CARBON MONOXIDE:
IDENTIFICATION OF DELAYED SEQUELAE AND OCCULT EXPOSURE

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Carbon monoxide is one of the most common causes of poisoning in the United States and other industrialized nations. There is significant morbidity and mortality associated with carbon monoxide poisoning. Sources of carbon monoxide include automobile exhaust, defective domestic heating and cooking appliances, industrial plant exhausts, mining accident, fires, and the conversion of methylene chloride to carbon monoxide in the body of an exposed individual.

Many primary care physicians are not familiar with the delayed or chronic symptoms of carbon monoxide poisoning, do not appreciate the underlying pathophysiology, and take too much comfort from low carboxyhemoglobin levels. Quite often they are not aggressive in their referral of patients for hyperbaric oxygen therapy.

Bartlett gives excellent examples of patients that can easily be missed: the patient complaining of "stress headaches" that are associated with work, or the patient who gives a history of chronic angina which is suddenly worse for no apparent reason. How about the intoxicated patient who was found passed out in a parked car several hours ago and still cannot be aroused in spite of a low blood alcohol level? Then there is the family of four returning to the E R for the second visit in a month complaining of the "flu" which they describe as myalgias, headache, vomiting, and malaise. They mention that several other families in the same apartment complex have the same type of "flu." The CH2OPD2 mnemonic (Community, Home, Hobbies, Occupation, Personal habits, Diet and Drugs), a history-taking tool, can help identify patients at risk for CO poisoning.

It has been known for decades that ***death from CO poisoning is due to hypoxia resulting from displacement of oxygen from the hemoglobin molecule.*** Among the survivors, 2.8% to 14% experience acute neurological impairment and anywhere from 12 to 20% will develop delayed neurological impairment.

Animal studies have suggested that the high clinical incidence of neurological deterioration after CO poisoning may be related to the propensity for CO to cause both a hypoxic insult as a result of carboxyhemoglobin (COHb) formation, and an ischemic insult due to a compromised cardiovascular status. Vasodilation occurs with CO exposure due to local tissue responses to hypoxia (lactic acidosis), direct activation of vascular smooth muscle guanylate cyclase, and possibly by inhibition of a cytochrome P450 hemoprotein involved with formation of the vasoconstrictor endothelin.

CO is known to bind to various O_2-carrying hemeproteins (hemoglobin, myoglobin, cytochrome-C oxidase, and cytochrome P-450). As a result, less O_2 is available to the tissues, creating a hypoxic environment. The hypoxia and the CO-bound cytochrome-C oxidase adversely affect cerebral energy metabolism, and oxidative stress is precipitated. This may cause primary neuronal cell membrane injury. In addition to cytochrome oxidase blockade, another mechanism for mitochondrial dysfunction may be related to free radical generation by platelets, in conjunction with the simultaneous release of nitric oxide (NO) by platelets. In the presence of free radicals, nitric oxide is converted to peroxynitrite which has a high affinity for heme proteins such as cytochrome oxidase. Peroxynitrite has been shown to inactivate mitochondrial enzymes and impair electron transport.

An ischemic reperfusion reaction has been found to occur in carbon monoxide poisoning which leads to cell wall lipid peroxidation and neuronal injury. The resulting free radicals perpetuate further injury and continued recruitment of polymorphonuclear leukocytes, resulting in brain lipid peroxidation which accumulates over time, producing the symptoms of delayed neurological sequel.

The structural changes within the brain involve the basal ganglia, cerebral cortical and subcortical white matter, hippocampus, loss of gray-white differentiation, and generalized edema. The vulnerability of white matter changes in addition to the hypodense pattern in the globus pallidus has also been demonstrated.

DIAGNOSIS OF CARBON MONOXIDE POISONING

The history of exposure and/or the initial presenting symptoms should lead to the strong suspicion of CO poisoning. The levels of COHb frequently do not correspond to the signs and symptoms found in the patient. The recent literature states that there is no correlation between COHb levels and the risk for subsequent morbidity. Research has documented that the COHb levels are variable and not reliable if low or normal.

A high clinical risk has been correlated with a history of unconsciousness from a suspected CO exposure, a history of a prolonged exposure (soak) of greater than one hour, pre-existing cardiovascular disease, age greater than 60 years, and pregnancy, due to higher fetal risk.

CO causes multiple neurological sequelae, and the exact nature and extent of symptoms vary significantly from person to person. Some victims show selective changes in personality and cognition. These changes may result in a victim denying any problem at the time of evaluation. As a result, misdiagnosing CO poisoning is common in the initial evaluation and management of the CO. Other diagnostic considerations include psychiatric illness, migraine headaches, stroke, acute alcohol intoxication, heart disease, flu, or even food poisoning.

CHRONIC CARBON MONOXIDE POISONING

Occult, or chronic carbon monoxide

poisoning may present with less characteristic symptoms than acute poisoning, and patients may initially be misdiagnosed. Chronic CO poisoning involves exposure to lower levels of carbon monoxide for many days, weeks or even months. The boundary between acute and chronic exposure, according to Cherry, is indistinct (acute: one exposure lasting less than 24 hours; chronic: exposures lasting 24 hours or more). The effects of longer lower level poisoning can be just as debilitating as more acute poisoning.

Chronic symptoms may present as a flu-like illness, headaches, tearfulness, depression, agitation, anxiety, decreased memory, attentional and concentration skills, poor reasoning skills, irritability, euphoria, and overall personality changes. Fatigue, headache and dizziness are the three most common symptoms.

Studies have shown that the most frequent sources of CO in chronic poisoning are furnaces, automobiles, and water heaters. Other sources include wood stoves, chimneys, and boats.

Chronic CO poisoning is more difficult to diagnose because the effects of exposure are often subtle and difficult to recognize. The fact that there even was a CO exposure frequently takes a while to be recognized. A malfunctioning furnace or water heater may not be discovered until servicemen are called, and a leaky car muffler may not be noted until the car is taken in for a tune-up. COHb levels are usually normal in chronic exposures, as are MRI and SPECT scans. The most useful tool in diagnosing chronic CO poisoning is neuropsychological testing.

One should have an elevated index of suspicion when patients complain of persistent lethargy and headaches. Also, the patient who presents with a long-standing "flu-like" illness should arouse suspicion. Other clues include multiple similar cases from the same location, or families that also have sick pets. Symptoms which improve away from the site of exposure (work, car, etc), should make one think of CO poisoning. Finally if the patient reports having discovered a faulty furnace, water heater, muffler, etc., one has the diagnosis handed to them.

Due to the nonspecific symptoms that can occur from chronic exposure, patients are frequently misdiagnosed as having such conditions as chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia, malingering, anxiety and depression.

Testing for the chronically exposed patient is difficult, as the COHb level will almost always be low or normal due to the intermittent exposure to carbon monoxide. Neuroimaging should be considered, as MRI, CT scanning and SPECT scan may demonstrate abnormalities. It has been noted by many investigators that the presence of a normal CT or MRI, especially early in the presentation, may not rule out CO poisoning. Psychometric testing may well be the "gold standard" for the diagnosis of chronic CO poisoning.

It is important to think of chronic CO exposure when patients present with multiple vague symptoms because they can be treated with hyperbaric oxygen, and as long as the source of the CO exposure can be eliminated, they can be significantly improved. We have successfully treated at least a half dozen patients with chronic CO poisoning who have done quite well. Our patients are evaluated with a detailed history, physical exam, appropriate lab work, and neuroimaging and neuropsychological testing. COHb levels are not routinely ordered, as they are invariably low and of no clinical significance. We treat at 2.0 ATA for 90 minutes, usually for 10 treatments, followed by neuropsychological reevaluation. If this is abnormal but improving, we will treat with another 5 or 10 treatments, either until there is no change, or the results are back to normal.

CLINICAL EXAMPLES

A 40 year-old executive secretary who began noticing that she was having some difficulty with spelling and memory at work, and needed to have a colleague check her work. She also started having unusual headaches, and couldn't remember the right exit off the freeway for her children's soccer practice. She happened to have her car checked, and the mechanic found a hole where the muffler attached to the engine. The auto club checked her car for CO with the engine running, and told her that because there was such a significant CO level, she shouldn't drive the car until it was fixed.

She presented to the ER with the complaint of CO poisoning. The ER doctor ran a COHb level, which was normal, and told her that she didn't have CO poisoning. He diagnosed her as having the flu. Fortunately she referred herself to the hyperbaric unit. She was referred for neuropsychological testing, which revealed classic changes found with carbon monoxide poisoning. She also had an MRI of the brain and an EKG, both of which were normal. She was treated for 10 sessions at 2.0 ATA

for 90 minutes. She felt normal after her treatments, and her neuropsychological exam returned to normal. She has been followed for over 10 years now, and remains asymptomatic.

DELAYED NEUROPSYCHOLOGIC SEQUELAE

As previously noted, the syndrome of Delayed Neuropsychologic Sequelae (DNS) occurs in a significant number of patients who survive acute CO poisoning. This occurs from 3 days to 8 months after the initial insult. Typically, after a lucid period, the development of DNS is sudden, with rapid deterioration over a few days. Neurologic symptoms and findings are myriad and include: impaired cognition, memory dysfunction, vertigo, ataxia, parkinsonism, muscle rigidity, gait disturbance, disorientation, mutism, urinary incontinence, fecal incontinence, cortical blindness, hearing loss, tinnitus, nystagmus, seizures, coma, electroencephalographic abnormalities, cerebral edema, leukoencephalopathy, diabetes insipidus and globus pallidus necrosis. The following psychiatric presentations have also been noted: personality changes, depression, flattened affect. Tourette's syndrome, anxiety, and poor impulse control.

While it may not be possible to accurately predict which patients are likely to develop DNS, advanced age, a prolonged "soak" with elevated lactic acid levels, syncope and transient hypotension all appear to be risk factors. Hypoxia alone is insufficient to explain the clinical manifestations. However, there appears to be no question of the vascular nature of CO-mediated neuropathology. This is confirmed by perfusion abnormalities of both the frontal and temporal lobes found on SPECT and MRI scans. Of interest as well are white matter hyperintensities noted on MRI scans, felt to be indicative of small vessel disease, which seem to correlate with cognitive sequelae. Lastly, the syndrome of DNS appears to be a consequence of a cascade of events involving oxidative stress and inflammatory responses.

While there is a relative paucity of controlled clinical studies in the medical literature, it appears that the timely treatment of acute CO poisoning with hyperbaric oxygen may decrease the incidence and severity of DNS. The use of multiple treatments is also associated with a positive outcome. In spite of the fact that up to 75% of patients with DNS may have a complete recovery within one year, recent information from the neuropsychological literature suggests that there may be residual undetected cognitive dysfunction. Some experts maintain that normal neuropsychologic and functional outcomes are possible after severe acute CO poisoning without the use of hyperbaric oxygen.

The role of hyperbaric oxygen in patients with established DNS is uncertain. This is an area that bears further attention and study. In the meantime, given its relative safety, and the debilitating nature of DNS, we advocate treating these patients with protocols similar to those used in chronic CO poisoning.

There continue to be great strides in understanding the pathophysiology of CO poisoning. Therein may lie some potential new treatment modalities. For example, given the fact that CO can form ligands with iron and copper sites, the potential for metabolic intervention is likely. Also, considering the role that oxidative stress plays, the use of antioxidants may play a significant role in the future. In the meantime, continued emphasis needs to be placed on prevention, early recognition and expeditious treatment.

NEUROPSYCHOLOGICAL ASSESSMENT

Neuropsychologists are increasingly involved in the assessment of patients reporting persistent neurologic sequellae (PNS) or delayed neuropsychologic sequellae (DNS). The need for research in determining the specific neurological impairments of CO poisoning has also increased. These findings are valuable in helping the team identify treatment goals and objectives and to document the recovery process of the individual. It has been suggested that the neuropsychological assessment procedure may help to provide a more cost-effective use of treatment resources in the rehabilitation of the injured individual.

Individuals exposed to CO are administered test batteries to determine the extent of brain behavior dysfunction and to tease out the negative effects of depression and anxiety on cognitive functioning levels. This testing is noninvasive and offers another means to assess the integrity of the central nervous system objectively through indirect measures of brain levels. Domains that are typically assessed include intellectual levels, attentional and concentrational levels, language skills, motor skills, sensory skills, constructional skills, visual perceptual skills, verbal and visual learning and memory skills, planning and organizational skills, conceptual flexibility levels, abstract reasoning skills, selective achievement levels, and social-emotional levels.

Patients who have persistent or chronic cognitive and psychological sequel will typically present with symptoms of depression, tearfulness, agitation, anxiety, decreased memory, attentional and concentrational skills, poor reasoning skills, irritability, low frustration tolerance, euphoria and overall personality changes. Those individuals with features of delayed sequel involve apathy, depression, dementia, disorientation, irritability, distractibility, emotional lability, impulsiveness, abnormal neurological signs, cognitive and executive function deficits. It is not known who is more prone to developing this latter syndrome, although it is widely accepted in the literature that this syndrome seems to occur in those patients with a positive history of neurological illness. Thus, the neuropsychological deficits associated with CO poisoning are highly variable.

Recent studies have documented that subtle but significant declines in cognitive performance, i.e., memory changes, may occur after assumed recovery from the major impairments. Patients may appear normal in daily functioning but may experience hardship on daily living tasks tapping their deficits. The presence of depression and anxiety may also further exacerbate cognitive compromises. It is for these reasons that neuropsychological testing is requested as part of the diagnostic workup to identify neurocognitive changes that cannot be predicted by neuroimaging studies alone. Thus, long term follow-up through the use of neuroimaging and

neurocognitive assessment is critical to identify any changes in the recovery or delayed effects following CO exposure.

The following brief case study examines, through neuropsychological and neuroimaging data over a time span of three years, the variable course of CO pathology in a 38-year-old male. This individual sustained loss of consciousness after exposure to CO vapors from an oil well. He received immediate medical and neuropsychological follow-up care along with rehabilitation. Neuropsychological examinations revealed diffuse brain-behavior involvement, with specific deficits across areas of motor skills, language skills, "executive" skills, fine motor integration skills, the learning and recall of verbal material, and positive features of depression. Neuroimaging procedures documented selective changes. This patient was treated in the hyperbaric unit for 27 treatments, with the patient improving over time based on clinical interviews, interviews with the treaters, neuropsychological test data, and neuroimaging data. Apparent recovery was documented. However, the patient began to complain of difficulties three years post-insult. Neuropsychological studies revealed no social-emotional involvement. However, deficits across areas of attentional and concentrational skills and selective "executive" levels were again documented. A serial SPECT scan demonstrated no significant findings. Despite these latter negative results, the neuropsychological examination documented delayed exposure effects, which could not be attributed to social-emotional involvement. Thus, this case study demonstrates that patients with high-level exposure to carbon monoxide and report of changes should be monitored across time to identify any changes across physical, cognitive, and social emotional functioning levels.

The neuropsychologist's role within the multidisciplinary context of the hyperbaric team can contribute to answering a variety of concerns. These then involve differential diagnosis, objective diagnostic assessments of the levels of cognitive compromise and strengths as well as the formulation of baseline measurements of brain-behavior levels from which improvement or deterioration can be accurately measured. It is this last area that is of particular interest to the hyperbaric team in assessing the rate and degree of cognitive recovery across hyperbaric treatments. The examination findings also provide vital information about an individual's strengths and weaknesses necessary for formulating treatment interventions. Clinical intervention and treatment strategies will be dependent on the individual's neurocognitive profile.

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