can be expected to decrease (18). It may be the better method to detect HBO2 effect than conventional brain MRI.

Functional examination is more suitable to evaluate the patient’s neuropsychiatric condition. Recent studies suggest that 99mTc-ECD brain SPECT is sensitive in detecting abnormal brain perfusion in patients with acute CO poisoning (19). We found that the increased regional cerebral blood flow on the previous hypoperfusion area could be analyzed by 99mTc-ECD brain SPECT when the patients finished a series of HBO2. Some patients showed much-improved brain SPECT after 10 sessions of HBO2.

Despite the changes in 99mTc-ECD brain SPECT, the 99mTc-TRODAT-1-SPECT scan might be better to evaluate the parkinsonian features, because patients with necrosis of the globus pallidi do not have motor dysfunction after HBO2 (20).

We used ERP, EEG, and MMSE to further evaluate the patients’ mental state and performance. The shortened P300 latency and increased response accuracy in ERP indicates that the patients could respond correctly after HBO2, although the latency was still longer than normal. Normal or nearly normal results of EEG and scores of MMSE show that the patients could perform activities of daily life and could even return to work. The functional changes were compatible with improvement of the patients’ symptoms.

Signs of DNS are the common complications after acute CO intoxication. There is no accurate measurement to predict whether patients who suffer acute poisoning will develop DNS later. In our department, clinicians always ask the patient to return for a follow-up visit at our outpatient department within one month after acute CO poisoning. The incidence of DNS depends on the

**FIGURE 3**

**Figure 3:** A 30-year-old man (patient 1) received 99mTc-ECD brain SPECT before (A) and after (B) HBO2. (A) 99mTc-ECD brain SPECT transverse-plane images show generalized hypoperfusion in the entire gray matter of the cerebral cortices, basal ganglia, thalami and cerebellum before HBO2 (B) After HBO2, brain SPECT demonstrated increased regional perfusion in the frontal, temporal and occipital lobes and basal ganglia compared with the previous images.
severity and duration of acute intoxication. Once the patient had developed DNS, symptomatic treatment with medication and rehabilitation is the only choice. Although over half of DNS patients can recover spontaneously, the symptoms causing their disability can persist for six months or more (21).

Long-term neurological deficits might persist in the most severely affected patients, such as those in decorticate posture, perhaps for life (22). Searching for an effective treatment is important for physicians to help patients recover and to prevent long-term disability. Utilizing HBO₂ to treat DNS patients is plausible because HBO₂ improves the pathogeneses of DNS including decreasing oxidative stress, especially lipid peroxidation caused by tissue hypoxia and the resulting cascade of inflammatory changes (3-5, 9, 23). Furthermore, Thom SR (24) indicated HBO₂ could improve postischemic/inflammatory tissue survival by increasing reactive species to temporarily inhibit β₂-integrin function of neutrophils as well as inducing antioxidant enzymes and anti-inflammatory proteins in many tissues.

Only one case report has described functional recovery from the neuropsychiatric symptoms after seven sessions of HBO₂ (25). We used brain MRI and functional neurological examinations as the first tests to evaluate the effects of HBOT on patients with DNS. However, we shortened the duration of the patients’ disability and improved their symptoms significantly compared with similar DNS patients not treated with HBO₂ reported in the literature and retrospective data. We almost gave up on the worst patient after 20 sessions of HBO₂ because he had shown few improvements, and these involved only the rigidity of his limbs. However, we found dramatic changes in his motor functions and mental state, and we were able to remove his nasogastric tube after a subsequent 10 sessions of HBO₂ He was functioning normally with mildly slow responses after receiving a total of 40 sessions of HBO₂ Thus, we succeeded in treating all patients from mild or moderate DNS to severe DNS.

In conclusion, our study suggests that HBO₂ is effective for treating DNS, although we cannot completely exclude an effect of drugs. The potential benefits of HBO₂ should be confirmed by a large, randomized, and prospective control trial. Preventing and predicting DNS will be another important issue to address.

Acknowledgments

This study was supported in part by the C Y Foundation for Advancement of Education, Sciences and Medicine. The authors thank Ms. K-W Zhuang, M-S Hsu, C-J Chang, Mrs. J-S Lan and Robert Liao for technical support and help in operating the hyperbaric oxygen chamber.

References


### TABLE 1 — Results for patients before HBO₂

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age</th>
<th>Interval (days) to DNS symptoms</th>
<th>Brain MRI</th>
<th>EEG</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M / 30</td>
<td>40</td>
<td>Diffuse white matter demyelination with necrosis of bilateral globus pallidi</td>
<td>Abnormal</td>
<td>24 / 30</td>
</tr>
<tr>
<td>2</td>
<td>F / 20</td>
<td>40</td>
<td>Diffuse white matter demyelination</td>
<td>Abnormal</td>
<td>19 / 30</td>
</tr>
<tr>
<td>3</td>
<td>M / 37</td>
<td>30</td>
<td>Diffuse white matter demyelination</td>
<td>Abnormal</td>
<td>19 / 30</td>
</tr>
<tr>
<td>4</td>
<td>F / 33</td>
<td>30</td>
<td>Diffuse white matter demyelination</td>
<td>Abnormal</td>
<td>19 / 30</td>
</tr>
<tr>
<td>5</td>
<td>F / 33</td>
<td>60</td>
<td>Diffuse white matter demyelination with necrosis of bilateral globus pallidi</td>
<td>Abnormal</td>
<td>15 / 30</td>
</tr>
<tr>
<td>6</td>
<td>M / 39</td>
<td>45</td>
<td>Diffuse white matter demyelination with necrosis of bilateral globus pallidi</td>
<td>Abnormal</td>
<td>20 / 30</td>
</tr>
<tr>
<td>7</td>
<td>F / 47</td>
<td>30</td>
<td>Diffuse white matter demyelination with necrosis of bilateral globus pallidi</td>
<td>Abnormal</td>
<td>21 / 30</td>
</tr>
<tr>
<td>8</td>
<td>F / 33</td>
<td>40</td>
<td>Diffuse white matter demyelination</td>
<td>Borderline</td>
<td>24 / 30</td>
</tr>
<tr>
<td>9</td>
<td>F / 37</td>
<td>50</td>
<td>Diffuse white matter demyelination with necrosis of bilateral globus pallidi</td>
<td>Normal</td>
<td>25 / 30</td>
</tr>
</tbody>
</table>

HBO₂, hyperbaric oxygen therapy; M, male; F, female; DNS, delayed neuropsychiatric sequelae; MMSE, mini-mental status examination.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sessions /HBO₂</th>
<th>Brain MRI</th>
<th>Latency &amp; accuracy/ERP</th>
<th>Increased perfusion/SPECT</th>
<th>EEG</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>No interval change</td>
<td>Improved</td>
<td>Bilateral F-P-T-B</td>
<td>Borderline</td>
<td>30/30</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>No interval change</td>
<td>Improved</td>
<td>Bilateral B, L-F</td>
<td>Normal</td>
<td>30/30</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>No interval change</td>
<td>Improved</td>
<td>Bilateral F-T, R-B</td>
<td>Normal</td>
<td>30/30</td>
</tr>
<tr>
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<td>13</td>
<td>No interval change</td>
<td>Improved</td>
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<td>30/30</td>
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<td>Bilateral F-T</td>
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<td>11</td>
<td>No interval change</td>
<td>Improved</td>
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<tr>
<td>9</td>
<td>8</td>
<td>No interval change</td>
<td>Improved</td>
<td>Bilateral B</td>
<td>Normal</td>
<td>27/30</td>
</tr>
</tbody>
</table>

HBO₂, hyperbaric oxygen therapy; ERP, event-related potential; MMSE, mini-mental status examination; R, right side; L, left side; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; B, basal ganglia; C, cerebellum.