Delayed Encephalopathy of Carbon Monoxide Intoxication and Treatment with Hyperbaric Oxygen: A Case Report

Karbonmonoksit İntoksikasyonuna Bağlı Gecikmiş Ensefalopati ve Hiperbarik Oksijen Uygulaması: Olgu Sunumu

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Summary

Delayed encephalopathy (DE) is a neuropsychiatric syndrome that can generally arise within 20 days of acute carbon monoxide (CO) intoxication after apparent recovery and involves variable degrees of cognitive deficits, personality changes, movement disorders and focal neurologic deficits. We report a 35-year-old female patient with delayed encephalopathy due to CO intoxication, presenting with cognitive impairment and mild parkinsonism despite receiving hyperbaric oxygen therapy (HBO). Magnetic resonance imaging (MRI) showed abnormal signal intensity and decreased diffusivity at both caudate nuclei and globus pallidus. She continued to receive additional HBO therapy and completely recovered within six months. The positive effects of early HBO therapy in selected patients on reversing the acute effects of CO intoxication is apparent. Here we also review the beneficial effect of HBO in preventing or limiting the late neurocognitive deficits associated with severe CO intoxication. (Turkish Journal of Neurology 2012; 18:35-39)

Key Words: Carbon monoxide (CO), intoxication, delayed encephalopathy, magnetic resonance imaging (MRI), hyperbaric oxygen therapy (HBO)

Özet


Anahtar Kelimeler: Karbon monoksit (CO), intoksikasyon, gecikmiş ensefalopati, manyetik rezonans görüntüleme (MRG), hiperbarik oksijen tedavisi (HBO)

Introduction

Carbon monoxide (CO) is an odorless, tasteless, colourless, non-irritant gas resulting from the burning of hydrocarbons. Toxic sources of CO include smoke inhalation, dysfuctioning heating systems such as water heaters, coal stoves, and motor vehicles in poorly ventilated areas. CO intoxication is a major cause of emergency room admissions and death from a toxic cause (1,2). CO binds to hemoglobin with a higher affinity than oxygen, transforms into carboxyhemoglobin (COHb) and impairs oxygen transport and utilization. In addition, CO initiates the inflammatory cascade resulting in peroxidation of lipids and delayed neurologic sequelae in the central nervous system (CNS) (3,4). Morbidity related to CO intoxication is essentially associated with delayed neurocognitive impairment and may be seen at a rate of up to 40% in severely affected
individuals. Severe delayed encephalopathy (LE) and cognitive sequelae are more rare, and were reported at a rate of 0.06%-11% in various series (5,6,7,8). Clinical picture consists of signs and symptoms of CNS impairment a few weeks after recovery from acute intoxication. While the pathophysiology is not completely clear yet, the underlying pathological lesion is believed to be the diffuse demyelination of the cerebral white matter (8).

In this article, we present a case of delayed encephalopathy developing after initial stabilization with magnetic resonance imaging (MRI), where hyperbaric oxygen therapy was administered following acute CO intoxication, as well as reviewing delayed neurological syndrome and hyperbaric oxygen therapy in the context of this case.

Case

A female patient of 35 years was brought to the emergency room 10 days after being found unconscious in the bathroom. Her arterial blood pressure was 110/60 mmHg, pulse rate was 128/minute, and respiratory rate was 30/minute at the emergency room. The patient’s spatial, temporal and personal orientation was not well, and was initially diagnosed with intoxication from a malfunctioning water heater; her level of COHb measured with CO-oxymetry was found to be 27%. She was reported to be a non-smoker. Her arterial blood gases PO2 and PH were within normal range. There was no pathology in the ECG and cardiac biomarkers, and a brain CT scan could not be performed due to the patient’s agitated status. CO intoxication was suspected and 100% O2 was administered via mask; the patient was discharged from the emergency room as her impaired consciousness improved almost completely within approximately 10-12 hours. Twelve (12) sessions of hyperbaric oxygen therapy was administered twice a day during the 6 days following her discharge, starting approximately 12 hours after the intoxication. After interrupting treatment for 2 days due to a holiday, she had to return to the emergency room with symptoms including headache, nausea, vomiting, forgetfulness, and abnormal behaviour. Her initial examination in the emergency room showed spatial – temporal disorientation, restriction in cooperation, and apathy. Her fundoscopic examination was normal. She was found to have mild parkinsonian signs including hypomimia, bradykinesia and mild decrease in associated movements. There was no pathology in other neurologic examination findings and CT scan. The cerebrospinal fluid, routine biochemical values, and viral - bacteriologic serology (HIV, hepatitis, Lyme disease etc) were within normal range. The patient was hospitalized with a preliminary diagnosis of encephalopathy. There was no pathology suggesting encephalopathy in the vasculitis markers, thyroid function tests and metabolic values. There was mild diffuse slowing in the electroencephalogram (EEG). Cranial MRG showed hyperintense lesions with no uptake of contrast material in the FLAIR and T2A sections in both caudate nuclei and globus pallidus (Figures 1A-1B). Images consistent with diffusion restriction and vasogenic edema were seen in the same areas in diffusion-weighted imaging and apparent diffusion coefficient map sequences (Figures 2A-2B). The patient scored 46/59 in the short cognitive examination (SCE) test (Kayatekin 1985). There was no frontal dysfunction. Following clinical and ancillary assessments the patient was diagnosed with delayed CO encephalopathy, and continued her current hyperbaric oxygen therapy twice a day, for a total of 50 sessions. EEG findings had completely improved at the 3 month follow-up, and scored 52/59 in the SCE test. She was observed to have difficulty with the questions related to permanent memory. At the six month follow-up short cognitive examination and the verbal memory, visual memory test, naming test, clock drawing test, verbal fluency tests, stroop test, luria series, graphomotor series, and the test battery assessing functional activities were performed for a detailed evaluation of the patient’s cognitive functions, and her performance was found to be normal.

Discussion

Acute carbon monoxide intoxication is diagnosed by suggestive history, physical examination and accompanying elevation of COHb level following CO-oxymetry measurement of venous blood sample (1,2). Standard pulse oxymetry is not helpful in assessment because carboxyhemoglobin cannot be distinguished from oxyhemoglobin. PO2 value provides the O2 value that is soluble in blood and this is not affected by CO9. Similar to our case, PO2 tends to be normal. The O2 binding to hemoglobin is clearly low in the presence of COHb. COHb baseline values are 10-15% in smokers and 3% in non-smokers, and any value above these levels suggests intoxication. COHb level is not exactly in correlation with the degree of intoxication and is not predictive for the development of delayed encephalopathy (1,2). The COHb level in our case was found to be above normal in the acute stage, and her history and clinical examination supported the diagnosis of acute CO intoxication at her initial presentation to the emergency room.

CO may cause injury in numerous organs, especially the central nervous system and cardiovascular system, which use a high amount of oxygen. CO intoxication causes nonspecific symptoms including headache, irritability, visual impairment, dizziness, nausea and vomiting. These are usually accompanied by mental impairment varying from mild confusion to coma. Cardiovascular and metabolic complications including seizures, syncope, coma, myocardial ischemia, ventricular arrhythmia, pulmonary edema, and lactic acidosis are seen in severe CO toxicity. Acut myocardial damage is found to determine mortality in long-term follow-up.2 Cognitive disorders such as impairment in memory, attention, visual – spatial abilities and operational functions, dementia, apraxia, mood disorders, and personality changes can be seen following CO intoxication.
Our patient developed mental confusion during the acute CO intoxication stage, but there were no cardiac complaints or findings.

CO rapidly diffuses in the pulmonary capillary membrane. Its affinity to the iron in "hem" is 240-fold higher than that of oxygen. Once CO binds to hemoglobin, there is a decrease in the ability of binding sites carrying oxygen to peripheral tissues. This causes a left shift in the oxyhemoglobin dissociation curve and impairs delivery of oxygen in tissues. CO also affects peripheral oxygen utilization. Ten to 15% of CO is extravascular, and affects oxidative phosphorylation at the mitochondria level by binding to molecules including myoglobin, cytochromes, NADPH reductase. The half-life of this binding is longer than that of COHb. This effect outside the hemoglobin is shown mostly in the heart. Moreover, it can impair peripheral oxygen utilization by inactivating cytochrome oxydase (3,4).

CO intoxication causes neuropathological changes through other biochemical mechanisms. Suggested mechanisms include cellular hypoxia resulting from various intracellular proteins binding to CO, neurotoxicity through hypersecretion of excitatory amino acids such as glutamate, neutrophil activation as a result of lipid peroxidation, endothelial accumulation of peroxynitrates causing damage in the blood vessel endothelium, and apoptosis or programmed cellular death (10,11,12,13,14,15).

Delayed encephalopathy is a clinical condition characterized by cognitive impairment of varying degrees, personality change, movement disorders and focal neurologic findings developing a few weeks after the initial improvement period in individuals severely exposed to CO. The interval varies between 3 days and 240 days (mean 20 days). Most frequent symptoms are mental impairment, incontinence, parkinsonism, gait disorder and mutism. Sequelae findings may persist for a year or even longer (5,6,7,8). Most cases have a history of loss of consciousness during the acute intoxication. Development of delayed encephalopathy is not directly proportional to the COHb level (16). Our patient was thought to have delayed encephalopathy resulting from CO intoxication due to her complete initial improvement after the CO intoxication, readmittance to the emergency room 10 days later with encephalopathy and mild parkinsonism, and after excluding other causes of encephalopathy.

![Figure 1a-b](image1.png) Hyperintense lesions in both the caudate nuclei and globus pallidus, in FLAIR and T2A sections.

![Figure 2a-b](image2.png) Diffusion restriction and vasogenic edema in both caudate nuclei and globus pallidus in the DWI and ADC sequences.
Hemorrhagic infarct of the globus pallidus and deep white matter involvement have been reported following acute CO intoxication, albeit rarely (17). Findings of delayed encephalopathy resulting from CO intoxication were well defined with conventional MRI (2,8,18,19,20). T2-weighted imaging typically shows bilateral symmetric, high signal intensity in the basal ganglia, as well as the periventricular deep white matter and the semi-oval centrum. Our patient had hyperintense lesions in the T2-weighted sequences in both caudate nuclei and globus pallidus, as well as diffusion restriction in these lesions. Literature suggests that mechanisms such as cytotoxic / vasogenic edema secondary to acute myelinopathy and cellular energy deficiency or the accumulation of toxic biochemical products may be responsible for late-onset diffusion restriction (8,20). Diffusion restriction consistent with vasogenic edema was found in our patient in the DWI and ADC sequences.

In the retrospective examination of 198 patients developing delayed encephalopathy, 15% of the patients were reported to have basal ganglion involvement, %70 subcortical white matter involvement, whereas 12.6% of the patients had both lesions and 2.1% had no lesions. There was basal ganglion involvement in our case, but no white matter lesions. The period between the onset of the condition and the initial improvement varied between 7 and 44 days, 21 with an average of 21 days. This period is shorter (10 days) in our case. Absence of white matter involvement, presence of lesions in only the basal ganglia and the short period between the onset and initial improvement are notable features in our case. There are reports in literature, similar to our case, of delayed encephalopathy cases with a short interval, subacute onset and no white matter lesions (22).

Basal ganglion lesions can also be seen in CO intoxication. Literature suggests that the basal ganglion lesions encountered after CO intoxication are seen not only in the group developing delayed encephalopathy, but also in the group not developing delayed encephalopathy (23). Presence of basal ganglion lesions in our patient in addition to impairment in consciousness following an interval, supports the delayed encephalopathy diagnosis.

Impairment of oxygen distribution and usage may not be responsible in delayed encephalopathy as in DE. Based on MRI findings, it is thought that the underlying pathological lesion is the diffuse demyelination in cerebral white matter. However, the mechanism of DE is not yet fully explained. Some of the proposed theories are the direct toxic effect of CO, cerebral blood vessel damage, cerebral edema and hypersensitivity reaction (11,12,13,14,15). Lipid peroxidation caused by toxic oxygen molecules due to xanthine oxidase is also believed to be a potential cause. Xanthine oxidase is manufactured in situ from xanthine dehydrogenase by enzymes released from white blood cells adhering to damaged endothelial cells (2,11,12,13,14,15). Events analogue to ischemia – reperfusion damage in the improvement process following CO acute intoxication and exposure to hyperoxia are suggested to increase the initial oxidative damage (2).

HBO therapy is among the treatment steps of CO intoxication, providing 100% O2 inhalation in supraphysiological pressure, varying severity of toxicity in patients receiving NBO and HBO, delay in treatment, and patients being lost to follow-up (27).
The prognosis of delayed encephalopathy due to CO intoxication is relatively well. One clinical study reports the improvement rate in patients at 1 year as 75%. However, sequelae including mild memory impairment and parkinsonism may persist. Levodopa and anticholinergic drugs are shown to be ineffective in parkinsonian symptom. Our data shows clearly that HBO has a role in the treatment of acute intoxication, whereas its neuroprotective role is controversial. If events analogue to ischemia – reperfusion damage are indeed involved in the pathogenesis, hyperoxemia may even be potentially harmful. We may talk about the positive effect of the HBO therapy, considering DE development when HBO therapy was interrupted, and the rapid improvement period when sessions were resumed; if there was no benefit worsening in neurological sequelae would be expected. HBO could also be limiting the DE clinical syndrome, considering the good prognosis in spite of DE development following adequate HBO therapy. However, randomized prospective studies are needed for a definitive conclusion on the role of HBO in the development and treatment of DE.

References