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Original Article

Clinical Characteristics and Neurological Findings of Pediatric Patients with Acute Carbon Monoxide Intoxication

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ABSTRACT

Aim: The aim of this study is to analyze children with acute carbon monoxide (CO) poisoning and to present two patients with rare neuroradiological findings.

Materials and Methods: We identified and reviewed the medical records of pediatric patients diagnosed with acute CO intoxication who were hospitalized in our department during a 10-year period. Epidemiologic and clinical data were collected and analyzed.

Results: A total of 326 children (166 girls, 160 boys; age range 1 to 17.8 years) with CO poisoning were identified. Their ages ranged from 1 to 17.8 years, with a mean of 8.3±4.8 years. Improperly vented coal or wood stoves were the most common (80.7%) cause of intoxication. The most common presenting symptoms were nausea/vomiting and headache. Seizure was seen in 32 patients (9.8%). Two patients died and the mortality was 0.6%. All patients received normobaric oxygen therapy until their carboxyhemoglobin (COHb) levels were decreased below 2% and their symptoms resolved. One hundred of the 326 patients (30.7%) also were treated with hyperbaric oxygen (HBO) therapy as indicated by the signs and symptoms or COHb levels. Brain imaging was performed in 19 patients (thirteen magnetic resonance imaging and six computerized tomography), and was normal in 15. Acute brain stem demyelination related to water pipe smoking developed in one patient. All patients showed complete recovery without neurological sequelae except one who had mild right hemiparesis at discharge.

Conclusion: Acute CO intoxication is an important health problem in our country, especially in winter, because of poorly functioning heating systems. The clinical spectrum including neurological findings varies during childhood. We suggest that HBO therapy could be used safely in children. We believe that the combined administration of pulse methylprednisolone and HBO treatment might reduce cerebral damage caused by CO poisoning in selected pediatric patients.

Keywords: Acute carbon monoxide intoxication, clinical features, neurological findings, children

Introduction

Carbon monoxide (CO) causes direct cellular damage and tissue hypoxia by shifting the oxyhemoglobin dissociation curve to the left as it competes with oxygen for binding to hemoglobin. As a result, tissue oxygen extraction is hampered and oxidative stress causes tissue damage and clinical symptoms. CO is highly toxic for cardiac and cerebral tissue as these tissues have a higher metabolic

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rate and thus are sensitive to hypoxia (1). Symptoms of mild CO intoxication such as fatigue, headache, nausea and vomiting are non-specific. Visual disturbances, confusion, ataxia, seizure, loss of consciousness and death have also been reported in cases of moderate or severe exposure. Children are more sensitive to the toxic effects of CO and become symptomatic earlier than adults since their blood volume is lower, basal metabolic rate is higher and tissue oxygen demand is greater (2). There are few studies on CO poisoning in children, especially concerning neurological and neuroradiological findings. The purpose of this study is to describe and analyze the clinical features, treatment, neuroradiological findings and outcomes in children who were admitted with CO intoxication.

Materials and Methods

This study was performed retrospectively among pediatric patients who were admitted to the Emergency Department of Dr. Sami Ulus Training and Research Hospital due to CO poisoning between January 2007 and December 2017. Clinical and laboratory data were obtained from electronic hospital records retrospectively. Carboxyhemoglobin (COHb) levels higher than 2% were considered as abnormal. A child having manifest symptoms of CO intoxication but a normal COHb level was accepted as acute CO poisoning if the child or family members had a history of CO exposure. Children with chronic pulmonary, cardiac, neurological or metabolic disease were excluded from this study. The age and gender of the patients, source of CO exposure, vital signs, Glasgow Coma scale (GCS) scores, laboratory results, treatment modalities, total hospital stay, results of computerized tomography (CT) and cranial magnetic resonance imaging (MRI) were recorded. Neurological abnormality was defined as altered consciousness, seizure, ataxia, or abnormal neurological examination findings at presentation. Cardiological abnormality was defined as changes in electrocardiography (ECG) and an increase in Troponin I or creatine kinase-myocardial band (CK-MB) levels and severe metabolic acidosis was defined as an arterial blood pH lower than 7.15.

All patients were treated with normobaric oxygen (NBO) therapy at a rate of 10 L/min with a non-rebreathing face mask. The indications for hyperbaric oxygen (HBO) therapy were positive neurological symptoms (seizures, coma, lethargy, syncope) at presentation, refractory neurological symptoms after NBO therapy, COHb level greater than 25% or cardiac abnormality. A military based HBO therapy center in our city was consulted in cases of HBO requirement as our center lacks a HBO chamber.

This study was approved by the ethics committee of Ankara Training and Research Hospital Local Ethics Committee. Informed consent was obtained from the parents/care givers of the patients.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± standard deviation for normal distributions, and median (range) for skewed distributions. Categorical data were described in terms of the number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann-Whitney U test was applied for comparisons of non-normally distributed data. While the differences in normally distributed variables among more than two independent groups were analyzed by One-Way ANOVA, otherwise, Kruskal-Wallis test was applied for comparisons of the non-normally data.

Results

A total of 326 children (160 males and 166 females) with CO poisoning were included in this study. They were between 1 month and 17.8 years old, with a mean of 8.3±4.8 years. The majority of poisonings happened during colder seasons (78.8%). The distribution of the patients according to the source of intoxication is summarized in Table I.

One hundred and forty-four of the patients (44.1%) arrived at the hospital on their own while 182 (55.8%) patients were brought by an ambulance. Before admission, 49.4% of the patients had been given NBO therapy and 6.7% had received HBO therapy in another center. COHb levels varied between 0.1% and 47.5% with a mean value of 15.4±9.6%. Fifty-one (15.6%) patients had an initial CO level greater than 25%. Forty-eight (14.7%) patients were asymptomatic but were accepted as possible poisonings

Table I. The distribution of the patients according to source of intoxication (n=326)

Source of exposure	Number of patients (%)
Coal or wood stoves	263 (80.7)
Natural gas	57 (17.5)
House fires	5 (1.5)
Hookah	1 (0.3)

since other family members had overt CO poisoning. The distribution of initial symptoms and COHb levels are given in Table II.

While most patients had normal physical examination findings (n=310, 95.1%), 9 patients were lethargic, 6 patients were in coma and 1 patient had internuclear ophthalmoplegia. It was observed that asymptomatic cases had lower COHb levels with statistical significance than all findings except altered mental status ($p<0.05$). Twenty-one patients were admitted to the intensive care unit with a mean stay duration of 111.3±106.7 hours (range: 10-480 hours). All patients with abnormal neurological examination and 5 patients with normal examination were followed up in the intensive care unit. One of these patients was a 1-month-old who had a plasma CO level of 19.4 and had seizures. Therefore, he was admitted to the intensive care unit for follow-up. The other 4 patients had a COHb level of over 25, and they had seizures prior to admission. Arterial blood gas measurements were performed in 281 patients, the mean pH level was 7.372 (range: 6.823-7.540); 3 children had severe metabolic acidosis. Lactate levels were elevated in 24 patients, CK-MB in 39 patients, troponin I in 30 patients and lactate dehydrogenase in 8 patients. No ECG abnormalities were detected except sinus tachycardia in two patients. Disseminated intravascular coagulation developed in five patients. Inhalation pneumonitis and acute respiratory distress syndrome developed in two of the five house fire victims. Two patients died because of sepsis and multiple organ failure. All surviving patients were discharged without sequelae except one patient with cerebrovascular ischemia.

All patients were treated with NBO therapy and 30.7% (n=100) with HBO therapy. The number of HBO treatment sessions varied between 1 and 16, with a mean of 2 and the mean COHb level was 17.2±13.1 (range: 0.1-47.5). The symptoms of patients who needed HBO therapy were syncope (n=42), a decreased level of consciousness (n=32), seizures (n=26), headache (n=19), nausea/vomiting (n=19) and vertigo (n=11). No HBO treatment related complications were observed.

Cranial imaging was performed in 19 patients (13 MRIs and 6 CTs) and 15 were normal. Abnormal findings in cranial scans were cerebellar tonsillar herniation due to severe brain edema in 2 patients, cerebrovascular ischemia in 1 patient, and brainstem demyelination with thalamic involvement in 1 patient. Detailed clinical information and cranial imaging findings are presented in Table III.

Two acute CO intoxication cases of interest along with their neurological and radiological findings are presented below.

Case 1

A 16-year old male was brought to the emergency department with headache and diplopia. Headache and nausea had begun after smoking two hookahs (water-pipes used to smoke tobacco) in a closed environment 24 hours earlier. He noticed that he had diplopia when he woke up the next morning. Neurological examination revealed impairment of adduction in the left eye and nystagmus in the right eye on the rightward gaze. His COHb level was 39% and NBO treatment was initiated. Cranial MRI scan performed at the 24th hour revealed high intensity lesions at the left paramedian section of the pons, the medial segment of the left thalamus and left middle cerebellar peduncle on T2 sequences which showed mild contrast enhancement on T1 weighted sequences. The lesion at the left paramedian portion of the pons showed restricted diffusion on diffusion-weighted images. (Figure 1A-C). When cranial MRI and neurological examination findings were evaluated together, internuclear ophthalmoplegia due to CO intoxication was considered. HBO treatment with

Table II. Symptoms and signs of the patients on admission and COHb levels

Symptoms and signs*	Number of patients (%)	Mean COHb% level (range)**
Nausea/vomiting	133 (39.9)	16.1 (0.1-39.5)
Headache	121 (37.1)	16.3 (0.7-39.9)
Syncope	69 (21.2)	17.9 (0.1-47.5)
Vertigo/dizziness	47 (14.4)	17.4 (0.3-30.8)
Altered mental state	42 (12.9)	12.7 (0.1-47.5)
Seizure	32 (9.8)	19.1 (0.3-45)
Asymptomatic	48 (4.7)	11.4 (3-26)

*Many patients had more than one presenting symptom, **Most of the patients received oxygen therapy (NBO or HBO) prior to admission to our center, COHb: Carboxyhemoglobin, NBO: Normobaric oxygen, HBO: Hyperbaric oxygen

Table III. Clinical characteristics of patients performed brain imaging

Patient	Age (year)/sex	Source of exposure	Initial presentation	Treatment before admission	First COHb level	Neurologic examination	Laboratory results	Brain imaging	Treatment/ outcome
1	16/male	Water pipe	Headache diplopia	NBO	33.1	Internuclear ophthalmoplegia	Normal	MRI: High signal intensity in left paramedian portion of the pons, in left middle cerebellar peduncle and in the medial segment of left thalamus on T2-weighted image,and showed restricted diffusion on diffusion-weighted imaging	HBOT and IV Pulsed Methylprednisolone/ discharged without sequelae
2	6/male	Coalor wood stoves	Coma	3 seans HBO	3	Coma (GCS=3)	Increased liver function tests, CK, CK-MB, Troponin I	MRI: Bilateral asymmetrical (left predominant) hyperintensity in the anterior and posterior border zone feeding areas on T2-weighted and diffusion-weighted image, consistent with acute border zone infarctions	HBOT/discharged with a little weakness in the right hand fingers
3	15/female	Natural gas	Syncope	NBO	20	Normal	Normal	MRI: Normal	NBOT/discharged without sequelae
4	Two and a half/male	Coalor wood stoves	Syncope and consciousness disturbance	HBO	0.7	Normal	Normal	CT: Normal	NBO/discharged without sequelae
5	13/female	Coalor wood stoves	Syncope	No treatment	22.9	Normal	Normal	MRI: Normal	HBO/discharged without sequelae
6	5/female	Coalor wood stoves	Consciousness disturbance	NBO	17.9	Lethargy (GCS=12)	Normal	MRI: Normal	HBO/discharged without sequelae
7	15/male	Coalor wood stoves	Coma	NBO	0.5	Coma (GCS=3)	Severe metabolic acidosis, increased liver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae

Table III. contiuned

8	10/female	Coalor wood stoves	Syncope	No treatment	16	Normal	Normal	CT: Normal	NBO/discharged without sequelae
9	3/female	House fire	Coma	2 seans HBO	1.6	Coma (GCS=3)	Severe metabolic acidosis, increased liver function tests, CK, CK-MB, Troponin I	CT: Brain edema and cerebellar tonsillar herniation	Died
10	3/female	Coalor wood stoves	Seizure	NBO	16	Normal	Normal	MRI: Normal	HBO/discharged without sequelae
11	16/female	Natural gas	Consciousness disturbance	NBO	28.2	Lethargy (GCS=12)	Increased iver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
12	5/female	House fire	Coma	NBO	39	Coma (GCS=3)	Increased liver function tests, CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
13	16/female	Coalor wood stoves	Consciousness disturbance	1 seans HBO	1	Normal	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
14	15/female	Coalor wood stoves	Syncope headache	NBO	3.7	Normal	Increased Troponin I	CT and MRI: Normal	HBO/discharged without sequelae
15	12/male	House fire	Coma	1 seans HBO	0.1	Coma (GCS=3)	Increased CK, CK-MB, Troponin I	CT: Brain edema and cerebellar tonsillar herniation	Died
16	12/male	Coalor wood stoves	Coma	1 seans HBO	0.3	Coma (GCS=3) and ARDS	Increased CK, CK-MB, Troponin I	CT: Normal	HBO/discharged without sequelae
17	5/female	Coalor wood stoves	Coma	NBO	21	Coma (GCS=3)	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae
18	17/male	Coalor wood stoves	Seizure	NBO	10.6	Normal	Normal	CT: Normal	HBO/discharged without sequelae
19	16/male	Natural gas	Seizure	NBO	30.1	Normal	Increased CK, CK-MB, Troponin I	MRI: Normal	HBO/discharged without sequelae

NBO: Normobaric oxygen treatment, HBO: Hyperbaric oxygen treatment, GCS: Glasgow coma scale, ARDS: Acute respiratory distress syndrome, CT: Computed tomography, MRI: Magnetic resonance imaging, CK: Creatine kinase, CK-MB: Creatine kinase-myocardial band

simultaneous pulsed methylprednisolone (30 mg/kg/day for 5 days) was initiated. On the third day of steroid and HBO treatment, double vision resolved and the impairment of adduction in the left eye was significantly reduced. The patient was discharged without any sequelae after 7 days of hospitalization. MRI performed on the third week of follow-up revealed that the left cerebellar and left thalamic lesions had completely resolved and the size of the pontine lesion had significantly diminished. The patient's neurological examination at the third week was completely normal.

Case 2

A 6-year-old male patient had been found in an unconscious state in a room with a coal heater and was immediately taken to a local hospital. His GCS score was 5. He was immediately intubated and was given high-flow oxygen therapy. His COHb level was 25.5%. The patient was transferred to our center after one session of HBO treatment at another center in the same city. Upon arrival at our intensive care unit, his GCS score was 7 and he was being ventilated mechanically. His COHb level was 0.3% after 1 session of HBO treatment. Creatine phosphokinase was 41537 IU/L, CK-MB was 9605 U/L, aspartate aminotransferase was 605 U/L, alanine aminotransferase was 260 U/L, blood urea nitrogen was 33 mg/dL, creatinine was 0.84 mg/dL, lactate was 27.3 mg/dL, troponin I was 47 ng/L, prothrombin time was 15.6 seconds, international normalized ratio was 2.29, D-dimer was 3373 ng/mL. ECG and echocardiography were normal. After 72 hours, he gradually awakened and was extubated. On the 5th day of follow-up, his muscle strength in upper extremity was 3/5. Cranial CT revealed no abnormalities but MRI revealed bilateral asymmetrical (predominantly on the left) hyperintense lesions in the anterior and posterior border zones of the watershed areas of the middle cerebral arteries on T2-weighted and diffusion weighted sequences, consistent with acute watershed infarcts (Figure 2A-F). HBO treatment was administered in 16 sessions and physical therapy and rehabilitation were initiated. After 20 days, the patient was discharged from the hospital with physical therapy and rehabilitation recommendations. On the second year of follow-up, brain MRI was normal and neurologic examination revealed a slight weakness in the right-hand fingers. The patient was able to walk without support and did not have any difficulties at school.

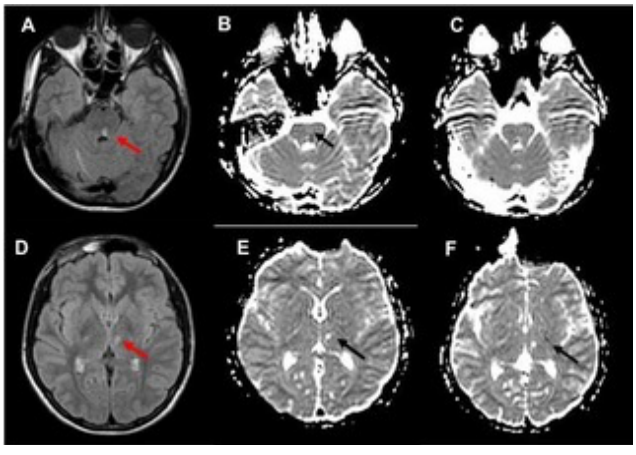

Figure 1. Initial 24 hr cranial MR scan of a 16-year old male with CO poisoning secondary to water pipe smoking shows high signal intensity lesion in the left paramedian section of the pons on Flair (A) (red arrow) which also shows diffusion restriction on ADC (black arrow) and is resolved on 3rd week control MR (C). Another lesion at the medial segment of the left thalamus on initial scan shows high signal on Flair (D) (red arrow) but no diffusion restriction on ADC initially (E) or on follow-up (F) (black arrows)
MR: Magnetic resonance, CO: Carbon monoxide, ADC: Apparent diffusion coefficient

Discussion

The incidence of CO poisoning depends on the region, geographical conditions, socio-economic status and seasons and it is more common in winter and in colder climates which are directly proportional to the need for heating. Stoves have been reported as the most common source of CO intoxication (3-5). Improperly vented coal or wood stoves were the most common (80.7%) source of CO intoxication in our study.

Interestingly, one patient had double vision following hookah smoking and internuclear ophthalmoplegia was detected in neurologic examination. The hookah, also known as nargileh, shisha, water-pipe or hubble-bubble is used to smoke tobacco. In recent years, it has become increasingly popular among adolescents and young adults. A widespread misconception is that the water purifies the smoke, thereby rendering it harmless. However, this type of smoking produces the same harmful substances as cigarette smoking (tar, nicotine, CO, etc.) and involves a serious risk of CO poisoning (6). A number of cases associated with

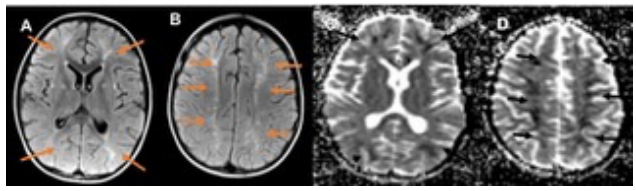

Figure 2. Cranial MRI of a 6-year old male intoxicated from stove shows bilateral asymmetrical hyperintensities in the anterior and posterior border zones on T2-weighted images (A-B) (red arrows) corresponding to areas of diffusion restriction on ADC images (C-D) (black arrows), consistent with acute border zone infarctions
MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient

hookah smoking have been previously reported (7-9). To the best of our knowledge, this is the first patient in the literature with internuclear ophthalmoplegia secondary to CO intoxication secondary to hookah smoking.

Children are more susceptible to the toxic effects of CO since they have fewer compensatory mechanisms against hypoxia and they need more oxygen due to their higher basal metabolic rate. Therefore, children become symptomatic earlier in the course of CO poisoning. Symptoms in pediatric patients are often non-specific, such as nausea and vomiting, and may be easily misdiagnosed as a viral infection (10,11). In our study, we found that symptoms such as nausea, vomiting, headache, syncope and impaired consciousness were the most common symptoms. The prevalence of seizures in CO poisoning in children has been reported at rates ranging from 2.1% to 23.3% in the literature (5,12,13). Seizures were observed in 32 cases (9.8%) in our study. We observed that the mean COHb levels of the patients presented with syncope and seizure were relatively higher than the others. Lower COHb levels were detected compared to all findings except for altered mental status in asymptomatic patients. However, no definite clinical relationship was found between the CO levels and clinical symptoms of the patients. This finding had a correlation with previous studies. This is why our hospital is a tertiary center so that patients with neurological symptoms such as syncope, seizures and altered mental status will highly referred.

COHb levels were greater than 25% in 51 (15.6%) patients and were normal in 23 (7%) patients. Before admission to our center, 49.4% of the patients had been given NBO therapy and 6.7% had been given HBO therapy in another center. The half-life of COHb is 4-5 hours in room air, and this decreases to 60 minutes when breathing 100% oxygen and further decreases to 15-30 minutes during HBO therapy (14). We believe that those patients who applied to the emergency department with normal CO levels had longer transportation times while receiving 100% oxygen treatment with a mask in the ambulance and thus, the measured values did not reflect the actual COHb levels. Therefore, we think that the presence of normal CO levels in children does not exclude the diagnosis of severe intoxication.

Tissue hypoxia is the main consequence of CO intoxication, so the basis of treatment is to give oxygen through the mask or in a hyperbaric chamber (15). HBO increases the dissolved oxygen level in the plasma thus enhancing oxygen delivery to the tissues. HBO also modulates mitochondrial oxidative metabolism, lipid peroxidation and neuronal apoptosis (16-19). Generally accepted indications for HBO treatment in children with acute CO poisoning are severe neurologic symptoms at presentation, continued neurologic symptoms after NBO therapy, myocardial ischemia and cardiac dysrhythmias, abnormal neuropsychiatric findings, high COHb levels and infants under six months with symptoms such as lethargy, irritability or poor feeding (20-22). It is recommended that the first session of HBO treatment be administered within 4-6 hours of poisoning and the recommended number of sessions is at least two (23,24). In our study, all patients were treated with NBO and 100 patients (30.7%) were treated with an average of 2 sessions of HBO treatment. HBO therapy was initiated within the first 24 hours and the most frequent indication for HBO treatment was syncope and altered mental status. HBO treatment is not free of side effects which include painful barotrauma, decompression sickness, pulmonary edema and hemorrhage, seizures and oxygen toxicity (25,26). In our study, almost all patients who received HBO treatment were discharged in a healthy condition.

The nervous system is highly sensitive to the toxic effects of CO. Some brain regions including the cerebral cortex, the white matter, the basal nuclei and the cerebellar Purkinje cells are highly sensitive to hypoxic damage. The globus pallidus is more prone to injury due to its high concentrations of heme-iron bound to CO and weak collateral blood supply (27,28). Nineteen patients (5.6%) underwent brain imaging and 13 patients had normal imaging. The typical globus pallidus involvement was not seen in any of the patients. One patient (Case 1) had acute brainstem demyelination, and 1 patient (Case 2) had acute watershed infarctions.

CO intoxication triggers inflammation and activation in N-methyl-D-aspartate neurons, and the subsequent overactivity of neuronal nitric oxide synthase causes perivascular changes that cause neutrophil sequestration/activation (29,30). Xiang et al. (31) stated that inflammation plays an important role in delayed encephalopathy induced by acute CO poisoning in rats and can be attenuated by dexamethasone by protecting myelin from inflammatory damage. In a recent study with adult patients, it was found that the combined application of dexamethasone and HBO therapy could yield better efficacy for patients than HBO therapy as a monotherapy (32). Pulse methylprednisolone therapy can be given with various indications such as acute demyelinating disorders, cerebral vasculitis and encephalopathy. High doses of steroid is believed to suppress inflammation, edema and demyelination. The

patient with internuclear ophthalmoplegia and acute brainstem demyelination was given pulse steroid therapy combined with HBO treatment. On the third day of this treatment regime, we observed that the patient's double vision disappeared and the impairment of adduction in the left eye had significantly subsided. We believe that the combined administration of corticosteroid and HBO treatment might reduce cerebral damage caused by CO poisoning.

Study Limitations

The study center is a research and education center, and some of the patients were referred from other hospitals. The patients referred from other hospitals were treated with oxygen during the transfer. Therefore, these patients' measured COHb values may be lower than their actual COHb values. Also, the absence of an institutional protocol of HBO therapy is another limitation of our study.

Conclusion

In this study, we presented our clinical experience in childhood CO poisonings with a large number of cases. In conclusion, acute neurologic manifestations following CO exposure are common in children. Detailed history, physical examination and a high level of suspicion are important in the diagnosis of CO poisoning. HBO therapy can be safely used in children who have CO poisoning. A combined treatment regime consisting of pulse methylprednisolone and HBO treatment may have a more therapeutic potential to prevent neuronal damage in selected pediatric patients with CO poisoning.

Ethics

Ethics Committee Approval: This study was approved by the ethics committee of Ankara Training and Research Hospital Local Ethics Committee.

Informed Consent: Informed consent was obtained from the parents/care givers of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ü.Ö., Design: Ü.Ö., D.Y., N.T., Data Collection or Processing: Ü.Ö., Ö.Y.K, E.A., Analysis or Interpretation: Ü.Ö., Ö.Y.K, E.A., D.Y., Radiological Evaluation: A.S.E., Literature Search: Ü.Ö., A.D., E.A., Writing: Ü.Ö., Ö.Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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