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Proposal of a management algorithm for delayed neurological syndrome following carbon monoxide poisoning

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Keypoints

This article proposes an algorithm for the evaluation and follow-up of Delayed Neurological Sequelae (DNS) or Post-Interval Syndrome in patients (adults, pregnant women, and pediatric cases) with carbon monoxide (CO) poisoning.

Abstract

Delayed encephalopathy or post-interval syndrome can develop some time after acute carbon monoxide (CO) poisoning and its hyperbaric treatment. The clinical presentation is highly heterogeneous and variable, and this syndrome is often underdiagnosed. Although there are no definitive predictive markers, several risk factors have been identified that may predispose individuals to its development. Post-interval syndrome is relatively unknown among healthcare professionals and should be considered in all CO-poisoned patients who develop neurological symptoms after a symptom-free interval. Proper training of healthcare providers and the implementation of standardized operational protocols are essential.

Keywords

Delayed neurological syndrome, hyperbaric treatment, poisoning, carbon monoxide, post-interval syndrome, delayed encephalopathy.

Introduction [1-7]

Carbon monoxide (CO) poisoning is a rare but potentially devastating event and remains the most frequent cause of poisoning in developed countries. In Italy, CO poisoning is a common cause of intoxication. It is estimated that 93% of cases are accidental. Each year, there are approximately 600 deaths, two-thirds of which are due to intentional acts. The incidence is about 20 cases per 100,000 inhabitants, with a fatality rate of 5.8%. In 51% of cases, the patients are male, and in 49% female. Pregnant women account for about 2.3% of all CO poisoning cases, while individuals under the age of 12 represent approximately 18%. CO poisoning occurs through inhalation: inhaled CO binds to hemoglobin to form carboxyhemoglobin (COHb). This bond is approximately 200–300 times stronger than the bond between hemoglobin and oxygen, thus preventing normal oxygen transport to peripheral tissues. There is a leftward shift in the oxygen-hemoglobin dissociation curve, leading to tissue hypoxia. CO toxicity is associated with two main mechanisms:

-Tissue hypoxia (indirect damage)

-Tissue inflammation (direct damage)

There are no pathognomonic signs or symptoms of CO poisoning; therefore, careful assessment of medical history and environmental/contextual factors is essential for diagnosis.

In cases of poisoning, the severity of clinical presentation is correlated with the concentration of CO in the environment and the duration of exposure. Symptoms, which do not necessarily correlate proportionally with severity, are related to the levels of CO and COHb in the blood and in target organs. Diagnostic thresholds are considered to be COHb >5% in non-smoking adults and children, and >10% in smoking adults.

Based on COHb percentage, poisoning can be classified as:

-Mild: < 10%

-Moderate: 10–25%

-Severe: > 25%

The clinical presentation can be highly variable and is often characterized by nonspecific signs and symptoms, which may mislead or delay diagnosis. (Table 1)

In the past, this classification was used as a therapeutic guideline. However, it does not correlate with prognosis, is not an indicator of severity, and does not reflect the extent of neurological damage. Hyperbaric oxygen therapy (HBOT) can reduce the half-life of CO from 6 hours in ambient air or 60–90 minutes in normobaric oxygen to just 23 minutes. This accelerates symptom resolution and reduces the incidence of neurological sequelae.

SEVERITY CLASS	**SIGNS AND SYMPTOMS**	
Grade 1: Asymptomatic(*)	Absent	
Grade 2: Mild	Headache Dizziness	Nausea Vomiting
Grade 3: Moderate	Mental confusion Slowed thinking Weakness Ataxia Behavioral abnormalities Alterations in psychometric tests	Dyspnea on exertion Tachypnea Tachycardia Palpitations Hypoacusis Blurred vision
Grade 4: Severe	Stupor Coma Seizures Syncope Disorientation Brain CT scan abnormalities Hypotension/shock Rhabdomyolysis	Chest pain Palpitations Arrhythmias ECG signs of ischemia Pulmonary edema Lactic acidosis Skin blisters Cardiac arrest

Table 1. Clinical signs and symptomps of CO poisoning (*) Patients with positive COHb levels.

Analysis[8-20]

Delayed Neurological Syndrome (DNS), also referred to as post-interval syndrome, is one of the potential consequences following carbon monoxide (CO) poisoning. Also known as delayed encephalopathy, it is a rare subtype of acquired leukoencephalopathy with characteristic pathological findings, including symmetric alterations of the globus pallidus, generalized or focal degeneration and necrosis of the cerebral cortex, and widespread demyelination of the white matter.

The estimated incidence of this syndrome varies widely – from 5% to 76%—depending on the diagnostic methods used and the length of follow-up. The disability rate associated with DNS can reach up to 78%, while the mortality rate may be as high as 31%, placing a significant burden on both families and society.

The pathogenesis remains unclear. Several mechanisms have been proposed, including:

-Hypoxic/ischemic injury secondary to impaired oxygen transport and/or delivery to tissues

-Cardiovascular alterations

-CO binding to mitochondrial cytochromes, leading to respiratory chain dysfunction

-Lipid peroxidation in the brain, resulting in MBP (Myelin Basic Protein) damage

-Leukocyte adhesion to the endothelium of the cerebral microcirculation

-The role of excitatory amino acids

-Inhibition of endogenous antioxidant defense mechanisms

-Neuronal apoptosis and necrosis

-Autophagy

-Inflammatory and immune-mediated reactions in brain tissue, with significantly increased levels of IL4, IL6, IL13, and tumor necrosis factor-alpha (TNF-α) in blood or cerebrospinal fluid (CSF)

-Pathological hyperactivation of excitatory neurotransmission, potentially leading to excitotoxicity and subsequent synaptic and neuronal degeneration

The latency period between intoxication and symptom onset is estimated to be approximately 22.4 days (ranging from 2 to 40 days). The clinical presentation is highly variable in terms of symptom characteristics and severity. *(Table 2)*

Memory impairment	Urinar and fecal incontinence
Difficulty concentrating	Gait and postural disorders
Cognitive decline	Cortical blindness
Seizures	Symptomps and signs similar to those of Multiple Sclerosis
Peripheral neurophaties	Personality changes
Wernicke's aphasia	Korsakoff syndrome
Agnosia	Mutism
Psychotic episodes	Bipolar disorder
EEG abnormalities	Motor disorders (parkinsonism, choreoathetotic movements)

Table 2. Clinical presentation signs and symptoms

Cognitive deterioration often coincides with increased physical activity and/or mental stimulation during the post-acute recovery phase. For this reason, patients exposed to carbon monoxide (at least those who are symptomatic) should observe an appropriate period of physical rest and avoid mental and psychological overload**.**

Although there are no definitive predictive markers for the development of this clinical condition, several predisposing factors have been identified. (Table 3)

Age > 40 – 45 years	GCS ≤ 9 in the acute phase
Pre-existing cardiovascular abnormalities	Duration of CO exposure
Coma lasting at least 2-3 days	Perstince of EEG abnormalities
Delay in starting hyperbaric therapy	Seizures/epilepsy

Table 3. Predisposing factors for delayed neurological syndrome

Most studies indicate that hyperbaric oxygen therapy (HBOT) is associated with a lower incidence of neurological sequelae (both clinical and subclinical), including post-interval neurological syndrome.

Delayed neurological syndrome may resolve spontaneously, require up to two years for clinical improvement, or in some cases, may be permanent. Once the acute phase has been resolved, follow-up becomes essential to monitor the resolution of potential cardiac damage and the appearance of neurological symptoms (i.e., delayed neurological syndrome).

All patients should undergo a thorough follow-up for a period of at least 8 months. The follow-up pathway should initially include:

-Serial neuropsychological testing,

-Possibly accompanied by a neurological evaluation.

Neuropsychometric tests should be administered to all patients exposed to CO (as evidenced by abnormal COHb levels and/or clinical signs and symptoms of intoxication).

These tests should be performed at the end of the oxygen therapy session (whether hyperbaric or normobaric) and repeated at regular intervals thereafter. Ideally, if clinical conditions allow, they should also be performed before the oxygen therapy session in poisoned patients. Neuropsychological tests should be compared with previous results to identify any abnormalities or changes. A thorough neurological examination before and after the oxygen therapy session is essential as a clinical baseline.

The assessment of delayed CO-related damage in patients with neurological disorders should also include neurophysiological investigations and neuroimaging techniques.

Electroencephalography (EEG) is a simple, non-invasive, and low-cost neurophysiological monitoring tool. In patients with post-interval neurological syndrome, EEG may reveal:

-Irregular theta waves of medium-low amplitude

-High-amplitude delta waves

Abnormalities may be detected even in the absence of clinical symptoms during the recovery phase. There is a correlation between the EEG alteration rate and the severity of delayed neurological syndrome. EEG may also have a predictive role in the onset of post-interval syndrome.

Brain Evoked Potentials (BEP) can reflect cerebral function by detecting electrical signals generated in response to specific stimuli (e.g., sound, light). These include:

-Visual Evoked Potentials (VEP)

-Somatosensory Evoked Potentials (SEP)

-Brainstem Auditory Evoked Potentials (BAEP)

Patients with post-interval neurological syndrome often show abnormal BAEP peak and inter-peak latencies. VEP, SEP, and BAEP are sensitive indicators for assessing brain dysfunction and predicting syndrome onset. However, the execution and interpretation of EEG and evoked potentials require trained professionals.

Among neuroimaging techniques, Magnetic Resonance Imaging (MRI) and Single-Photon Emission Computed Tomography (SPECT) are more sensitive than standard CT scans in detecting, even at early stages, central nervous system abnormalities. In some cases, the combination of multiple techniques can improve diagnostic accuracy.

Delayed neurological syndrome must be included in the differential diagnosis with other major neurological disorders, such as:

-Meningoencephalitis

-Dementia syndromes

-Parkinson's disease and parkinsonism

-Expansive intracranial processes

-Cerebrovascular diseases

-Psychiatric syndromes

-Epilepsy, etc.

For this purpose, all instrumental and laboratory diagnostic tools should be employed. A detailed clinical history (CO poisoning, predisposing factors for delayed neurological syndrome, hyperbaric treatment), along

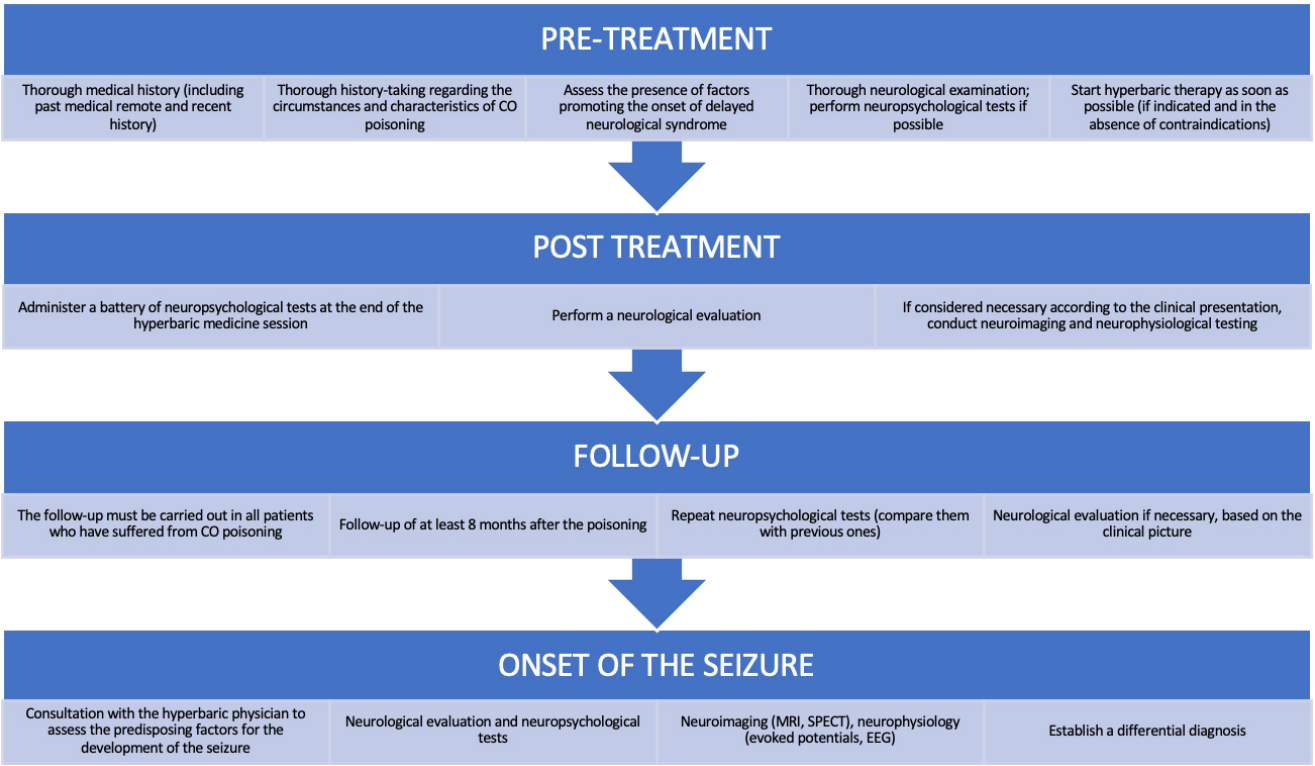
with consultation with the hyperbaric physician, is essential for an accurate diagnosis.

Currently, due to limited awareness among healthcare professionals, this syndrome is underestimated, and diagnosis is often challenging and/or incorrect. Follow-up is frequently inadequate or not implemented, either due to lack of sensitivity or organizational and logistical issues. This inevitably leads to delayed or missed diagnoses.

Often, patients who develop symptoms consult a neurologist, but the lack of connection to their history of CO poisoning may hinder the diagnostic process.

The use of simple clinical algorithms could help draw attention to this syndrome and facilitate evaluation.

Below, we propose a simple algorithm for the assessment and management of delayed neurological syndrome. (Figure 1)



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