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Co-morbidities in the multiple victims of the silent killer in carbon monoxide poisoning

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Abstract

Carbon monoxide (CO) remains an insidious and silent killer due to its physical and chemical properties; its lethal effects are encountered in cases of household accidents, occupational hazards or suicide. Deaths due to CO poisoning were studied retrospectively in the period 2000–2018 at the Institute of Forensic Medicine, Timişoara, Romania. These cases represent 1.75% of all the autopsies and 0.63% of all violent deaths. There have been cases of single deaths and cases with multiple victims – concomitant deaths. The analysis of lethal CO intoxication cases that occurred in different circumstances (incomplete burning with CO accumulation, fires – associated with burns, death in the fountain – due to fossil fuel pump failure, suicide due to exhaust gases) was based on the examination of 298 autopsy files. In this type of poisoning, the forensic examination of the body is marked by the non-specific character of most of the macroscopic and microscopic changes. Although inconstant, these types of changes (*e.g.*, red discoloration of *livor mortis*) raise the suspicion of death by CO poisoning; the essential contribution to establishing cause of death resides in the determination of carboxyhemoglobin (COHb) concentration by spectroscopy. In all cases, the cerebral and cardio-pulmonary modification and their contribution to the cause of death were studied. Co-morbidities interfere with the cause of death in cases with average COHb concentrations, in the 20–50% range, where CO blood levels alone are not reason enough to explain the onset of death.

Keywords: carbon monoxide poisoning, multiple victims, co-morbidities.

Introduction

Data published in the last years show that carbon monoxide (CO) intoxication is the number one cause of death due to intoxications in Romania, while in the US is responsible for more than half of the lethal intoxications [1], although the number of deaths decreased with more than 50% [2], from 3500 to 1319 [3–5].

Because of its physical and chemical properties and its non-specific symptomatology CO is called "the silent killer" [6]. CO is a colorless, odorless and tasteless gas that contains 57.13% oxygen and 42.83% carbon (1 kg of CO contains 0.428 kg C and 0.5713 kg O_2), with a molecular weight of 28.01. CO is less dense than air, which makes it rise to the upper parts of enclosures. Because of its density, CO easily diffuses through porous walls, even through thin, overheated, iron or cast iron walls of coal or wood-burning stoves [7]. It has high affinity for O_2, a strong reducing character [8] and 2–6 months half-life in the atmosphere [9].

The toxic properties of CO derive from its capacity to rapidly combine with hemoglobin, thus forming carboxy-hemoglobin (COHb). Due to its incapacity to transport O_2, COHb diminishes the blood content of O_2 and it diminishes tissular oxygenation because it is a much stable compound than HbO_2 [10]. The effects of CO intoxication on the human body are called oxycarbonism, which can be acute or chronic, depending on the quantity and length of exposure to the gas. The most affected organs are the most sensitive to lack of O_2 (brain, heart), or those with intensive metabolic activity (the liver), where the hypoxic or toxic factor manifests before the onset of clinical symptoms [7].

The external sources of CO are the metallurgical and chemical industry and the household appliances. An often-neglected source of CO is methylene chloride, an aliphatic halogenated hydrocarbon, with sweet taste, resembling chloroform [11]. It is a usual component of paint removers and other solvents [12]. Methylene chloride is absorbed in the lungs, digestive tract and through the skin. Inhaling is, however, the main gate into the human organism [11]. The metabolism of methylene chloride to CO is complex, especially considering the possibility of concomitant exposure to CO [13]. Possible household sources of CO include: clogged chimneys; improperly ventilated fireplaces, gas or wood-burning stoves; non-ventilated, fuel heaters; faulty gas exhaustion pipes; fuel-based engines running in closed spaces; coal barbeques burning in closed spaces; gas water heaters or other improperly ventilated devices [14]. The result of the massive increase in the numbers of cars was a rapid increase of CO emissions, even more so in urban areas

where traffic is much more intense [15]. Increased CO concentrations can also appear in tunnels [1]. CO emissions of motor vehicles increase dramatically in the cold season. That is because, on one hand, engines require more fuel to start up at low temperatures and, on the other hand, because some gas emission control devices (*e.g.*, the O_2 sensor) are less efficient when cold [16].

Lethal intoxications can accidentally occur due to the CO content of exhaustion gases in garages [17], where lethal COHb concentrations can be reached in approximately 10 minutes [18]. These types of incidents are also more likely to happen in cold weather, when ignited engines are left running in garages. Faulty gas evacuation systems of either moving or stationing vehicles can also lead to lethal intoxications [19].

CO emissions of motor vehicles vary within a large range, depending in the type of car, horsepower, the overall technical state of the engine [15] and the car model [19]. Catalytic convertors, which transform CO in CO_2 and water, can reduce CO emissions up to 80% [16].

Endogenous CO sources are represented by the oxidative catabolism of the heme complex, through the heme oxygenation enzymes. CO acts as a neuromodulator, by regulating cellular proliferation, platelet aggregation and apoptosis [20, 21]. When heme metabolism is abnormally increased (*e.g.*, in hemolysis), the CO production raises significantly [22]. High endogenous CO values have been also detected in severe sepsis [23]. Certain drugs, such as nicotinic acid [24], compounds with alyl complex (acetamides, barbiturate) [25], diphenylhydantoin [26], progesterone [27], contraceptives, increase the endogenous CO production. Generally speaking, any substance that increases the bilirubin production will also increase the CO levels [24]. Marks *et al.* launched the hypothesis that endogenous CO might play a role in certain biological processes [28]. Recent studies demonstrated that CO plays an intracellular messenger role, with anti-inflammatory [29], anti-apoptotic [30] and vasodilatation effects [31].

The aim of our study was to identify the contribution of the underlying pathology to the cause of death in cases with multiple victims, the differences between COHb concentrations among victims and the acute changes that occurred due to CO intoxication.

Materials and Methods

The study group was represented by 298 autopsy files regarding deaths due to CO intoxication and fire incidents. We also included deaths due to concurrent factors, if one of them was CO intoxication. The study covered a 19-year (2000–2018) period in the Institute of Forensic Medicine, Timişoara, Romania. The database contained information form 199 autopsy files. We used Microsoft Excel, component of Microsoft Office 2007. The data were also statistically processed using the STATA 12 program (STATA Corp, College Station, TX, USA). Besides Hematoxylin–Eosin (HE) staining, in some cases we also used Goldner–Szekely (GS) trichrome staining.

Results

In most cases, victims were found dead at home, or were victims of fires at home. Only a small percentage of deaths occurred within traffic accidents followed by fire incidents, in incidents where victims were found dead in garages, in running vehicles, in aircraft accidents, after electrocutions followed by fires or in situations where the victims died while cleaning a well with a gas pump, or descended in the well while the fossil fuel pump was running.

The distribution of locations is, as in other types of accidental and suicidal deaths, centripetal – most deaths occur at the victim's home, followed by other locations.

In most cases, the cause of death was CO acute intoxication (Figure 1).

From the epidemiological point of view, the study group is dominated by male victims, the centripetal distribution of locations (mostly victims' homes) and the case crowding in the cold seasons (Figure 2).

Victims are mostly men because men are more frequently involved in potentially dangerous activities (driving vehicles and planes) or CO intoxication, some in peculiar circumstances (engine repairs, well cleaning), and also because of the higher suicide rates for the male gender.

The monthly distribution of cases shows that 84.65% of deaths occurred in the cold season, between October and March. The result is similar with data reported in literature; numerous authors underline the seasonal character of this type of death, along with other hibernal causes of deaths, such as hypothermia.

The death cause was mostly CO intoxication, followed by thermal burns and death due to concurrent causes or other causes. In most of CO intoxication deaths, burns were completely absent. In the rest of the cases, the associated burns were severe and extended over more than 50% bodily surface.

In fire victims, the CO blood concentration is very important in establishing the moment of death, in correlation with the fire onset. A 10% or lower COHb concentration indicates the fact that death onset before the burns; values between 10% and 30% are difficult to interpret; values between 30–40% or higher indicate that the burns where produced ante mortem [32]. In cases of fire with multiple victims, COHb values can indicate both the moment of death, in correlation with the fire onset and the moment of one person's death in correlation with the moment of death of the other victims.

Out of the 63 fire victims who died due to CO poisoning, in 31 cases soot was found in the upper air passages (Figure 3) and lower air passages (Figure 4). The lungs had a specific hypoxic aspect in 11.26% of the cases and presented sub-pleural petechiae in 25% if cases; pulmonary edema was described in 38.18% and pulmonary stasis in 50% of the cases.

In more than half of the cases (57.81%), the blood alcohol level at the time of death was zero. There was no significant correlation between the blood alcohol level and the COHb concentration (p=0.46).

Under the age of 19, with two exceptions, the underage were victims of household incidents, dead on the scene,

either due to CO poisoning, probably because of improper heating devices, or due to fire-related injuries. Active age groups – 20 to 49 years old – show a larger variety of circumstances for death onset. In most cases death occurred at home, either due to CO poisoning, or due to fire-related injuries; there were also cases in which death was secondary to other various occupational hazards. In victims over 50 years old, with one exception – a person found dead in the car, all cases were victims of household incidents.

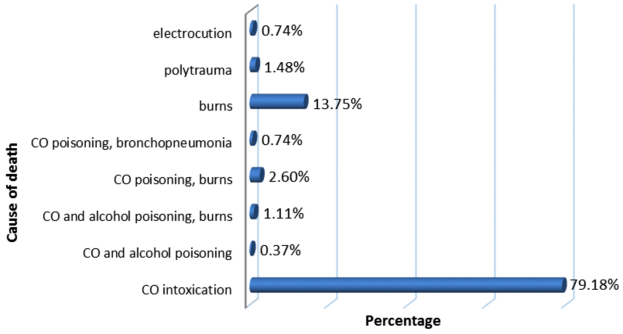

Figure 1 – ***Case distribution according to the cause of death. CO: Carbon monoxide.***

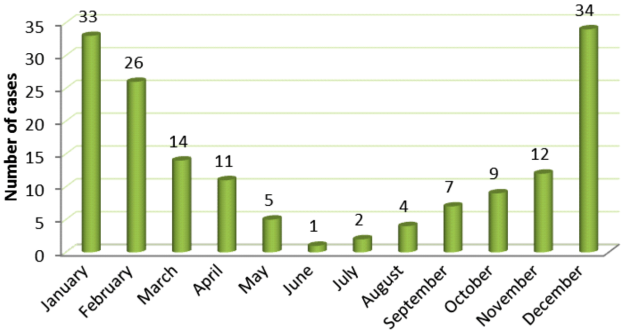

Figure 2 – ***Monthly distribution of the cases. (Case distribution based on the date of death).***

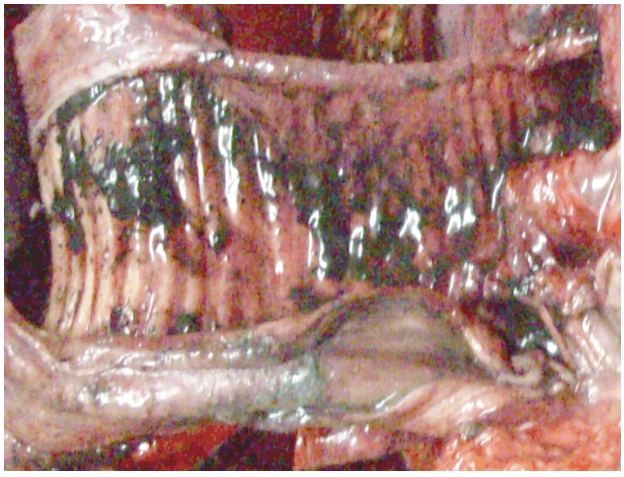

Figure 3 – ***Macroscopic image of trachea with soot deposits.***

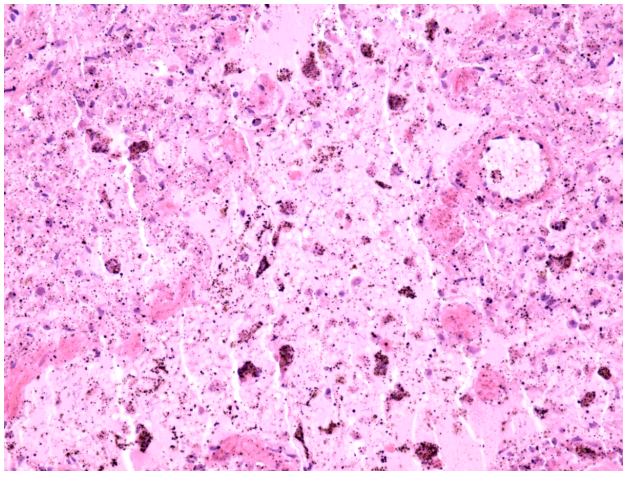

Figure 4 – ***Lung parenchyma with serohematic edema and black powder deposits (HE staining, ×200).***

We found no significant differences between COHb concentrations in victims of extreme ages (less than one year and over 65 years old) and the other age groups – $t(218)=0.92$, $p=0.35$.

The only specific sign – the particular discoloration of *livor mortis* (Figure 5) – is a constant indicator when violent death due to CO intoxication is suspected; it signifies the presence of COHb, which can be proven by the spectroscopic examination of the blood.

We believe that cerebral edema is an early manifestation of CO poisoning. Cerebral changes depend on the severity and the length of O_2 depriving, but also on the mechanism of O_2 levels decrease, more so then on the cause of the lack of O_2. In our study, cerebral edema characterized by perivascular and perineuronal edema, was associated with, granular dystrophy in the cortical neurons (Figures 6 and 7), leptomeningeal edema, perivascular hemorrhage in the Virchow–Robin space (Figure 8) and cerebral vascular stasis. Other identified acute changes was perivascular hematic extravasations in the subcortical brain matter, myocardial edema and, edema, emphysema and micro-hemorrhages pulmonary (Figures 9–11).

In our study, they did not exist statistically significant correlation between the COHb concentrations in cases with or without associated cardio-pulmonary or cerebral pathology.

Although, in most cases (83.36%) death occurred at COHb concentrations over 70%, CO could cause death at concentrations below 50%, when pre-existing organic conditions were associated (the autopsy most frequently revealed: myocardial fibrosis, cardiac lipomatosis, pulmonary sclero-emphysema, pulmonary tuberculosis, pulmonary carcinoma, pulmonary fibrosis, pneumonia or hyaline membrane disease – in a 2-weeks-old suckling). Degenerative cardio-pulmonary conditions (myocardial fibrosis and systemic atherosclerosis) as the most frequent, followed by hepatic dystrophy and steatosis and renal dystrophy (Figures 12 and 13).

Although in multiple deaths cases, because of the similar conditions of death onset, one would expect COHb concentrations to be similar, practice shows that this is not always the case. The COHb blood concentrations of multiple victims incidents can differ with as much as 50% and this can even lead to concluding towards different causes of death within the same incident.

In our study, we identified a case with multiple victims – three men with ages between 25 and 55 years

old, found dead in a well in which a fossil fuel generator was running. COHb concentrations were 73%, 87% and 91%, respectively.

With three exceptions, the differences in COHb concentrations in multiple victims' incidents were lower than 15% (Figure 14).

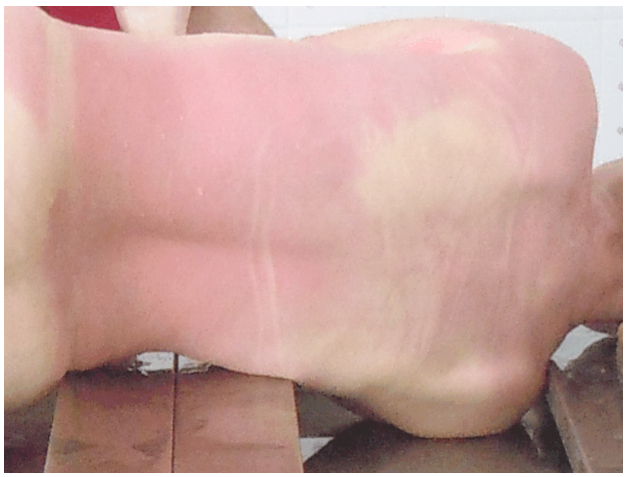

Figure 5 – ***Red discoloration of livor mortis.***

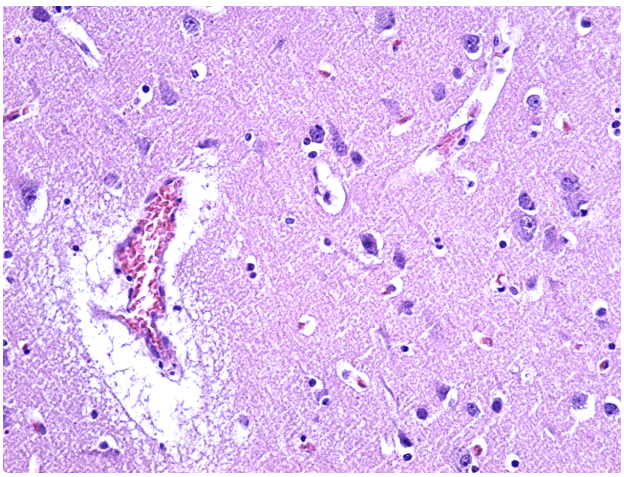

Figure 6 – ***The cerebral hemisphere with edema: diffuse large around the neurons and perivascular spaces with dissection of the nervous parenchyma (HE staining, ×200).***

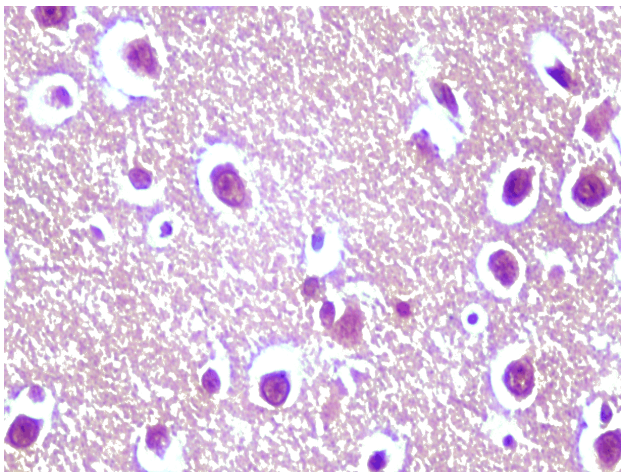

Figure 7 – ***Image of an area of cerebral parenchyma with perineuronal edema and granular dystrophy of the cerebral cortex' neurons (HE staining, ×200).***

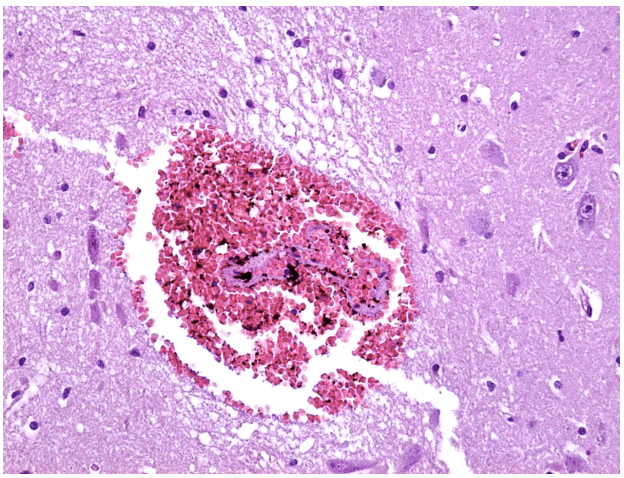

Figure 8 – ***Perivascular hemorrhage in Virchow–Robin space, in a cortical area (HE staining, ×200).***

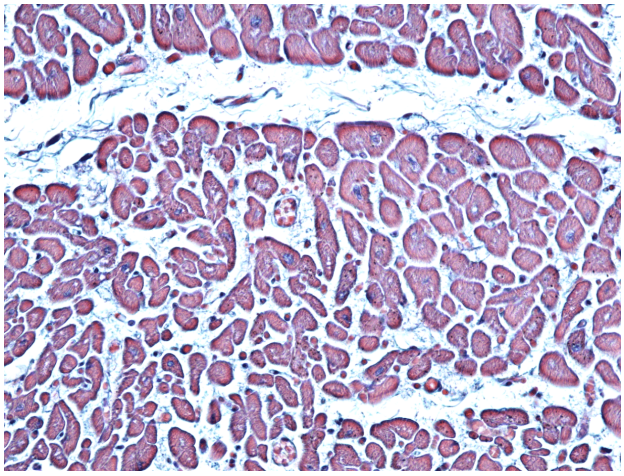

Figure 9 – ***Myocardium area with diffuse interstitial edema, characterized by the interstitial space (GS trichrome staining, ×100).***

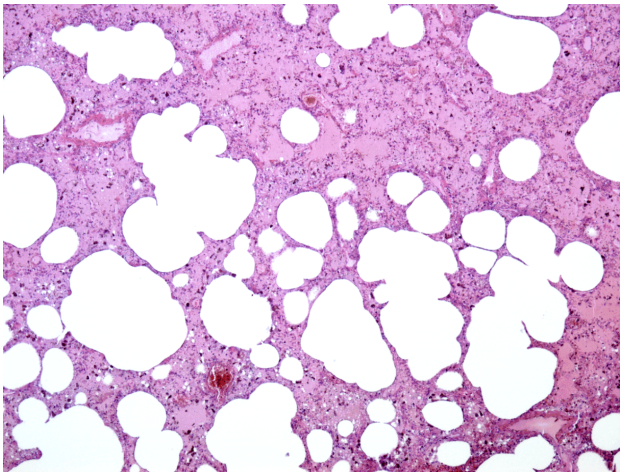

Figure 10 – ***Parenchyma pulmonary with areas of edema and emphysema (HE staining, ×40).***

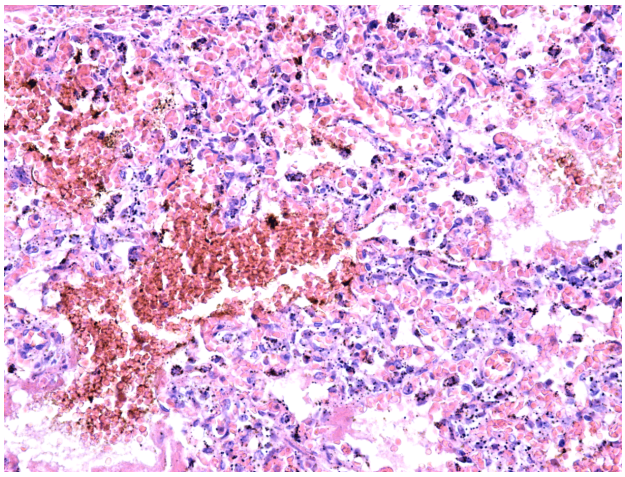

Figure 11 – ***Lung parenchyma area with vascular congestion and microhemorrhages (HE staining, ×200).***

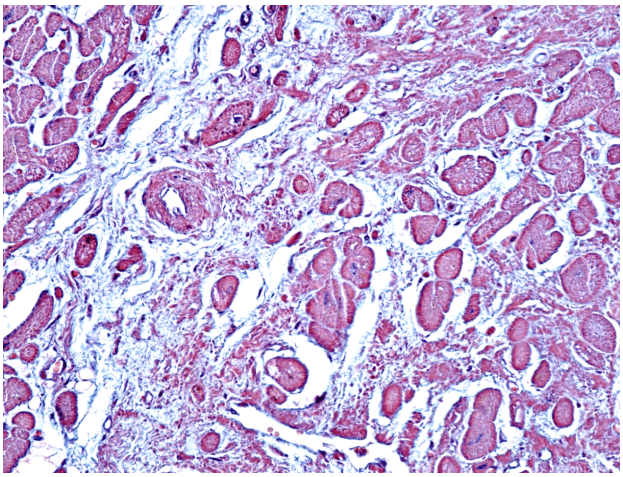

Figure 12 – ***Myocardial fibrosis: diffusely interstitial and perivascular bluish collagen fibers (GS trichrome staining, ×100).***

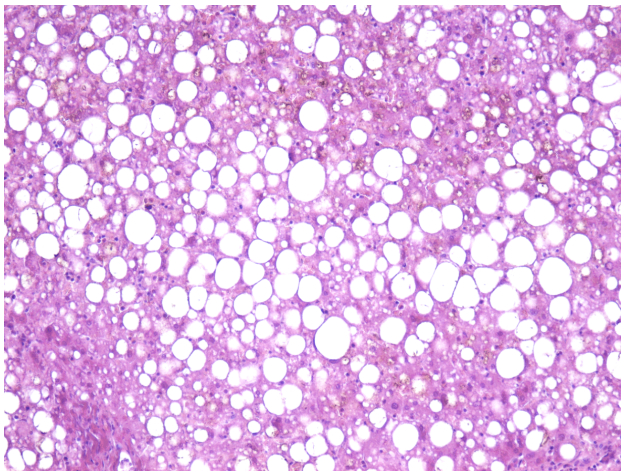

Figure 13 – ***Image of extensive macrovacuolar hepatic steatosis (HE staining, ×100).***

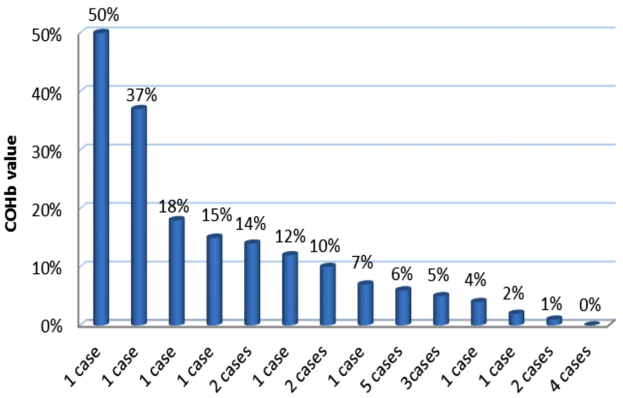

Figure 14 – ***The differences in COHb levels in multiple victims' incidents. COHb: Carboxyhemoglobin.***

Discussions

Due to its physical features, CO is an insidious danger. Its lethal effects manifest in connection with household accidents, occupational hazards or suicidal gestures.

In most cases, death due to CO intoxication is accidental, it occurs in domestic or work environments; it can make single as well as multiple victims. A peak of lethal CO intoxication is reported in the cold months of the year when faulty heating devices are used and the ventilation systems are closed.

Numerous studies have shown that clinical symptoms begin to appear once the toxic dose is reached, which corresponds to the blood CO level or the COHb concentration that causes the progressive onset of symptoms [32, 33]; the toxicity threshold is very important in practice as it is an essential objective for establishing the cause of death [13].

Wollersen *et al.* present three cases of CO intoxication, each with two victims. In all cases, COHb concentrations were high, the difference between concentrations were 3%, 14% and 8%, respectively [34].

Another study refers to an accidental exposure of 38 soldiers to CO, in an enclosure, adjacent to a small room with a gas generator. The authors show that, against all expectations, no correlations could be made between COHb concentrations and the distance of victims from the generator room [35].

Thus, values below 2–3% COHb are considered normal in non-smokers, people who smoke or inhale smoke may reach values up to 10% or even 15% COHb [36–39]. The 20–30% COHb range is more difficult to interpret, when interactions with other combustion gases such as cyanide, hydrogen sulphide (H_2S), acrolein, or methylene chloride (chlorinated hydrocarbon) spray applications can be suspected. The endogenous CO formation from heme degradation can also be discussed [40].

The probability that death is due to CO intoxication increases at concentrations between 30–50% COHb especially if risk factors are associated – we are taking into consideration organic diseases susceptible to decompensate the bodily functions associated with CO intoxication within average levels. Death occurs rapidly at values above 50% [41].

Death occurs when the exposure, even short-term, at lethal doses, takes place, which is when a concentration of 66% COHb is reached, respectively when 2/3 of the total hemoglobin is combined with CO. Under normal atmospheric conditions, this coefficient corresponds to a concentration of 1/500 CO.

The study shows that the lethal dose varies, depending on the amount of CO in the air, the length of exposure, the individual and the environmental conditions. The lethal dose for children and elderly is lower than for adults and the lethal dose for individuals addicted to morphine is higher than that of average adults [42]. As far as age is concerned, children are much more sensitive than adults because of the higher respiratory rate. Women tolerate CO better than men do [7].

Physical activity, pulmonary and coronary diseases induce increased O_2 consumption and can cause death at lower COHb concentrations. Regarding the length of exposure, this is inversely proportional to the CO concentration in the air – the higher the CO concentration in the air, the shorter the exposure time for reaching lethal levels and vice versa [13].

Some autoptic findings are considered to be risk factors that contribute, in association with the COHb elevated levels, to death onset; recently, massive subarachnoid hemorrhage has been incriminated, along with CO intoxication. Exposure to CO may be a primary cause, or it can act in corroboration with the vasodilator effects of CO on the cerebral endothelium, to determine loss of vascular integrity with subarachnoid hemorrhage [43].

Alcohol consumption is known to be a risk factor for deaths during fires. However, it is less clear whether there is a physiological interaction between ethanol and CO, which changes the saturation level of COHb (saturated COHb), identified as a certain etiological factor for death onset.

Some studies indicate that ethanol does not affect the COHb levels in cases where CO intoxication is the cause of death, because ethylic alcohol does not directly interact with COHb formation [44].

COHb and oxyhemoglobin can only be detected in fresh blood, because if the blood is putrefied hemoglobin is converted to alkaline hematin (under the effect of NH_4^+), which then passes into hemochromogen (under the effect of H_2S). The hemochromogen spectrum is similar to that of oxyhemoglobin.

The spectroscopic method, slightly sensitive but very specific, is indicated for the identification of COHb, with the condition that the sampled blood is not putrefied [45].

Conclusions

In order of frequency, the acute changes induced by CO intoxication were: cerebral edema, pulmonary stasis, pulmonary edema, cerebral stasis, leptomeningeal edema, the hypoxic lung, perivascular cerebral hemorrhage and subarachnoid hemorrhages.

Cardio-pulmonary conditions, such as pulmonary fibrosis, pneumonia, pulmonary sclero-emphysema, myocardial or liver fibrosis and lipomatosis, highlights the contribution of the underlying pathology in the cause of death, when the COHb concentration ranges between 20% and 50%, thus determining the cause of death.

Although the statistical analysis did not show any significant correlations between COHb concentrations lower than 50% and the pre-existing pathology, the interpretation of death-generating mechanisms took pre-existing conditions into account, as risk factors for death onset.

In CO intoxications with multiple victims, because the circumstances are almost identical and the death-generating mechanisms are similar, the differences between COHb concentrations among victims were situated between 0% and 15%. Our study does not exclude the possibility that, in the same incident, multiple victims can have completely different COHb values (even with 50%). The forensic algorithm of interpreting the onset of death in such events can even lead to different causes of death.

Conflict of interests

The authors declare that they have no conflict of interests.

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