Neurobehavioral aspects of the delayed encephalopathy of carbon monoxide intoxication: case report and review

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We report the neurobehavioral aspects of the delayed encephalopathy of carbon monoxide (CO) intoxication in a 29 year old woman and review the literature. Four weeks after CO poisoning, the patient developed a frontal lobe syndrome, visuoperceptual impairment, and diffuse white matter lesions with an otherwise normal neurological examination. In contrast, patients with the classical syndrome also have a parkinsonian state or an akinetic–mute state. The delayed encephalopathy of CO poisoning usually results from demyelination of subcortical white matter, necrosis of the globus pallidus, or both. The clinical aspects, risk factors, neurobiological features, and therapy and prognosis are discussed.

Keywords: Carbon monoxide – Demyelination

INTRODUCTION

Carbon monoxide (CO) is a powerful toxin. CO is a colorless, tasteless gas produced in large amounts by automobile exhausts, inadequately vented furnaces and other heating equipment, fires, and methylene chloride from paint removers (Ellenhorn and Barceloux, 1988). Although the concentration of CO in the atmosphere is only about 0.1 p.p.m., these sources can increase the atmospheric CO over 1000%. Moreover, hemoglobin binds CO over 200 times more readily than it binds oxygen. It is not surprising that CO is a common cause of poisoning.

In addition to the effects of acute intoxication, a delayed encephalopathy may follow recovery from CO poisoning. After a lucid interval of 3 days to 6 weeks, up to 40% of survivors develop a neurobehavioral syndrome characterized by personality and cognitive changes, movement disorders, diffuse white matter changes, and lesions of the globus pallidus (Choi, 1983; Myers *et al.*, 1985). Clinicians may miss or misdiagnose this syndrome, particularly in the absence of known CO exposure. Furthermore, the clinical manifestations of the delayed encephalopathy of CO intoxication are variable and can be limited to an isolated and potentially subtle behavioral disorder (Jefferson, 1976). We review the literature on this syndrome and describe a previously healthy patient

with the delayed encephalopathy of CO presenting as a personality change in the absence of neuromotor findings.

CASE REPORT

A 28 year old woman had a toxic exposure to CO when her furnace malfunctioned. She was found comatose with an initial Glasgow Coma Scale of 3 and an arterial blood CO saturation of 11%. After 90 min of hyperbaric oxygen therapy, her mental status cleared over the next 24 h. Five days after hospitalization, the patient went home fully recovered except for mild residual irritability.

Six weeks later, she was rehospitalized with "confusion". Her family described a personality change which began 4 weeks after recovery from her acute CO intoxication. The patient stopped engaging in her usual activities and would lie in bed unclothed. She would allow her small son to wander unattended and would greet strangers in an undressed state. Previously, she was "strong-willed", "uptight", and "analytical". Subsequently, she became "nonchalant" and "emotionally labile". Furthermore, the patient had trouble finding her way in her surroundings.

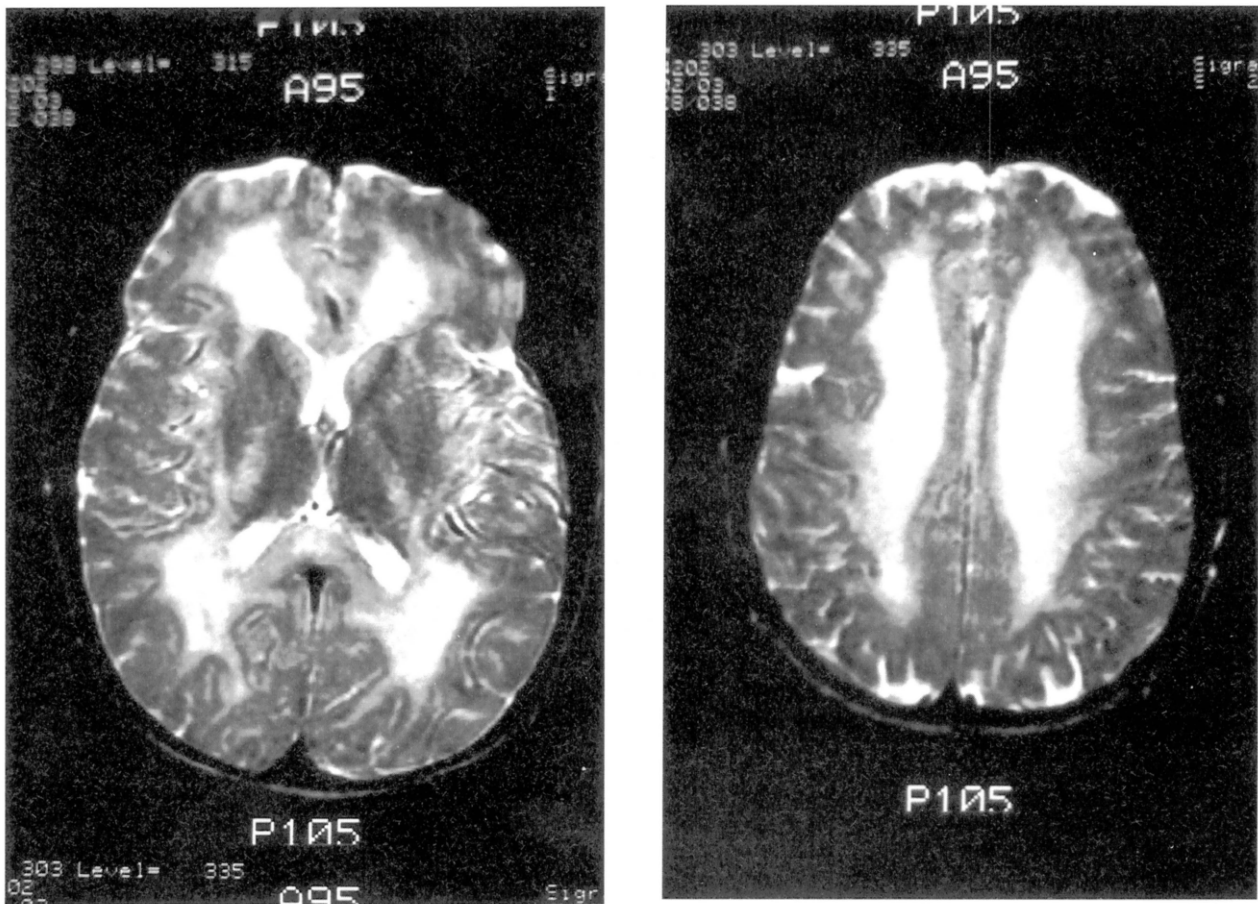On examination, the patient was alert, oriented,

FIG. 1. Magnetic resonance images show extensive, confluent hyperintensities involving cerebral white matter on the long TR sequences. There may be slight involvement of middle cerebellar peduncle and posterior limbs of the internal capsules. The globi pallidi did not appear abnormal.
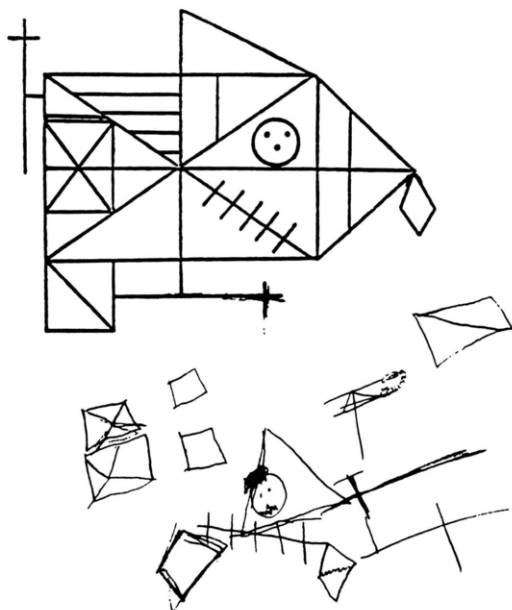

FIG. 2. Rey–Osterrich Complex Figure Copy showing extreme degree of fragmentation of her copy.

and easily engaged in conversation. Her interview was marked by confabulation and a lack of concern for her hospitalized condition or for her son's status. Mental status testing showed an attentive patient with normal language and adequate recent and remote memory, but abnormal visual constructions. The rest of her neurological examination was normal, without rigidity, bradykinesia, gait difficulty, or tremors. Laboratory and electroencephalographic examinations were also normal, but her magnetic resonance imaging (MRI) scan showed diffuse white matter changes (see Fig. 1).

On neuropsychological testing, the patient did well except for frontal executive functions and visuoperceptual abilities. Sustained attention was normal. Her delayed recall was 8 out of 16 words, but she recognized 15 of the words and did satisfactorily on the Logical Memory Test. Her scores on an abbreviated Boston Aphasia Battery and the Boston Naming Test were normal. On measures with a frontal executive component, however, she did very poorly, includ-

ing a Porteus Mazes age of 4 with perseverations and scores of less than the second percentile on the Stroop Color–Word Test. In addition, she was slow in recognizing complex pictures or drawings, and there was a breakdown of her constructions into smaller units (see Fig. 2). Her scores were less than second percentile on the Benton visual tests (Facial Discrimination, Line Orientation, Complex Figure Discrimination).

After an evaluation for rehabilitation, the patient went to a transitional care facility. On repeat neuropsychological testing 4 months after hospitalization, she continued to perform at less than the tenth percentile on the Porteus Mazes, Stroop Color–Word Test, and Benton visuoperceptual tasks. Follow-up MRI imaging at 6 months showed minimal change from her prior scans. At 1 year, her family reported the patient's behavior to be much improved, however, she remained disengaged and disinterested in performing housework or in returning to work.

CLINICAL FEATURES

This patient developed a persistent frontal lobe syndrome, visuoperceptual impairment, and white matter lesions following recovery from acute CO intoxication. Her behavioral change included apathy, disinhibition, confabulation, perseveration, poor judgement, and a dysexecutive syndrome. Similar to prior reports of apperceptive visual agnosia (Benson and Greenberg, 1969; Mendez, 1988), our patient could not immediately derive the global image from pictures or drawings and reverted to a slow, systematic analysis of visual details. She differed from most patients who develop the delayed encephalopathy of CO intoxication in the isolated behavioral presentation and the absence of Parkinsonian features or movement disorders (Choi, 1983; Lee and Marsden, 1994).

The immediate effects of acute CO intoxication are quite varied (Winter and Miller, 1976). Mild CO intoxication is frequently misdiagnosed as a flu-like illness, migraine headache, or other disorder (Barret et al., 1985; Dolan et al., 1987) and can be associated with significant changes on neuropsychological tests (Messier and Myers, 1990). More severe CO exposure results in delirium, coma, or death. After an initial period of unconsciousness, a subgroup of patients develop an apathetic, akinetic–mute state which fails to improve. Among 31 patients with neuropsychiatric sequelae at 1 year, eight (26%) had a progressive course, and these were younger patients with an initial coma of about 2 days (Lee and Marsden, 1994).

The delayed encephalopathy is distinct from these acute CO effects. In the largest reported series of CO intoxication, delayed encephalopathy occurred in 2.8% of 2369 patients and in 11.8% of the 549 patients that were hospitalized (Choi, 1983). The frequency of this complication is probably underreported given that, in the absence of gross deficits, subtle neuropsychiatric changes are usually missed (Smith and Brandon, 1973; Sawa et al., 1981; Myers et al., 1985; Hart et al., 1988). Like our patient, most delayed encephalopathy patients are initially comatose, awaken within 24–48 h, and have a normal lucid interval averaging 2–40 days before they again deteriorate (Choi, 1983; Werner et al., 1985).

Delayed encephalopathy patients may develop apathy and akinetic mutism, irritability and other personality changes, memory difficulty, visuoperceptual problems, and parkinsonism or other movement disorders. Among 65 patients, Choi (1983) described a triad of mental deterioration (98%), gait disturbance (82%), and urinary incontinence (88%). In another series of 15 patients with delayed encephalopathy, mental dysfunction was the most common symptom, including memory difficulty, disorientation, and unspecified "abnormal behavior" (Chang et al., 1992). The mental problems were usually personality changes with apathy or poor impulse control (Smith and Brandon, 1973). Memory difficulty may persist years after the CO intoxication (Shillito et al., 1936; Lacey 1981; Choi 1983), and other patients have various forms of "psychic akinesia" (Lugaresi et al., 1991). There is also a spectrum of visuoperceptual difficulties ranging from cortical blindness to apperceptive visual agnosia to mild residual perceptual deficits (Benson and Greenberg, 1969; Choi, 1983; Mendez, 1988). Most patients with the delayed encephalopathy have a parkinsonian state, but other movement disorders occur such as dystonias, tremors, chorea, myoclonus, and Giles de la Tourette's syndrome (Choi, 1983; Lee and Marsden, 1994). A few patients develop behavioral changes suggestive of the Klüver–Bucy syndrome with hyperoral behavior, a tendency to touch things, hypersexuality, and placidity (Starkstein et al., 1989; Lee and Marsden, 1994). Finally, there are reports of major depression following CO intoxication which may be a direct consequence of the brain disease (Jaeckle and Nasrallah, 1985; Myers et al., 1985; Bruno et al., 1993).

RISK FACTORS

No specific risk factors reliably predict the development of the delayed encephalopathy of CO intoxication. The severity of the initial acute intoxication is the most reliable. An initial comatose state correlates with the subsequent development of delayed encephalopa-

thy and neurobehavioral symptoms, particularly if the coma is prolonged (Smith and Brandon, 1973; Choi, 1983; Min, 1986); however, loss of consciousness is not necessary for developing delayed symptoms. An age greater than 30 years is a second potential risk factor, although this apparent risk may emerge because of a better likelihood that younger people survive the acute intoxication. Third, individual patient susceptibilities are a consideration, such as the increased metabolic activity of children and pregnant women (Lacey, 1981; Seger and Welch, 1994). Fourth, an abnormal neuroimaging study at the time of acute CO poisoning may predict subsequent delayed encephalopathy, particularly with the presence of both white matter and globus pallidus changes (Miura et al, 1985; Lee and Marsden, 1994). The association between specific clinical symptoms and neuroimaging is not robust, and MRI scans may show progressive changes in the absence of clinical symptoms (Bruno et al., 1993). Fifth, carboxyhemoglobin levels do not strongly correlate with either the amount of CO exposure or the risk of developing the delayed encephalopathy (Ginsberg, 1974; Mathieu et al., 1985; Norkool and Kirkpatrick, 1985). Finally, other laboratory tests such as blood pH, paO_2, and electroencephalograms fail to predict which patients will·develop the delayed encephalopathy (Ellenhorn and Barceloux, 1988; Vieregge et al., 1989).

NEUROBIOLOGICAL FEATURES

The most characteristic neuropathological changes are in the cerebral white matter and in the globus pallidus (Shillito et al.,1936; Finck, 1966; Kobayashi et al., 1984; Chang et al., 1992; Zagami et al., 1993). Most of the lesions of the cerebral white matter reflect potentially reversible areas of symmetrical, periventricular demyelination which enlarge progressively during the latency period (Hayashi et al., 1993). If severe, there may be fragmentation of axis cylinders and extensive diffuse necrotic lesions. The lesions in the inner globus pallidus reflect ischemia and hemorrhagic necrosis (De Poorter et al., 1991; Chang et al., 1992; Silverman et al., 1993). We do not understand why some patients develop white matter changes and others develop globus pallidus changes. In addition, there may be degeneration of the spongy cerebral cortex, necrotic lesions of the hippocampus and mesial temporal lobe, lesions in the thalamus, and Purkinje cell loss (Lapresle and Fardeau, 1967; Ginsberg, 1985; Tuchman et al., 1990).

The mechanism for this delayed neuropathology is unclear and may represent a maturation effect of the neuropathology (Siesjö, 1985). CO encephalopathy may result from hypoxia–ischemia in areas of poor anastomotic blood supply, watershed zones, and periventricular arterial distributions. The neuropathological changes of CO can be difficult to distinguish from changes after a cardiorespiratory arrest, and CO-induced neuropathological changes in primates may be indistinguishable from hypoxic–ischemic lesions (Ginsberg et al., 1974). Hypoxia–ischemia is not the whole story, however, particularly since white matter is not as vulnerable to hypoxia as cerebral gray matter, and globus pallidus lesions seldom occur with hypoxia. CO probably has an added neurotoxic effect as suggested by similar basal ganglia lesions from other poisonings, such as methanol and hydrogen sulfide poisoning. CO neurotoxicity could result form lipid peroxidation in brain by conversion of xanthine dehydrogenase to xanthine oxidase (Seger and Welch, 1994). Other theories include cellular toxicity secondary to cytochrome malfunction, increased leukocyte adherence to endothelia of brain microvasculature, and the effects of metabolic acidosis.

Recent advances in neurobiology and in neuroimaging have increased our understanding of frontal–subcortical circuits and their relationship to the basal ganglia (Cummings, 1993). Frontal lobe syndromes result from dysfunction of prefrontal connections in the subfrontal white matter and in the caudate. Similar to disorders such as multiple sclerosis and vascular dementia, the delayed encephalopathy of CO may develop a "frontal" lobe syndrome as seen in our patient. A midline frontal syndrome is also suggested from reports of akinetic mutism in nearly one-third of delayed CO encephalopathy patients (Choi, 1983; De Poorter et al., 1991; Maeda et al., 1991; Chang et al., 1992; Hayashi et al., 1993). Prior studies indicate a frontal predominance pattern of demyelination in the delayed encephalopathy of CO which may correlate with "abnormal behavior" (Kobayashi et al., 1984; Chang et al., 1992). Subtraction single photon emission tomography (SPECT) studies in these patients show a diffuse, but frontal-dominant, hypoperfusion in gray and white matter (Maeda et al., 1991). In addition, hypoxia–ischemia may explain the visuoperceptual changes due to bilateral parieto-occipital watershed ischemia, and the involvement of globus pallidus may be instrumental in producing the parkinsonism and other movement disorders.

THERAPY AND PROGNOSIS

The initial therapy of acute CO intoxication includes the administration of supplemental oxygen until carboxyhemoglobin levels are significantly reduced. The added efficacy of hyperbaric oxygen for the delayed

encephalopathy is unclear. Hyperbaric oxygen causes higher oxygen tension that dissolves enough oxygen in the plasma to bypass the reliance on hemoglobin for oxygen transport. Animal research and clinical studies suggest that hyperbaric oxygen therapy shortens the duration of acute symptoms (Mathieu et al., 1985; Norkool and Kirkpatrick, 1985). When hyperbaric oxygen is administered to patients with CO intoxication, their SPECT scans show improved metabolism when the pre-treatment and post-treatment scans are compared (Maeda et al., 1991; Van Meter et al., 1994). There is no evidence, however, that shortening the duration of acute symptoms will decrease the incidence and severity of delayed sequelae. Patients who received hyperbaric oxygen continued to develop the delayed encephalopathy (Choi, 1983; Lee and Marsden, 1994).

· In addition to rehabilitation, symptomatic therapies may be appropriate. Some of the neurobehavioral manifestations from CO intoxication can be managed with psychoactive or neurological medications. Although personality changes and memory disorders are difficult to treat, symptoms of depression may respond to antidepressant medications. Initial reports suggest that the parkinsonian state responds poorly to L-dopa drugs (Jaeckle and Nasrallah, 1985; Lee and Marsden, 1994).

The prognosis for recovery is good in the majority of patients with this delayed encephalopathy. Most clinical symptoms and neuroimaging changes resolve after 1–2 years (Choi, 1983; Chang et al., 1992; Bruno et al., 1993). In the oldest series of patients with CO intoxication, the recovery rate in those with sequelae was 53–75% (Shillito et al., 1936), and in a recently published series, 61% improved (Lee and Marsden, 1994). Most recovery occurs during the first 3 months, although residual personality, memory, and parkinsonian findings often persist. Three years after CO exposure, Smith and Brandon (1973) reported a persistent personality change in 33% and memory difficulty in 43%. In some patients, the delayed encephalopathy continues to deteriorate or can lead to death (Ginsberg, 1979). The presence of extensive changes on neuroimaging may mean a poorer prognosis, especially if there are both globus pallidus and severe white matter changes, or a late appearance of either of these findings (Destee et al., 1985; Vieregge et al., 1989; Zagami et al., 1993; Lee and Marsden, 1994).

CONCLUSIONS

Our patient illustrates the spectrum of the delayed encephalopathy from CO intoxication. Clinicians need a high index of suspicion for the neurobehavioral aspects of this syndrome, particularly since it can occur without parkinsonism or neuromotor changes. In patients with subtle behavioral changes, investigate a history of CO exposure and, if indicated, draw carboxyhemoglobin levels and obtain neuroimaging studies. In particular, the presence of a frontal lobe syndrome, visuoperceptual disorders, and parkinsonian signs suggests the delayed encephalopathy of CO intoxication. Further systematic study of a large series of these patients would facilitate the characterization of their neurobehavioral features.

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