LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Complications of Carbon Monoxide Poisoning: A Case Discussion and Review of the Literature

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Have you ever wondered whether you could make the diagnosis of carbon monoxide (CO) poisoning? Have you ever wondered how you should best treat the signs and symptoms of CO poisoning? Have you ever wondered whether there would be long-term consequences of CO poisoning and how they could be treated? If you have, then the following case vignette and review of the literature should serve to highlight aspects of CO poisoning and its complications.

Case Vignette

Ms. A, a 57-year-old woman with a history notable for alcoholism and depression, attempted suicide by ingesting a large amount of alcohol and medications, then lying down in a bathtub next to a pan of lit charcoal briquettes in a closed room. Police found her some hours later after her therapist called 911 when Ms. A failed to show for a regularly scheduled appointment. She was rushed to a nearby city hospital. On arrival, her vital signs were stable, but she was obtunded; her CO level was elevated (31.7%; normal, < 5%). Quetiapine, zolpidem, oxycodone, and citalopram were present in her serum. She was intubated for airway protection and was transferred to a large general hospital, where she received 1 hyperbaric oxygen (HBO_2) treatment at a pressure of 3.0 atm for 90 minutes. Her CO level after HBO_2 therapy was 7.3%. She was admitted to the medical intensive care unit, where she was treated for an aspiration pneumonia (with intravenous antibiotics), and she was extubated.

Her mental status examination was notable for profound psychomotor retardation, hypophonia, and prolonged speech latency. While lying on the bed (hugging a pillow and curled into a fetal position), she exhibited athetoid movements of her trunk, feet, and hands. Her eye contact was poor, her affect was flat, and she manifested word-finding difficulty. She endorsed poor sleep, a lack of interests, feelings of guilt, low energy, poor concentration, lethargy, and a continued desire to end her life. The next week in the general hospital she received antibiotics (for aspiration pneumonia) and hydration for mild rhabdomyolysis. A brain magnetic resonance imaging (MRI) scan revealed a focus in the right globus pallidus consistent with a subacute stroke and no other abnormalities. She was transferred to the inpatient psychiatric unit for further treatment of her depression and thoughts of suicide.

Screening neuropsychological tests to assess cognitive deficits included a 100-point Mental Status Examination; her score (97 of 100) was not indicative of gross cognitive impairment. Her score on a test of

working memory, the Wechsler Memory Scale Digit Span subtest, was in the normal range, and she reported no subjective cognitive dysfunction. Her psychological evaluation revealed that she was socially detached and had difficulty asserting herself and reaching out to others in times of distress, with no evidence of thought disorder or personality pathology. After 1 week, she was discharged from the unit to a residential program.

Three days after discharge, Ms. A grew more withdrawn, became less communicative, and developed odd, stereotyped movements (such as holding a sock in the air for minutes at a time and slowly crossing and uncrossing her legs). She was admitted to a second inpatient psychiatric unit for depression with catatonic features. Results of screening laboratory tests, a chest x-ray, and an electrocardiogram, as well as her vital signs, were all unremarkable. However, she displayed bizarre posturing and waxy flexibility, frequently grimaced, was mute, had urinary and fecal incontinence, and was resistant to passive movement. She also manifested periodic nonpurposeful athetotic movements in her limbs (e.g., repetitive fanning of the fingers). She was abulic and spoke in short phrases (e.g., "This is torture"). Her muscles were not rigid, and there was no evidence of autonomic instability. Her mental status failed to improve with oral or intramuscular lorazepam; a CO-related encephalopathy was considered. Brain MRI demonstrated new diffuse, bifrontal white matter T2 hyperintensities as well as partial necrosis of the right globus pallidus, consistent with anoxic injury due to CO poisoning. An EEG revealed moderate to severe generalized slowing with diffuse sharp elements intermixed, suggestive of moderate to severe cortical dysfunction; no epileptiform activity was observed. A trial of dextroamphetamine (10 mg daily) led to minimal improvement in her affect and ability to engage with others. After a 16-day hospital stay with negligible change in her clinical status, Ms. A was transferred to a rehabilitation hospital for further care.

What Signs and Symptoms Suggest CO Poisoning?

Carbon monoxide poisoning is a common phenomenon. According to a 1991 study by the Centers for Disease Control and Prevention, 56,133 deaths occurred in the United States because of CO poisoning over a 10-year period from 1979 to 1988. Of that number, 25,889 deaths, or approximately 46% of all CO poisonings, were suicides by CO poisoning.[1]

Unfortunately, the symptoms of CO poisoning are subtle and nonspecific. When CO poisoning is mild, it can go unrecognized, as its symptoms can mimic those of other illnesses.[2] As a general rule, as the level of CO in the blood (carboxyhemoglobin [COHgb]) increases, so does the severity of symptoms. However, the ability of CO levels to predict sequelae of CO poisoning is poor. At low levels (COHgb < 25%), headache is the most common symptom, and it may be accompanied by malaise, nausea, and dizziness.[3] At higher levels (COHgb 25%–50%), mental status changes (including confusion), dyspnea, and syncope may occur. Carboxyhemoglobin levels greater than 50% to 60% often lead to myocardial ischemia, ventricular arrhythmias, pulmonary edema, lactic acidosis, hypotension, coma, seizures, and death.[3] Survivors of severe, acute CO poisoning can develop long-term neurologic sequelae (e.g., impairments in memory, concentration, and speech, as well as depression and parkinsonism).[4] These sequelae may arise immediately after CO poisoning or may be delayed (occurring 2–21 days after CO poisoning).[4]

How Does CO Poisoning Cause Damage?

Carbon monoxide absorption in plasma is diffusion-limited and binds 200 to 250 times more avidly to hemoglobin than oxygen, effectively displacing oxygen from heme-binding sites. CO decreases oxygen saturation in dose-dependent fashion and shifts the oxygen dissociation curve to the left, despite a normal partial pressure of oxygen (PO_2). A leftward shift of the oxygen dissociation curve causes decreased binding of oxygen to hemoglobin.

In addition to binding to hemoglobin, 10% to 15% of CO binds to other proteins, particularly myoglobin within cardiac muscle.[5] This binding interferes with oxidative phosphorylation, which is necessary for myocardial contraction, and impairs intracellular mitochondrial cytochrome oxidase function. Chest pain, arrhythmias, hypoperfusion, and myocardial injury/ischemia can occur with moderate exposure.[6] The cardiovascular compensatory mechanisms to maintain O_2 concentration in the brain can be overwhelmed by the hypoxemic hypoxia of CO.[7,8] Nonetheless, the formation of COHgb alone does not account for all the pathophysiologic sequelae. In dog studies, Goldbaum and colleagues[9] found that neither the transfusion of erythrocytes containing 80% COHgb nor the intraperitoneal injection of CO gas produced CO toxicity, even though the serum COHgb level was above 50%. Dogs inhaling CO died within 2 hours, with an average COHgb level of 65%. This difference in effect is thought to be related to the compensatory cerebrovascular vasodilation and increased cardiac output to maintain O_2 delivery to the central nervous system (CNS).[10,11] In addition to cardiovascular hypoperfusion, CNS toxicity also occurs from synergistic effects of COHgb-mediated hypoxic stress and intracellular oxidative disruption.[12]

Multiple hypotheses explain the mechanism by which CO toxicity leads to cerebral injury. There are acute and delayed neuropathologic changes related to direct CO toxicity (i.e., they are independent of hypoxia-induced injury). Animal models and postmortem human studies suggest the following: (1) Neurotoxicity is

secondary to a massive release of excitatory amino acids, particularly glutamate. Glutamate release triggers an ischemic cascade that causes excessive calcium influx, free radical–mediated injury, and inhibition of antioxidant defenses.[12,13] (2) Carbon monoxide activates neutrophils that produce reactive O_2 species and cause brain lipid peroxidation. Peroxidation leads to the degradation of unsaturated fatty acids and the reversible demyelination of CNS lipids.[14,15] (3) Carbon monoxide increases the production and deposition of peroxynitrite (a potent oxidant) within blood vessel endothelium and brain parenchyma, leading to vascular compromise and cell death in neurons and neuronal cell lines.[16] (4) Reoxygenation injury occurs secondary to the production of partially reduced oxygen species, created during HBO_2 treatment. Oxygen species can oxidize essential proteins and nucleic acids, creating injury similar to reperfusion damage.[5]

What Laboratory Tests Confirm the Diagnosis of CO Poisoning, and How Are They Graded?

Acute CO poisoning is suspected on the basis of a history suggestive of CO exposure; neither standard criteria nor laboratory tests make a diagnosis of acute CO poisoning.[4] COHgb levels, measured by CO-oximetry of a blood gas sample, correlate imprecisely with the degree of poisoning and are not accurate predictors of delayed neurologic sequelae. Partial pressure of oxygen measurements tend to be normal because PO_2 reflects O_2 dissolved in the blood, and CO does not affect this measurement. Although some textbooks describe a "cherry red" appearance of the lips and skin as indicative of CO poisoning, this observation is an insensitive sign.

Carboxyhemoglobin levels above 25% are considered potentially lethal and warrant treatment with HBO_2.

What Are the Initial Treatments for CO Poisoning?

The treatment of CO poisoning rests on the rapid restoration of oxygenation to bodily organs. The elimination half-life of CO is 4 to 5 hours; however, with the administration of 100% O_2 via a tight-fitting face mask at normal atmospheric pressure, the half-life can be reduced to 1 hour.[4] Use of 100% O_2 increases the conversion of COHgb and carboxymyoglobin to hemoglobin and myoglobin, thus increasing the oxygen saturation of the plasma and the end-organs.[17]

Hyperbaric oxygen therapy involves the administration of 100% oxygen in a pressurized chamber. It further hastens the reversal of CO's binding to hemoglobin and to myoglobin and can provide oxygen to tissues independent of hemoglobin.[17] When administered at 2.5 atm absolute pressure, HBO_2 therapy decreases CO's elimination half-life to 20 minutes.[5,18] In addition to restoring tissue oxygenation, HBO_2 therapy appears to improve mitochondrial function, to alter inflammatory responses induced by CO, and to reduce postischemic brain damage in those exposed to CO.[5,17] Although HBO_2 therapy is widely endorsed in the United States as a treatment for patients with severe CO poisoning, its use varies as a result of limited availability, limited evidence that it significantly reduces post-CO neurologic deficits when compared with 100% O_2, and conflicting treatment recommendations and algorithms.[4,19,20] Use of HBO_2 therapy is generally accepted in cases that involve a loss of consciousness and/or a pregnancy.

What Are the Neuropsychiatric Sequelae of CO Poisoning?

Neuropsychiatric sequelae of CO poisoning occur in up to 50% of all patients who sustain toxic levels of CO[21–24]; the prevalence varies based on the criteria used to quantify the severity of the CO poisoning event. For instance, an epidemiologic study of 2360 patients with CO poisoning noted delayed-onset neuropsychological sequelae in only 2.75%, because the vast majority of those patients were not ill enough to require admission to the hospital.[25] Symptoms may arise immediately or follow an asymptomatic period. Lucid intervals of up to 240 days have been observed after CO poisoning, although the mean latency for development of cognitive and behavioral symptoms is 3 weeks.[6,18,25–27] The patient featured in our case (Ms. A) abruptly developed neuropsychological impairment approximately 3 weeks after attempting suicide by CO poisoning, consistent with the literature on the delayed onset of symptoms after CO poisoning.

Unfortunately, studies have not clearly supported a link between the COHgb level and physical symptoms and the subsequent development of long-term neuropsychological sequelae[21,23,24,28]; therefore, all patients with suspected CO poisoning may be at risk and should be treated aggressively—with at least 100% normobaric oxygen or HBO_2 if there is evidence of severe poisoning (metabolic acidosis [pH < 7.1], myocardial ischemia, chest pain, loss of consciousness, or, in pregnant women, a COHgb > 20% or evidence of fetal distress).[4,6] Age above 36 years and a duration of CO exposure longer than 24 hours have been implicated as independent risk factors for cognitive sequelae; patients with these characteristics also warrant aggressive treatment.[28] While the evidence for the benefits of HBO_2 for the prevention of delayed neuropsychiatric sequelae is conflicting,[6] 1 recent randomized controlled trial found that treatment with HBO_2 led to a reduction in cognitive deficits 6 weeks and 1 year after CO poisoning, as compared to treatment with normobaric oxygen.[22]

Neuropsychological deficits and neuroimaging-confirmed lesions after CO poisoning are numerous and diverse; there are no pathognomonic findings.[29] However, observed deficits can be divided into 3 categories:

affective, behavioral (motor), and cognitive, with most patients demonstrating abnormalities in more than 1 area of function.

Up to 30% of patients with CO poisoning exhibit some degree of cognitive decline, ranging from subtle impairments that are only detectable on neuropsychological testing[27] to a decline in gross intellectual function[30] with dementia.[6] Findings commonly observed include disorientation and deficits in attention, concentration, executive function, visuospatial skills, verbal fluency, speed of information processing, and memory.[6,21,23–25,27,29,30] Patients may confabulate in an attempt to hide significant memory problems[29]; impairment in attention and concentration often have profound effects on the ability to learn new tasks.[23,27] In the case presented, neuropsychological testing immediately after CO poisoning was unremarkable, although 3 weeks later, the patient exhibited marked cognitive changes, decreased verbal expression, and an inability to care for herself.

Movement disorders are also well documented, particularly delayed-onset parkinsonian symptoms (including bradykinesia, masked facies, reduced facial expression, rigidity, and shuffling gait).[24–26,31,32] Delayed movement disorders have been noted in 13% of 242 CO-poisoning patients, most frequently with parkinsonism (72%) and dystonia, chorea, and myoclonus.[33] Urinary and fecal incontinence is also a common problem in those who have been severely affected.[6,26,27,29,33] Dopaminergic agents (e.g., levodopa), anticholinergics, and electroconvulsive therapy (ECT) do not ameliorate CO toxicity-associated parkinsonian symptoms, although data supporting these observations are limited.[24,25] Fortunately, the prognosis for recovery from motor symptoms appears good, with 75% of patients resolving their parkinsonism 1 year after its onset.[26] Although several of the motor symptoms featured in the case presentation could be interpreted as parkinsonian (limited facial expression, bradykinesia, unsteady gait), the patient's motor patterns were more consistent with catatonia (e.g., purposeless, repetitive movements with posturing, waxy flexibility, and a resistance to passive movement). Case reports (e.g., that of a 57-year-old man with CO poisoning after a suicide attempt with a constellation of cognitive and motor symptoms) describe symptoms similar to those of Ms. A, including frequent nonpurposeful movements, incontinence, an inability to care for oneself, disorientation, and depressed consciousness; significant improvement is seen with dextroamphetamine (25 mg daily).[29] Finally, obsessions and compulsions, which are very likely secondary to disruption of the cortical-subcortical processing circuits at the level of the basal ganglia, have been reported.[23,34]

Affective disturbances after CO poisoning have been described less often and are difficult to distinguish from premorbid disorders, particularly in cases of suicide attempts by CO poisoning. Personality changes may occur,[6] and case studies have described prominent depression, anxiety, and irritability several years after accidental CO poisoning.[23] Residual cognitive deficits, executive dysfunction, and impairments in memory and concentration may all contribute to deterioration in mood. Conversely, impairment in attention, concentration, and memory may be symptoms of depression and may be falsely attributed to cognitive decline.

Lesions seen on neuroimaging are as varied as the spectrum of clinical signs and symptoms observed after CO poisoning; there are no pathognomonic radiographic changes seen on computed tomography, MRI, magnetic resonance spectroscopy, or single photon emission computed tomography. However, certain brain regions (including the white matter, basal ganglia, hippocampus, thalamus, and Purkinje cells of the cerebellum) appear particularly vulnerable to hypoxic injury.[6,21,24,27,30,31] In particular, the globus pallidus is commonly affected, possibly due to its lying in a "watershed" area between vascular supplies.[6] General findings include petechial hemorrhages of white matter, necrotic lesions, and diffuse low-density lesions throughout the brain.[6,31,32] Similarly, white matter (particularly in subcortical areas, such as the periventricular regions) may be more susceptible to anoxic injury than gray matter, where there is less collateral arterial supply. The anoxic leukoencephalopathy associated with CO poisoning is at least in part due to demyelination and axonal damage[21,24,31,32]; it typically occurs later in the course of CO poisoning than do gray matter lesions[24] and temporally corresponds to the delayed onset of neuropsychiatric symptoms observed in some patients.

Carbon monoxide may also activate neutrophils, leading to delayed (but reversible) demyelination seen as white matter hyperintensities on MRI scans.[27] Finally, CO may have a direct cytotoxic effect on vulnerable brain regions by inducing lipid peroxidation.[27] Gale and colleagues[35] suggested significant relationships between the results of imaging techniques and neuropsychological impairments of attention, memory, executive function, and processing speed. Interestingly, lesions of the globus pallidus and other basal ganglia structures have not been definitively linked to movement disorders,[21,25,26,31,32,36] although there have been some reports of an association between white matter hyperintensities, parkinsonism,[32,37] and cognitive impairment.[21] In addition to lesions in particular areas of the brain, global atrophy has also been observed after CO poisoning.[31,35]

What Type of Follow-Up Testing Should Be Done After CO Poisoning?

Messier and colleagues[38] developed the Carbon Monoxide Neuropsychological Screening Battery (CONSB) to use in emergency settings as a potential indirect

assessment of cerebral involvement in CO-poisoned patients during and after treatment with HBO_2. They performed case-control testing to delineate disruption in short term memory, concentration, visuospatial ability, construction apraxia, aphasia, dyscalculia, and agnosias in patients with CO-induced cerebral impairment. Statistically significant differences ($p < .05$) were observed between pretreatment and posttreatment testing, with improvement in all domains after treatment. Posttreatment scores can be used for comparative data if late sequelae of CO poisoning occur.

Guidelines for follow-up of neuropsychiatric symptoms of CO poisoning are lacking. In 75% to 100% of cases, symptoms resolve.[4]

When Is HBO_2 Therapy No Longer Necessary After CO Poisoning?

Unfortunately, there is no consensus regarding a standard protocol for HBO_2 therapy in CO poisoning. Although the ability of serial COHgb levels to predict morbidity, mortality, or outcome is poor, COHgb levels are frequently used to decide whether to initiate HBO_2 therapy. The COHgb threshold used to initiate treatment at an HBO_2 treatment center in the United States ranges between 5% and 40%; however, a COHgb saturation level of 25% is most commonly used. Other recommended criteria for initiating HBO_2 therapy include loss of consciousness, neurologic symptoms, cardiovascular dysfunction, or metabolic acidosis.[4] An initial HBO_2 treatment recommended by the Undersea and Hyperbaric Medicine Society consists of using 100% O_2 administered in a chamber pressurized to 2.5 to 3 atm.[20] A randomized study of 30 patients comparing those treated with HBO_2 at 2.4 atm for 90 minutes versus 3.0 atm found no significant difference in immediate and delayed neurocognitive testing.[39]

In addition, there are no reliable criteria to decide when HBO_2 therapy is no longer necessary once it has been initiated. In a 2001 survey of 204 hyperbaric oxygen treatment centers around the United States, only 46 facilities (23%) automatically gave more than 1 HBO_2 treatment per CO-poisoned patient.[40] Among those that did, 20 facilities (10%) gave 3 treatments per patient. Conversely, 136 (67%) sometimes gave more than 1 treatment, and 12 facilities (6%) gave only 1. Thus, there is considerable variability in the number of HBO_2 treatments given after CO poisoning. Consideration for further treatments often relies on persistent signs or symptoms of CO poisoning (e.g., loss of consciousness). There is no evidence that continued elevation of CO level (i.e., > 5%) in the absence of continued symptoms necessitates further treatment.

Consideration of extended HBO_2 therapy should take into account the adverse effects of HBO_2 (e.g., inner-ear barotraumas, anxiety, oxygen toxicity, pulmonary edema and hemorrhage, tension pneumothorax, decompression sickness, nitrogen emboli, and the risk of seizure). The one absolute contraindication to HBO_2 treatment is an untreated pneumothorax. Relative contraindications to HBO_2 include claustrophobia, otosclerosis, bowel obstruction, chronic obstructive pulmonary disease, and need for care that is not suitable for a hyperbaric chamber.[20,41] A study of 626 patients receiving HBO_2 therapy for post-operative ileus found an adverse event rate of 3.8%; most of these events were not serious.[42]

The cost-effectiveness of HBO_2 versus normobaric oxygen has not been studied. HBO_2 treatments range in cost anywhere from $100 to over $1000 for a single treatment.[43]

Conclusion

Timely diagnosis and effective treatment can improve outcomes for patients with CO poisoning and its complications. Primary care physicians should be knowledgeable about the signs and symptoms of CO poisoning and its dread complications to facilitate appropriate treatment.

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