**Original Article**

# Predictors of Delayed Neurological Sequelae after Acute Carbon Monoxide Poisoning at Zagazig University Hospitals

**Safaa Zakaria Gaballah [1], Iman Abdel-Rady Elkhishin [1], Noha Ali Hashim [2], Omaima Ibrahim Abdel Hamid [1]**

[1] Forensic Medicine and Clinical Toxicology & [2] Neurology Departments, Faculty of Medicine, Zagazig University, Egypt.

**ABSTRACT**

**Background:** Carbon monoxide (CO) is an odorless, tasteless and colorless gas that causes a potentially fatal illness with a tremendous burden due to significant mortality and morbidity. Carbon monoxide poisoning leads to the development of delayed neurological sequelae (DNS). **Aim:** To assess the possible risk factors that can predict the development of DNS after acute CO poisoning. **Subjects and methods:** The patients were recruited between January 2018 and December 2018. The study included 37 cases with acute CO poisoning. The medical history was taken thoroughly. Patients underwent general and neurological clinical assessments with laboratory investigations, including arterial blood gases (ABG), carboxyhemoglobin (COHb), cardiac enzymes, and serum lactate. At the time of admission, all patients were subjected to an electrocardiogram (ECG) and brain imaging (CT or MRI) of the brain. They were followed up three and six months after discharge for complete neurological examination and cognitive functions assessment using the Mini-Mental State Examination (MMSE).

**Results:** Two patients died, both presenting with coma and hemodynamic instability. Five cases were excluded due to a lack of comprehension and refusal to follow-up. Out of the 30 patients who completed the follow-up, 67% survived with no complication, while DNS developed in 33% of the patients. Several predictors for development of DNS were identified. They included lower Glasgow coma score, duration of CO exposure, high COHb level, decrease in blood pH, elevated serum levels of creatine kinase and lactate, and abnormalities in brain structure. The time of DNS development extended to six months post-exposure. **Conclusion:** We conclude that several clinical and laboratory parameters can predict DNS. **Recommendations:** proper and accurate clinical and laboratory evaluation of any suspected case of acute CO poisoning should be performed especially those parameters proved to be predictors for DNS. The follow-up of cases should continue at least for six months post-exposure.

*Corresponding author*

Omaima I. Abdel Hamid

Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Zagazig University, Egypt.

Email

dr_omaima2006@yahoo.com

**Keywords:** Carbon monoxide poisoning, Cognitive function, Delayed neurological sequelae predictors, Minimental state examination

## I. Introduction

Carbon monoxide (CO) is a non-irritating, colorless, tasteless, and odorless gas (Rose et al., 2017). It is named the "silent killer" as it is responsible for a considerable number of poisoning incidences worldwide (Khadem-Rezaiyan and Afshari, 2016). Carbon monoxide is produced by incomplete combustion of carbonaceous material. The potential sources of CO, other than fires, include poorly functioning heating systems, improperly vented fuel-burning devices (e.g., kerosene heaters, charcoal grills), and motor vehicles operating in poorly ventilated areas e.g., in parking garages, warehouses (Hampson and Dunn, 2015).

Carbon monoxide poisoning is one of the predictable and preventable health-related conditions (Khadem-Rezaiyan and Afshari, 2016). Despite the considerable advances in managing it, CO toxicity is still the leading cause of unintentional poisoning deaths worldwide (Hashemzaei et al., 2016).

Carbon monoxide has been recognized as an acute and chronic toxic agent (Bleeker, 2016). It is readily absorbed by the lungs and diffuses from the alveoli to the blood in pulmonary capillaries across the alveolar-capillary membrane. After absorption, 90% of CO is taken up by hemoglobin, 10% binds to myoglobin and cytochrome oxidase, and less than 1% is dissolved in plasma (Henz and Maeder, 2005). Carbon monoxide binds to hemoglobin, forming carboxyhemoglobin (COHb), as it has 200–300 times more affinity to hemoglobin than oxygen (Rajiah and Mathew, 2011). Its deleterious effects are observed mostly in organs with high oxygen demands, such as brain and heart (Wolf et al., 2017). Binding of CO to cytochrome oxidase, an essential enzyme in energy-production, subsequently leads to oxidative stress as it disturbs mitochondrial functions, causing more complications like lipid peroxidation and apoptosis (Weaver, 2009). Additionally, CO increases nitric oxide (NO) release; excess NO produces peroxynitrite, which further impairs mitochondrial function and worsens tissue hypoxia (Thom et al., 2006). Hashemzaei et al. (2016) reported that an increase in the CO levels in the air causes a shift of the oxyhemoglobin dissociation curve to the left, thus hindering oxygen delivery to the tissues. Hypoxic and oxidative stresses predispose to cerebrovascular, cardiovascular, and neurological insult (Lee et al., 2015). Also, carboxyhemoglobin increases the sticking of white blood cells to endothelial surfaces, especially in the brain tissue, leading to leukocyte-dependent inflammatory reactions with white matter demyelination and focal necrosis (Rajiah and Mathew, 2011).

Acute CO poisoning has a wide range of symptoms such as headache, nausea, vomiting, dizziness, weakness, palpitation, loss of consciousness, coma, confusion, and seizures. The demographics at a higher risk and more prone to toxicity include children, elderly, and patients with pulmonary or heart diseases, individuals living in high areas, smokers, and those with high COHb levels (Sönmez et al., 2015). While chronic or occult CO poisoning can produce vague and unfamiliar presentations to the patient and the physician, it can result in headaches, fatigue, dizziness, paresthesias, chest pain, palpitations, and visual disturbances (Wright, 2002). Low-level, chronic exposure may also lead to neurological and cognitive deficits that do not resolve after removal of the patient from the CO source, suggesting neurological damage even at low levels of COHb and environmental CO (Townsend and Maynard, 2002).

Two syndromes occur after acute CO poisoning—(i) persistent neurological sequelae where the patient showed no recovery of the neurological manifestation of acute CO poisoning and (ii) the interval form of CO poisoning. The latter may occur in 15–40% of survivors of acute CO poisoning (Prockop and Chichkova, 2007). In patients with the interval form of CO poisoning, neurological impairment occurs within days to weeks after a lucid period (Hopkins and Woon, 2006). In both syndromes, deficits usually include motor and neuropsychiatric symptoms (Hawkins et al., 2000). DNS development mostly occurs after an interval, lasting from 4 days to 4–5 weeks from the initial recovery of acute CO poisoning (Vezzani, 2007). Clinically, DNS manifests with broad-spectrum neurological deficits, such as ataxia, intention tremors, Parkinson-like syndrome, peripheral neuropathy, and incontinence. Other symptoms of cognitive deficits include dementia, memory loss, personality changes, psychosis, and depression (Tomaszewski, 2006).

The aim of the present study was to investigate the predictors of DNS after acute CO exposure, through follow-up of patients for six months.

## II. Subjects and methods

- **Patients:**

The present study included 37 patients with acute CO poisoning, admitted to the Poison Control Center at Zagazig University, Egypt, between the beginning of January 2018 and the end of December 2018.

The Institutional Review Board of Faculty of Medicine, Zagazig University, approved the design of our study (IRB approval no. 4197/2-1-2018). Written informed consent was obtained from the patients or their legally authorized representative, after fully explaining the aim and procedures of the study and after ensuring complete confidentiality of the data.

The diagnosis of CO poisoning was based on several factors—(i) history of exposure to CO source, (ii) clinical symptoms and sign such as headache, dizziness, seizure, vomiting (Pepe et al., 2011), and (iii) presence of elevated COHb level (> 5%) in non-smokers and (> 10%) in smokers (Olson and Smollin, 2008).

We excluded patients with certain chronic medical diseases (hypertension, diabetes mellitus, hepatic or renal failure), patients with history of neurological diseases (dementia, Parkinsonism, stroke or neuropathy), patients with cardiac compromise, heavy smokers (20 cigarettes or more per day), patients of concurrent severe head trauma, patients of toxicity with another poison, and pregnant women.

- **History taking:**

All patients were subjected to a thorough and complete medical history taking including complete personal data with stress on occupation and present history including the presenting signs and symptoms, past and family histories, and the history of smoking. In addition, the data regarding CO poisoning were collected including the source of exposure, duration, mode of exposure (accidental or intentional).

- **Clinical examination:**

Then, a clinical assessment of every patient was performed, including heart rate, blood pressure were measured. The conscious level was assessed using the Glasgow Coma Scale (GCS) (Teasdale et al., 1979). The scores were collated, where a score of 14 indicates mild dysfunction, a score of 11 to 13 indicates moderate dysfunction, and a score of 10 or less indicates severe dysfunction.

- **Laboratory and radiological investigations:**

Electrocardiogram (ECG) was performed. Venous blood samples were collected from the subjects into EDTA-containing tubes at the time of admission. These samples were used for the following laboratory investigations; serum lactate, creatine kinase, and cardiac enzymes. In addition, COHb level was measured using a spectrophotometer. Arterial blood samples were taken to measure the arterial blood gases (ABG) using an automated analyzer (Cobas B221). In addition, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain was performed in the Radiology Department.

- **Patient treatment:**

Patients were managed according to the following protocol; all patients were initially treated through administration of oxygen via non-rebreathing mask or endotracheal intubation in order to provide nearly 100% of oxygen. This leads to quickly clearing the COHb from blood, shortening the half-life of CO from 320 min on normal air to 80 min (Weaver, 2009).

Patients with disturbed levels of consciousness and desaturation were intubated and ventilated in the ICU. The 100% normobaric oxygen (NBO) was administered until the COHb was normal (< 5%) and the symptoms of CO poisoning had resolved. This would usually take about 6 h.

Hyperbaric oxygen (HBO) was administered in patients with transient loss of consciousness or ongoing altered mental status, metabolic acidosis, hypotension, COHb greater than 25%, and evidence of myocardial injury after considering the potential risks and benefits of transport to the HBO facility (Wolf et al., 2017).

In order to treat brain edema, the head was elevated by 15–30° to promote cerebral venous drainage (Biller and Bruno, 1997). Moderate hyperventilation to lower pCO2 to around 30 mm Hg was transiently used to reduce the raised intracranial pressure (ICP), as the cerebral vasculature is most sensitive to changes in the arterial partial pressure of carbon dioxide (pCO2) around the normal level of 40 mmHg. However, pH was carefully monitored, as hypocarbia itself can cause hypoxia and ischemic cell damage (North and Reilly, 1990). Mannitol was used in a dose of 0.25 to 2 g/kg using a 20–25% solution every 8 hours by IV infusion over at least 30 min provided that renal function and urinary output are adequate (Jha, 2003). Steroids, such as dexamethasone, were given to reduce brain edema. The initial dose is 10 mg intravenously or orally, followed by 4 mg every 6 hours. Corticosteroids should be tapered within 2 to 3 weeks. This can be done by decreasing the dose by 50% every 4 days (Abdallah et al., 2015). They lower intracranial pressure primarily in vasogenic edema because of their beneficial effect on the blood vessel (Rosenberg, 2000). Before discharge from the hospital, the patients were advised to avoid exertion and minimize physical activity to limit tissue oxygen demand as well as to avoid smoking.

- **Patient follow-up:**

Patients were provided with follow-up cards, informing them of their follow-up dates at 3 and 6 months after discharge. We advised the patients to be accompanied by a family member for the follow-up appointment to provide their observations. Both the follow-ups consisted of full neurological examination and cognitive assessment using the Arabic version of the Mini-Mental State Examination (MMSE) (Albanna et al., 2017).

The test administration took 5 to 10 min and a score of 26–30 indicated normal function, 20–25 was mild cognitive impairment, 10–19 was moderate cognitive impairment, and 0–9 denoted severe cognitive impairment (Davey and Jamieson, 2004).

Delayed neurological sequelae was diagnosed in patients with full consciousness recovering from acute CO poisoning events, with the development of neuropsychological symptoms within days or months.

**Statistical analysis:** Data were collected, tabulated, and managed using Statistical Package for Social Science version 16 (SPSS Inc., Chicago, IL). Continuous data were presented as the mean ±standard deviation (SD) if normally distributed or as median (range) if not normally distributed. Categorical data were presented as count and percentage. A p-value of $< 0.05$ was considered statistically significant. Kaplan–Meier survival plot was used to illustrate the survival curve and to estimate the time to development of complications.

## III. Results

The study included 20 male and 17 female patients. Table (1) demonstrates the demographic data and baseline characteristics of poisoning. The mean age was 28.8 ±13.1 years, ranging between 10 and 70 years. Smoking was present in 38% of the patients. The mean estimated duration of exposure to CO was 4.1 ±3.3 hours, ranging from 5 to 15 hours. The sources of exposure were broadly classified into charcoal burning 35%, water heater 24%, vehicle exhaust 19%, gas generator 11%, electric cable 5%, and kerosene gas tube 5%.

In clinical assessment, as shown in table (2), the mean systolic blood pressure was 102 ±15.3 mmHg with a range of 60–140 mmHg, and the mean heart rate was 97.2 ±13.7 bpm with a range of 75–140 bpm. Oximeter monitoring revealed mean oxygen saturation (SO2) of 90.8 ±6.6%, range 75–99%. Dizziness was prominent in 62% of the cases, headaches in 38%, vomiting in 49%, confusion in 51%, and seizures in 19%. ABG level was determined, and its abnormalities in the form of metabolic acidosis were prominent in 22% of the patients. Abnormal ECG was detected in 32% (Figure 1). Serum lactate was elevated in 57% of the cases. Abnormal levels of cardiac enzymes provided evidence of myocardial injury; levels of troponin I (TnI) and total creatine kinase (CK) were elevated in 32% and 54% of the cases, respectively. COHb level was elevated by 89%. Abnormal findings in brain imaging were detected in 46% of the patients (Figure 2)

The patients were admitted for management with a mean hospital stay of 4 ±3.2 days, range 1–15 days. Only 11% of the patients received hyperbaric oxygen (HBO) therapy. Two patients died, both presenting with coma and hemodynamic instability. Five cases were excluded due to a lack of comprehension and refusal to follow-up. Out of the 30 patients who completed the follow-up, 67% survived with no complication, while DNS developed in 33% of the patients. Of these, 17% developed DNS within the first three months post-exposure; 7% were determined by MMSE, 7% by neurological assessment, and 3% by both MMSE and neurological assessment. The other 16% developed DNS between three and six months (Figure 3); 10% of them having neurological defects only, while 6% determined via both MMSE and neurological assessment (Table 3).

Baseline characteristics, such as age, sex, smoking habit, and source of CO, were similar in patients with non-DNS and DNS ($p > 0.05$), except for the duration of exposure (Figure 4) and the length of hospital stay

(Figure 5). Patients with DNS had a significantly longer duration of carbon monoxide exposure and hospital stay compared to the non-DNS patients, with $p < 0.001$ and $p = 0.002$, respectively (Table 4)

Compared with those in the non-DNS group, patients in the DNS group had significantly lower GCS scores ($p = 0.002$). However, no other specific signs and symptoms distinguished the DNS and non-DNS groups. According to the laboratory findings, the DNS group patients had significantly elevated levels of serum COHb ($p = 0.015$), lactate ($p = 0.017$), and creatine phosphokinase ($p = 0.002$) as well as higher chances of metabolic acidosis ($p = 0.009$) compared to the non-DNS group patients. Only troponin had a non-significant difference between both the groups. Abnormality in radiological brain imaging (F was significantly higher among the DNS group patients ($p < 0.001$) (Table 5).

Table (1): Demographic data and basic poisoning characteristics in the carbon monoxide poisoned patients involved in the study:

| **Variables** | **Mean ±SD** | **Median (Range)** |
|---|---|---|
| **- Age (years)** | 28.8 ±13.1 | 25 (10–70) |
| **- Duration of exposure (hours)** | 4.1±3.3 | 4 (5-15) |
| **Variables** | **Number** | **Percent** |
| **-Sex** | | |
| **- Female** | 17 | 46% |
| **- Male** | 20 | 54% |
| **-Smoking** | | |
| **- Smoker** | 14 | 38% |
| **- Non-smoker** | 23 | 62% |
| **-Occupation** | | |
| **- potential exposure to CO** | 8 | 22% |
| **- no potential exposure to CO** | 29 | 78% |
| **- Sources of exposure** | | |
| **- Charcoal burning** | 13 | 35% |
| **- Water Heater** | 9 | 24% |
| **- Vehicle exhaust** | 7 | 19% |
| **- Gas generator** | 4 | 11% |
| **- Electric cable** | 2 | 5% |
| **- Kerosene gas tube** | 2 | 5% |
| **-Mode of exposure** | | |
| **- Accidental** | 36 | 97% |
| **- Suicidal** | 1 | 3% |

Table (2): clinical and laboratory findings of CO poisoned patients included in the study:

| Variables | Mean ±SD | Median (Range) |
|---|---|---|
| **Systolic blood pressure (mmHg)** | 102±15.3 | 100(60-140) |
| **Heart rate (bpm)** | 97.2±13.7 | 95(75-140) |
| **SO2%** | 90.8±6.6 | 92(75-99) |
| **Variables** | **Number** | **Percent** |
| **Glasgow coma scale** | | |
| - **Mild dysfunction (14)** | 17 | 46% |
| - **Moderate dysfunction (11-13)** | 8 | 22% |
| - **Sever dysfunction (≤10)** | 12 | 32% |
| **Dizziness:** | | |
| - **No** | 14 | 38% |
| - **Yes** | 23 | 62% |
| **Headache:** | | |
| - **No** | 23 | 62% |
| - **Yes** | 14 | 38% |
| **Vomiting:** | | |
| - **No** | 19 | 51% |
| - **Yes** | 18 | 49% |
| **Confusion:** | | |
| - **No** | 18 | 49% |
| - **Yes** | 19 | 51% |
| **Seizures:** | | |
| - **No** | 30 | 81% |
| - **Yes** | 7 | 19% |
| **Arterial blood gases** | | |
| - Normal | 29 | 78% |
| - Metabolic acidosis | 8 | 22% |
| **ECG** | | |
| - Normal | 25 | 68% |
| - abnormal | 12 | 32% |
| **Serum lactate** | | |
| - Normal | 16 | 43% |
| - Elevated | 21 | 57% |
| **Serum Troponin** | | |
| - Normal | 25 | 68% |
| - Elevated | 12 | 32% |
| **Serum Creatine kinase (CK)** | | |
| - Normal | 17 | 46% |
| - Elevated | 20 | 54% |
| **COHB (%)** | | |
| - **<5%** | 4 | 11% |
| - **5–10%** | 5 | 13% |
| - **10–25%** | 24 | 65% |
| - **>25%** | 4 | 11% |
| **Brain imaging** | | |
| - Normal | 20 | 54% |
| - Abnormal | 17 | 46% |

CO: carbon monoxide; SO2: arterial oxygen saturation; ECG: electrocardiograph; COHB: carboxy hemoglobin level

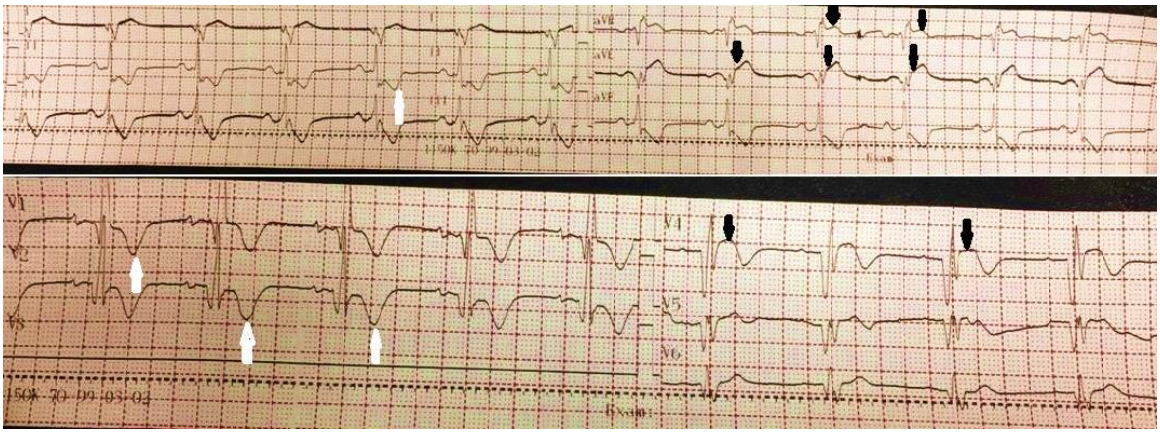

**Figure (1):** Electrocardiogram trace of patient with acute carbon monoxide poisoning showing ischemic changes in the form of raised ST segment (black arrows) and inverted T wave (white arrws)

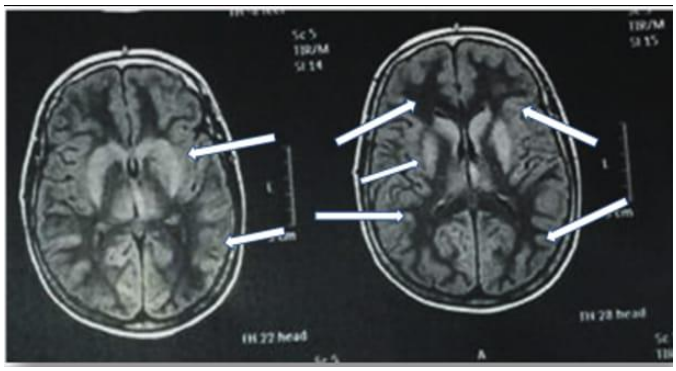

**Figure (2):** MRI brain shows bilateral symmetric involvement of the thalamus and lentiform nucleus with the hyper intensities (white arraws) in flair axial images suggesting sub-cortical white matter toxic demyelination

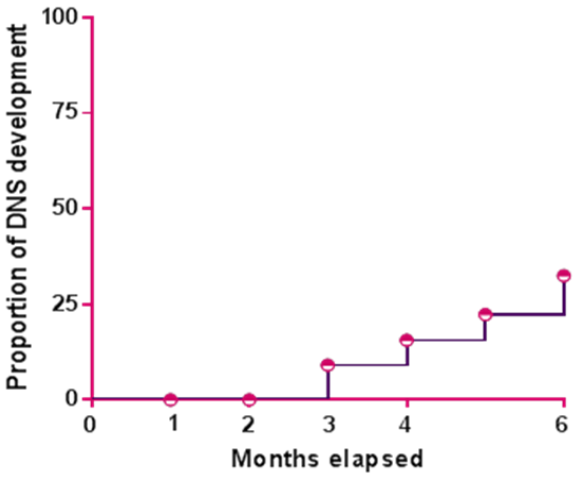


**Figure (3):** Kaplan-Meier survival plot showing time to development of delayed neurological sequelae (DNS) among carbon monoxide-poisoned patients during the six-month follow-up period. At the end of the follow-up period, 33% of patients developed DNS. Two patients died and five patients were lost during the follow-up period.

Table (3): Outcome and associated complications of CO poisoned patients and results of MMSE and neurological examination at 3 and 6 months:

| Variables | Total number (32) | Percent |
|---|---|---|
| **Death(during admission)** | 2 | 6% |
| **No complications** | 20 | 63% |
| **Complications:** | | |
| - Tremors | 3 | 9% |
| - Gait disturbance | 3 | 9% |
| - Headache | 4 | 13% |
| - Memory and Cognitive affection | 9 | 28% |
| **Three months post-exposure MMSE** | | |
| -normal | 26 | 86% |
| -mild cognitive impairment | 2 | 7% |
| -moderate cognitive impairment | 2 | 7% |
| **Neurological examination** | | |
| -normal | 27 | 90% |
| -abnormal | 3 | 10% |
| **Six months post-exposure MMSE** | | |
| - Normal | 25 | 83% |
| - Mild cognitive impairment | 5 | 17% |
| **Neurological examination** | | |
| - Normal | 21 | 70% |
| - Abnormal | 9 | 30% |

CO: carbon monoxide MMSE: Mini-Mental State Examination.

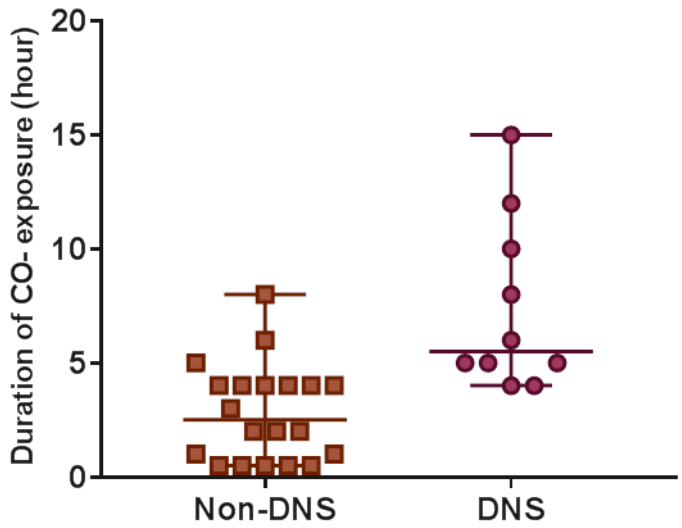


**Figure (4):** Scatter dot plot representing the duration of exposure to carbon monoxide non-DNS vs DNS. Data were median (range), each dot/square represents a patient.

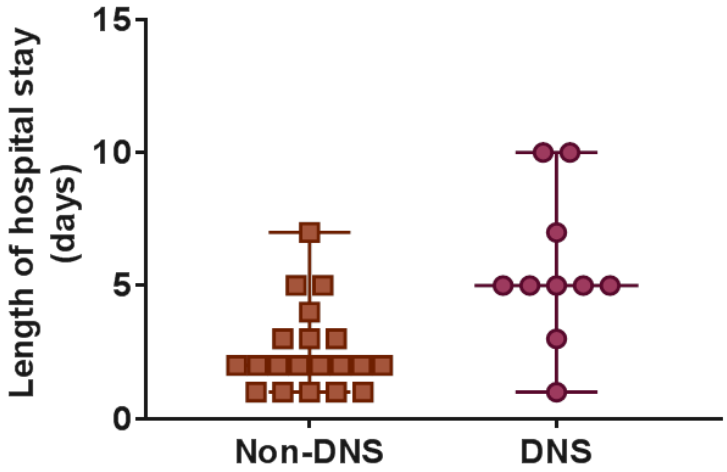


**Figure (5):** Scatter dot plot representing the length of hospital stay in non-DNS vs DNS of carbon monoxide-poisoned patients. Data were median (range), each dot/square represents a patient.

Table (4): Baseline characteristics of CO poisoned patients according to DNS (No=30):

| Variables | Non-DNS (n=20) | DNS (n=10) | Test of significance | P-value |
|---|---|---|---|---|
| **Age (years)** | | | Mann-Whitney U test=14.5 | .074 |
| - median(range) | 23(15-40) | 37(18-55) | | |
| **Sex** | n, (%) | n, (%) | Fisher's Exact Test | 0.70 |
| - Female | 8(40) | 3(30) | | |
| - Male | 12(60) | 7(70) | | |
| **Smoking, n, (%)** | | | Fisher's Exact Test | 0.26 |
| - No | 13(65) | 4(40) | | |
| - Yes | 7(35) | 6(60) | | |
| **Duration of exposure (hours)** | | | Mann-Whitney U test=178.5 | <0.001 * |
| - median(range) | 2.5(0.5-8) | 5.5(4-15) | | |
| **Sources of CO exposure** | n, (%) | n, (%) | Fisher's Exact Test=2.8 | 0.89 |
| - Water Heater | 4(20) | 2(20) | | |
| - Charcoal burning | 7(35) | 4(40) | | |
| - Vehicle exhaust | 5(25) | 2(20) | | |
| - Electric cable | 0(0) | 1(10) | | |
| - Gas generator | 3(15) | 1(10) | | |
| - Kerosene gas tube | 1(5) | 0(0) | | |
| **Hospital stay length (days)** | | | Mann-Whitney U test= 166.5 | 0.002 * |
| - Median (range) | 2(1-7) | 5(1-10) | | |
| **HBO therapy** | n, (%) | n, (%) | Fisher's Exact Test | 0.58 |
| - No | 18(90) | 8(80) | | |
| - Yes | 2(10) | 2(20) | | |

CO: carbon monoxide; HBO: hyperbaric oxygen.*= significant

Table (5): Clinical and laboratory data of CO poisoned patients according to DNS

| Variables | Non-DNS (n=20) | DNS (n=10) | Test of significance | P-value |
|---|---|---|---|---|
| **Glasgow coma scale, n, (% )** | | | | |
| - Mild | 13(65) | 1(10) | $\chi 2$=12.4 | 0.002 * |
| - Moderate | 5(25) | 2(20) | | |
| - Severe | 2(10) | 7(70) | | |
| **Systolic blood pressure (mmHg)** median(range) | 100(90-140) | 108(80-130) | Mann-Whitney U test=46.5 | 0.35 |
| **Heart rate (bpm)** ( mean± SD) | 96.5±11.3 | 93.5 ±8.8 | -t test=-0.74 | 0.47 |
| **SO2%** median(range) | 94(80-99) | 108(80-130) | Mann-Whitney U test=57 | 0.06 |
| **Dizziness** | n, (%) | n, (%) | Fisher's Exact Test | >0.99 |
| - No | 7(35) | 3(30) | | |
| - Yes | 13(65) | 7(70) | | |
| **Headach** | n, (%) | n, (%) | Fisher's Exact Test | 0.12 |
| - No | 9(45) | 8(80) | | |
| - Yes | 11(55) | 2(20) | | |
| **Vomiting** | n, (%) | n, (%) | Fisher's Exact Test | 0.26 |
| - No | 11(55) | 3(30) | | |
| - Yes | 9(45) | 7(70) | | |
| **Confusion, n, (% )** | n, (%) | n, (%) | Fisher's Exact Test | 0.058 |
| - No | 12(60) | 2(20) | | |
| - Yes | 8(40) | 8(80) | | |
| **Seizures** | n, (%) | n, (%) | Fisher's Exact Test | 0.66 |
| - No | 16(80) | 7(70) | | |
| - Yes | 4(20) | 3(30) | | |
| **Arterial blood gases** | n, (%) | n, (%) | Fisher's Exact Test | 0.009* |
| - Normal | 19(95) | 5(50) | | |
| - Metabolic acidosis | 1(5) | 5(50) | | |
| **ECG findings** | n, (%) | n, (%) | Fisher's Exact Test | 0.33 |
| - Normal | 20(100) | 9(90) | | |
| - Tachycardia | 0(0) | 1(10) | | |
| **Serum lactate** | | | Fisher's Exact Test | 0.017* |
| - Normal | 12(60) | 1(10) | | |
| - Elevated | 8 (40) | 9(90) | | |
| **Troponin** | n, (%) | n, (%) | Fisher's Exact Test | 0.078 |
| - Normal | 17(85) | 5(50) | | |
| - Elevated | 3(15) | 5(50) | | |
| **Creatine phosphokinase (CK) n, (% )** | n, (%) | n, (%) | $\chi^2$=9.6 | 0.002* |
| - Normal | 14(70) | 1(10) | | |
| - Elevated | 6(30) | 9(90) | | |
| **COHB, n, (% )** | n, (%) | n, (%) | Fisher's Exact Test | 0.015* |
| - Normal | 16(80) | 3(30) | | |
| - Elevated | 4(20) | 7(70) | | |
| **Brain imaging, n, (% )** | n, (%) | n, (%) | Fisher's Exact Test | <0.001* |
| - Normal | 16(80 | 1(10) | | |
| - Abnormal | 4(20) | 9(90) | | |

CO: carbon monoxide; SO2: arterial oxygen saturation; ECG: electrocardiograph; COHB: carboxy hemoglobin level; $\chi^2$, Chi-squared test, *=significant

## IV. Discussion

Carbon monoxide (CO) poisoning is a major clinical problem that results in significant morbidity and mortality globally (Kim and Choi, 2018). The most crucial problem following an acute CO poisoning is the development of delayed neurological sequelae (DNS) (Nah et al., 2020). It is a distressing condition that is characterized by several degrees of cognitive deficits, personality changes, movement disorders, and focal neurologic deficits, persisting for a year or longer (Sung et al., 2015). It is extremely critical to identify CO-poisoned patients at risk of developing DNS.

Our analysis revealed that 33% of the patients with acute CO poisoning developed DNS which is higher than previously reported by Thom et al. (1995); Pepe et al. (2011) and Kuroda et al. (2015); they reported DNS in 20-24% of patients. The commonly encountered neurological manifestations were headaches (13%), memory and cognitive loss (28%), tremors (9%), and gait disturbances (9%). Several studies have previously reported the development of DNS in 20–24% of their patients of CO poisoning. The patients with DNS in the current work displayed significantly lower MMSE scores, 3 and 6 months post-exposure than the non-DNS patients, which is in accordance with the findings of Ku et al. (2010).

The current study revealed no significant difference between the patients who did or did not develop DNS with respect to age and gender, in accordance with Dianat and Nazari (2011) and Kitamoto et al. (2016). On the contrary, Weaver et al. (2007) and Zhang et al. (2020) suggested that old age was a significant risk factor for developing DNS, possibly due to age-related mechanisms including apoptosis.

In the present study, proximity to charcoal burning and water heater were the most common sources of CO poisoning. However, the source of the poisoning was not a significant predictor of DNS ($p > 0.05$). Similar to our findings, El Sayed and Tamim (2014) reported that the use of indoor charcoal burning grills, as an alternative heating method, is a significant source of CO poisoning (44.4%), the second identified source of CO poisoning was a fire (37%).

In our cohort study, the patients spent an average of 4 ±3.2 days in a hospital stay. Patients with DNS showed significantly longer hospital stay than the non-DNS patients, which was in accordance with Ku et al. (2010) and Liao et al. (2018). Longer duration of exposure in poisoned patients will cause higher CO load, with CO accumulation in tissues and hemoglobin and susceptibility to CNS insult and DNS (Zhang et al., 2020).

In agreement with the results of Giuseppe et al. (2011), Chan et al. (2016) and Zhang et al. (2020) we observed significantly lower initial GCS scores in patients who developed DNS than those in non-DNS patients. Hence, we hypothesize that CO-induced tissue hypoxia leads to loss of consciousness and reoxygenation injury to the central nervous system. This facilitates the production of reactive oxygen species (ROS) resulting in a characteristic reperfusion injury in addition to the lipid peroxidation and demylination of neurons (Sönmez et al., 2015).

Regarding the cardiovascular effects of CO poisoning, blood pressure, and heart rate, ECG findings were not recognized as predictors for DNS in our study, as also reported by Kitamoto et al. (2016). However, according to Pepe et al. (2011) systolic blood pressure of $\leq 90$ mmHg is considered as a risk factor for the development of DNS and Lin et al. (2018) reported that patients with

myocardial injury have a higher risk for DNS. Our study also suggested that oxygen saturation was not a predictor of DNS. This is in contrast to the conclusion of Kuroda et al.(2015) that patients with DNS had a statistically significant decrease in oxygen saturation (SO2) compared to the patients who did not develop DNS. This can be explained by differences in the measurement tools in the two studies. We can have an accurate assessment of arterial oxygen content in such patients only by analyzing the arterial blood with a laboratory CO-oximetry (Hampson, 1998). Also, we observed significantly high metabolic acidosis, and elevated serum creatinine kinase (CK) and lactate levels in the DNS group compared to the non-DNS group, in line with Kitamoto et al. (2016) but contrary to Liao et al. (2018). Accumulation of toxic metabolites and free radicals formed by CO-induced hypoxia contribute to cerebral autoregulation, and further cause abnormalities in gray matter, white matter, and globus pallidus, including the pallidoreticular pathway (Hansen et al., 2014; Hassan and Hamdy, 2018). The elevated CK level may be associated with and be indicative of both, CO-mediated muscle necrosis and rhabdomyolysis, in comatose patients (Torres et al., 2015). In acute CO poisoning cases, hypoxia and impaired cellular respiration induce damage to multiple organs. Thus, CK elevation might reflect prolonged exposure to CO and the severity of poisoning.

In the current work, we detected a statistically significant elevation in COHb level in the DNS group compared to non-DNS group. Conversely, other reports concluded that COHb concentration was not a significant predictor for the development of DNS (Cevik et al., 2006; Guan et al., 2016). This variation may be related to factors such as the time once CO inhalation is stopped, the time of withdrawing blood samples, and the efficiency of oxygen administration. In addition, the percentage of patients with abnormal brain imaging was significantly higher in the DNS group than the non-DNS group, in concordance with Ku et al. (2010) and Liao et al. (2018). The presence of white matter lesion in MRI was also associated with DNS in the study performed by Nah et al. (2020).

## V. Conclusion:

The current work revealed several predictors of DNS after acute CO poisoning, including the initial GCS score, duration of CO exposure, COHb level, decrease in blood pH, high serum CK and lactate levels, and abnormality in brain structure. This work also demonstrated that the DNS may continue to appear till six months after acute poisoning.

## VI. Recommendations:

Proper and accurate clinical and laboratory evaluation of any suspected case of acute CO poisoning should be performed especially those parameters proved to be predictors for DNS. In addition, the follow-up of cases should continue at least for six months post-exposure.

## VII. Conflict of interest:

There is nothing to declare as competing interest for any of the authors including the corresponding author.

## VIII. References:

Abdallah, M.S.; Madi, A.F. and Rana, M.A. (2015): The best use of systemic corticosteroids in the intensive care units, review. Journal of Steroids & Hormonal Science; 6:1

Albanna, M., Yehya, A., Khairi, A., Dafeeah, E., Elhadi, A., Rezgui, L., Al Kahlout, S., Yousif, A., Uthman, B., and Al-Amin, H. (2017): Validation and cultural adaptation of the Arabic versions of the Mini-Mental Status Examination - 2 and Mini-Cog test. \

Neuropsychiatric Disease and Treatment; 13:793–801.

Biller, J. and Bruno, A. (1997): Acute ischaemic stroke. Current Therapy In Neurologic Disease: 5th ed. St Louis: Mosby; pp.191-197.

Bleecker, M. L. (2016): Carbon monoxide intoxication. Handbook of Clinical Neurology 131: 191-203

Cevik, A.A.; Unluoglu, I. and Yanturali, S. (2006): Interrelation between the Poisoning Severity Score, carboxyhaemoglobin levels and in-hospital clinical course of carbon monoxide poisoning. International Journal of Clinical Practice; 60: 1558–1564.

Chan, M.Y.; Au, T.T.; Leung, K.S. and Yan, W.W. (2016): Acute carbon monoxide poisoning in a regional hospital in Hong Kong: historical cohort study. Hong Kong Medical Journal; 22(1): 46-55.

Davey, R. J. and Jamieson, S. (2004): The validity of using the mini mental state examination in NICE dementia guidelines. Journal of Neurology, Neurosurgery & Psychiatry; 75(2): 343-344.

Dianat, I. and Nazari, J. (2011): Characteristics of unintentional carbon monoxide poisoning in Northwest Iran - Tabriz. International Journal of Injury Control and Saftey Promotion;18:313–320.

El Sayed, M. and Tamim, H.(2014): Carbon monoxide poisoning in Beirut, Lebanon: Patient's characteristics and exposure sources. Journal of Emergency Trauma & Shock; 7:280.

Giuseppe, P.; Matteo, C.; Peiman, N.; Simone, V.; Massimo, D. P. and Francesco, G. (2011): Delayed neurological sequelae after carbon monoxide poisoning, predictive risk factors in the emergency department: A retrospective study. Scandinavian. Journal of Trauma and Resuscitation Emergency Medicine; 19:.16.

Guan, L.; Li, Z.Y.; Zhang, Y.L.; Cong, C.C. and Zhao, J.Y. (2016): Early biomarkers in 1h nuclear magnetic resonance spectroscopy of striatal pathological mechanisms after acute carbon monoxide poisoning in rats. Biomedical and Environmental Science; 28:728-737.

Hampson, N. B. and Dunn, S. L. (2015): Carbon monoxide poisoning from portable electrical generators. Journal of Emergency Medicine; 49(2):125-129.

Hansen, M.B.; Kondziella, D.; Danielsen, E.R.; Larsen, V.A. and Jansen, E.C. (2014): Cerebral proton magnetic resonance spectroscopy demonstrates reversibility of N-acetylaspartate/creatine in gray matter after delayed encephalopathy due to carbon monoxide intoxication: a case report. Journal of Medical Case Reports; 8: 211.

Hashemzaei, M.; Barani, A.K.; Iranshahi, M.; Rezaee, R.; Tsarouhas, K.; Tsatsakis, A.M.; Wilks M.F. and Tabrizian, K. (2016): Effects of resveratrol on carbon monoxide-induced cardiotoxicity in rats. Environmental Toxicology and Pharmacology; 46:110-115.

Hassan, O.A. and Hamdy, S.A.A.L. (2018): A Prospective comparative study between three chemical markers for predicting delayed neurological sequelae in patients with acute carbon monoxide poisoning of Poison Control Center in Minia University Hospital. Ain Shams Journal of Forensic Medicine and Clinical Toxicology; 31: 23-32.

Hawkins, M.; Harrison, J. and Charters, P. (2000): Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. British Journal of Anaesthesia; 84:584–586

Henz, S. and Maeder, M. (2005): Prospective study of accidental carbon monoxide

poisoning in 38 Swiss soldiers. Swiss Medical Weekly; 135(27-28):398–408.

Hopkins, R.O. and Woon, F.L. (2006): Neuroimaging, cognitive, and neurobehavioral outcomes following carbon monoxide poisoning. Behavioral and Cognitive Neuroscience Reviews; 5:141–155

Jha, S. K. (2003): Cerebral edema and its management. Medical Journal, Armed Forces India; 59(4): 326.

Khadem-Rezaiyan, M. and Afshari, R. (2016): Carbon monoxide poisoning in Northeast of Iran. Journal of Forensic Legal Medicine; 41:1–4.

Kim, H.H. and Choi, S. (2018): Therapeutic aspects of carbon monoxide in cardiovascular disease. International Journal of Molecular Sciences; 19(8):2381.

Kitamoto, T.; Tsuda, M.; Kato, M.; Saito, F.; Kamijo, Y. and Kinoshita, T. (2016): Risk factors for the delayed onset of neuropsychologic sequelae following carbon monoxide poisoning. Acute Medicine and Surgery; 3: 315–319.

Ku, H. L.; Yang, K. C.; Lee, Y. C.; Lee, M. B. and Chou, Y. H. (2010): Predictors of carbon monoxide poisoning-induced delayed neuropsychological sequelae. General Hospital Psychiatry; 32:310–314.

Kuroda, H.; Fujihara, K.; Kushimoto, S. and Aoki M (2015): Novel clinical grading of delayed neurologic sequelae after carbon monoxide poisoning and factors associated with outcome. Neurotoxicology; 48:35-43

Lee, F. Y.; Chen, W. K.; Lin, C. L. and Kao, C. H. (2015): Carbon monoxide poisoning and subsequent cardiovascular disease risk: a nationwide population based cohort study. Medicine (Baltimore); 94:e624.

Liao, S. C.; Mao, Y. C.; Hung, Y. M.; Lee, C. H. and Yang, C. C. (2018): Predictive role of QTc prolongation in carbon monoxide poisoning-related delayed neuropsychiatric sequelae. Biomedical Research International; 2018: 2543018.

Nah, S.; Choi, S.; Kim, H.B.; Lee, J.; Lee, S.U.; Lee, Y.H.; Kim, G.W.; Han, S. (2020): Cerebral white matter lesions on diffusion-weighted images and delayed neurological sequelae after carbon monoxide poisoning: a prospective observational study. Diagnostics (Basel); 10(9):E698.

North, B. and Reilly, P. (1990): Raised intracranial pressure: a clinical guide. first ed. Heinemann Medical Books; Oxford; pp. 71–85

Olson, K. and Smollin, C. (2008): Carbon monoxide poisoning (acute). BMJ Clinical Evidence; 2008: 2103.

Pepe, G.; Castelli, M.; Nazerian, P.; Vanni, S.; Del Panta, M.; Gambassi, F and Grifoni, S. (2011): Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the Emergency Department: A retrospective study. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine; 19(1): 16.

Prockop, L. D. and Chichkova, R. I (2007): Carbon monoxide intoxication: an updated review. Journal of Neurology Science, 262:122–130.

Rajiah, K. and Mathew, E. M. (2011): Clinical manifestation, effects, diagnosis, monitoring of carbon monoxide poisoning and toxicity. African Journal of Pharmacy and Pharmacology; 5:259-264.

Rose, J. J.; Wang, L.; Xu, Q.; McTiernan, C. F.; Shiva, S.; Tejero, J. and Gladwin, M. T. (2017): Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. American Journal of Respiratory and Critical Care Medicine, 195(5), 596-606.

Rosenberg, G.A. (2000): Brain edema and disorders of cerebrospinal fluid circulation. In: Bradley WG, Daroff RB, Ferichel GM, Marsden CD, editors, Neurology in clinical practice, Vol. 2, 3rd ed. Butterworth Heinmann: Boston; pp. 1545–1559.

Sönmez, F. T.; Güneş, H.; Saritaş, A. and Kandiş, H. (2015): Carbon monoxide poisoning: clinical manifestations, consequences, monitoring, diagnosis and treatment of toxicity. Konuralp Medical Journal/Konuralp Tip Dergisi, 7(3).

Sung, Y. F.; Chen, M. H.; Peng, G. S. and Lee, J.T. (2015): Generalized chorea due to delayed encephalopathy after acute carbon monoxide intoxication. Annals of Indian Academy of Neurology; 18(1): 108–110.

Teasdale, G.; Murray, G.; Parker, L.; Jennett, B. (1979): Adding up the Glasgow coma score. Acta Neurochir Suppl (Wien); 28(1):13-6.

Thom, S. R.; Bhopale, V. M.; Fisher, D. (2006): Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental carbon monoxide toxicity. Toxicology and Applied Pharmacology; 213:152–159

Thom, S.R.; Taber, R.L.; Mendiguren, I.I.; Clark, J.M.; Hardy, K.R. and Fisher, A.B. (1995): Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Annals of Emergency Medicine; 25:474–480.

Tomaszewski, C. (2006): Carbon monoxide. In Goldfrank's toxicologic emergencies. Eighth edition. Edited by: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Robert S, Nelson LS. New York: Mc Graw-Hill; pp: 1689-1704

Torres, P.A.; Helmstetter, J.A.; Kaye, A.M. and Kaye, A.D. (2015): Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner Journal; 15(1):58-69.

Townsend, C.L. and Maynard, R.L. (2002): Effects on health of prolonged exposure to low concentrations of carbon monoxide. Occupational Environmental Medicine; 59:708–711

Vezzani, G. (2007): Post-interval syndrome: a pathogenetic hypothesis. Med Sub Iperb, 2: 68-70.

Weaver, L. K. (2009): Clinical practice: Carbon monoxide poisoning. New England Journal of Medicine; 360:1217e25.

Weaver, L. K.; Valentine, K. J. and Hopkins, R. O. (2007): Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. American Journal of Respiratory and Critical Care Medicine; 176(5): 491-497.

Wolf, S. J.; Maloney, G. E.; Shih, R. D.; Shy, B. D. and Brown, M. D. (2017): American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Carbon Monoxide Poisoning. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. Annals of Emergency Medicine; 69:98-107.

Wright, J. (2002): Chronic and occult carbon monoxide poisoning: we don't know what we're missing. Emergency Medicine Journal; 19(5): 386-390.

Zhang Y, Lu Q, Jia J, Xiang D and Xii Y (2020): Multicenter retrospective analysis of the risk factors for delayed neurological sequelae after acute carbon monoxide poisoning. The American Journal of Emergency Medicine (article in press); Doi: 10.1016/j.ajem.2020.06.090

**الملخص العربي**

**مؤشرات الاعتلال العصبي المتأخر بعد التسمم الحاد بأول أكسيد الكربون بمستشفيات جامعة الزقازيق**

صفاء زكريا جاب الله[١]، ايمان عبد الراضي الخشن[١]، نهي علي هاشم[٢]، أميمة ابراهيم عبد الحميد[١]

[١] قسم الطب الشرعي والسموم الإكلينيكية،[٢] قسم المخ والأعصاب، كلية الطب البشري، جامعة الزقازيق

**المقدمة:** أول أكسيد الكربون هو غاز عديم اللون والرائحة وغير مثير ويسبب إصابات خطيرة للبشرية. ويعتبر التسمم به واحدا من أهم أسباب الوفيات الأكثر شيوعا في العالم. ويسبب التسمم الحاد بأول أكسيد الكربون نتيجة لنقص الأكسجين اعتلال الدماغ بدرجات متفاوتة تتراوح بين الهذيان والغيبوبة العميقة. وفي حين ان معظم الحالات تتعافي الا ان ما يقرب من ٣٠% يحدث لهم اضطرابات نفسية عصبية وادراكية من ١-٦ اسابيع بعد التعرض للغاز تسمي هذه الاضطرابات "الاعتلال العصبي المتأخر".

**الهدف من الدراسة:** تهدف هذه الدراسة المستقبلية الي دراسة وتقييم مؤشرات الاعتلال العصبي المتأخر لمرضي التسمم الحاد بغاز أول أكسيد الكربون في مستشفيات جامعة الزقازيق.

**المرضي والطرق المستخدمة:** تضمنت هذه الدراسة حالات التسمم بغاز أول أكسيد الكربون الواردة لمستشفيات جامعات الزقازيق في مركز مكافحة السموم أو بالعنايات المركزة في الفترة من يناير ٢٠١٨ الي ديسمبر ٢٠١٨. وتم تشخيص الحالات بناء علي: تاريخ مرضي للتعرض لغاز أول أكسيد الكربون، وجود الصورة السريرية للتسمم مثل الصداع، الغثيان والقئ، الدوار والضعف والخفقان وفقدان الوعي المؤقت ، الهذيان والغيبوبة، ارتفاع مستوي الكربوكسيهيموجلوبين بالدم أكثر من ٥% بدون تدخين. وقد تم استبعاد الحالات التالية: الأمراض المزمنة الشديدة مثل داء السكري وضغط الدم المرتفع، الامراض العصبية مثل الخرف والشلل الرعاش والاعتلال العصبي والتدخين الشديد (٢٠ سيجارة يوميا أو أكثر)، اعتلال القلب، الحمل ، التزامن مع حوادث تصادم الرأس أو التسمم بأكثر من مادة .وقد شملت الدراسة ٣٧ حالة تم اخذ التاريخ المرضي لهم كاملا واشتمل علي مواصفات التعرض للمادة السامة من حيث مصادر ومدة وطريقة التعرض وقت التعرض ووقت الحضور للمستشفي والاجراءات العلاجية. كما تم فحص الحالة اكلينيكيا وعمل الفحوصات التي اشتملت علي غازات الدم الشرياني، مستوي الكربوكسيهيمجلوبين، رسم كهربي للقلب، انزيمات القلب، مستوي اللاكتات والكرياتين كينيز بالدم بالاضافة الي الاشعه المقطعية للمخ.

**النتائج:** قد توفي حالاتان بسبب التسمم الحاد بأول اكسيد الكربون وتم فقد متابعة خمس حالات في حين ظهر الاعتلال العصبي المتأخر في ٣٣% من مجمل ٣٠ حالة متبقية (١٧% منها ظهرت خلال متابعه ال٣ اشهر واكتمال ظهور الحالات خلال متابعة ال ٦ اشهر). وقد شملت أعراض الاعتلال العصبي المتأخر رعشة (٩%) ، صداع (١٣%)، اضطراب المشي (٩%)، فقدان في الذاكرة واضطراب معرفي (٢٨%).وقد اظهرت النتائج وجود ارتفاع ذو دلالة احصائية في متوسط مدة التعرض، مدة الاقامة في المستشفي،لاكتات الدم، الكرياتين كيناز، نسبة الكربوكسيهيموجلوبين في الدم وايضا وجود تغيرات بالاشعة المقطعية للمخ في المرضي الذين حدث لديهم الاختلال العصبي المتأخر .بالاضافة الي ذلك اظهرت النتائج ايضا انخفاض ذو دلالة احصائية في مقياس جلاسجو للغيبوبة، نسبة حموضة الدم في الحالات التي تطورت الي اعتلال عصبي متأخر

**الاستنتاج:** وقد تم استنتاج وجود العديد من عوامل التنبؤ الاكلينيكية والمعملية لحدوث الاعتلال العصبي المتأخر بعد التسمم الحاد بأول أكسيد الكربون, وتشمل متوسط مدة التعرض، مدة الاقامة في المستشفي، مقياس جلاسجو للغيبوبة، نسبة حموضة الدم ،لاكتات الدم، الكرياتين كيناز، نسبة الكربوكسيهيموجلوبين في الدم وايضا وجود تغيرات بالاشعة المقطعية للمخ بالاضافة الي وجوب متابعة هذه الحالات لمدة لاتقل عن ستة أشهر بعد التعرض.

**التوصيات:** يجب إجراء تقييم سريري ومختبري سليم ودقيق لأي حالة مشتبه فيها للتسمم الحاد بأول أكسيد الكربون خاصة تلك المؤشرات التي ثبت قدرتها علي التنبئ بحدوث الاعتلال العصبي المتأخر. ويجب أن تستمر متابعة الحالات لمدة ستة أشهر على الأقل بعد التعرض