

# Heterotopic Ossification as a Complication of Carbon Monoxide Intoxication

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## Abstract-

**Purpose:** Gait impairment due to encephalopathy and neuropathy has been reported in carbon monoxide (CO) intoxication. Heterotopic ossification (HO) as a cause of gait impairment after CO intoxication has never been reported. In this study we report a patient with HO after CO intoxication.

**Case Report:** A 21 year-old woman developed HO after CO intoxication, which resulted in progressive difficulties in ambulation. Bone scan 3 months later revealed HO around bilateral femoral joints and extended to proximal thighs. Selective involvement of bilateral iliopsoas, tensor fascia lata, rectus femoris, sartorius, and quadriceps muscles were found by muscle magnetic resonance imaging. Surgical intervention improved ambulation. A repeated bone scan 6 months after the operation showed no focal recurrence.

**Conclusion:** CO intoxication can lead to HO through ischemic reperfusion injury. HO should be considered in patients with ambulation difficulties after CO intoxication. Excision of HO may be a treatment option to correct limitations in locomotion.

**Key Words:** carbon monoxide intoxication, heterotopic ossification

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## INTRODUCTION

Burning charcoal in enclosed spaces has become the most common method of committing suicide in Asia<sup>(1)</sup>; this has led to an increase of more than 20% in the overall suicide rate<sup>(2)</sup>. Survivors of charcoal-burning suicide attempts can present with sequelae of carbon monoxide (CO) poisoning, including acute or delayed neuropsy-

chiatric complications.

Heterotopic ossification (HO) is a formation of mature lamellar bone within soft tissue. While HO is sometimes congenital, it has also been observed to occur around large joints in cases of paralysis, traumatic brain or head injuries, and severe burns<sup>(3)</sup>. The mechanisms underlying HO have been postulated to involve osteogenic precursor cells in a permissive envi-

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ronment. It has been theorized that a hypoxic environment is critical in the osteogenetic cascade. However, no reports regarding HO after CO intoxication were found. Here, we present a case of a 26-year-old woman with HO in the quadriceps femoris muscle after CO intoxication. The relatively unremarkable medical history prior to CO intoxication suggests that this condition is associated with the development of HO.

## CASE REPORT

A 26-year-old woman who had an independent daily activity before attempted suicide by burning charcoal in an enclosed room. At the time of admission to the emergency room, she was unconscious. Carbon monoxide (CO) intoxication was diagnosed on the basis of the history and an elevated carboxyhemoglobin level of 23.6% (reference < 2 %). Metabolic acidosis with a pH level of 7.262 (reference 7.35-7.5) was detected. Blood tests revealed a myoglobin level of 520 ng/L (reference <80mg/dl), creatinine of 1.2 mg/dl (reference 0.4-1.4mg/dl), blood urea nitrogen 21.3 mg/dl (reference 7-20mg/dl), creatine phosphokinase (CPK) 3929 U/L (reference 15-130), aspartate aminotransferases of 66 IU/L (reference <40IU/L); alanine transaminase of 41 IU/L (reference <40IU/L), leukocyte count of 17,711/mm<sup>3</sup>. Urine analysis showed proteinuria (+++). She regained consciousness four hours later. Rhabdomyolysis was considered and fluid support was given. A follow up serum CPK one day later revealed a level of 3258 U/L and four days later 518 U/L.

Three days after the incident, she experienced difficulty in balancing during walking and a gradual decline in ambulation. She was unable to run steadily. The coordination of fine movement was intact in the upper limbs. Three months later, she was completely bedridden and was admitted to our ward for examination.

On examination, the patient was found to be alert, oriented, and cooperative and she provided an accurate history. With regard to cognition, she experienced difficulties in retaining what she read; she also occasionally repeated questions and misplaced objects. She also complained of difficulties in finding appropriate words.

However, she did not require any assistance in dressing, transferring from bed to chair, and maintaining personal hygiene. Her score of Cognitive Ability Screening Instrument (CASI) was 95.4 (around 50 percentile), with a short-term memory score, 10.4, drawing 8 and attention score<sup>(7)</sup>.

The findings of cranial nerve examination were normal. She had normal strength in the upper limbs; however the muscle power in the lower limbs was graded as 4 based on the Medical Research Council (M.R.C.) scale. Curiously, she was unable to flex her hips and abduct both thighs. Hypertonia was noted in the lower limbs. During passive movement of the lower limbs, increased resistance and limited passive range of motion were also noted at both hip joints. Deep tendon reflexes were symmetrically normal in the upper limbs but absent in the lower limbs. Babinski sign was not elicited. No dystonia, tremor, chorea, nor rigidity was noted. Sensation to pinprick and joint position sense was normal. Cerebellar function including the finger-nose-finger test was normal, but the patient was unable to perform the heel-to-shin test since she failed to flex the hip joints required in this task.

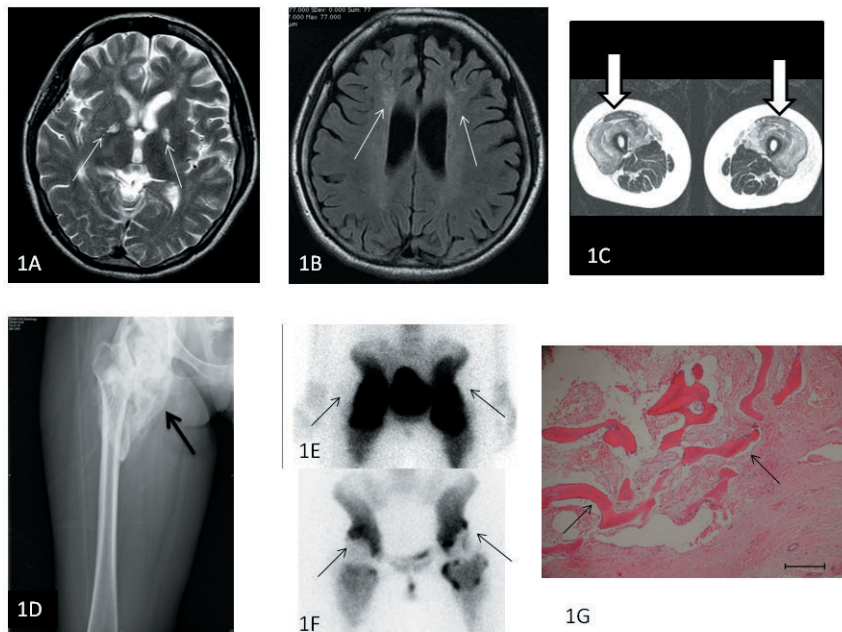
During admission, laboratory tests were normal for the following parameters including complete blood counts, fasting blood glucose, serum lactate and pyruvate, erythrocyte sedimentation rate, serum calcium and phosphate, myoglobin, and CPK.

A serial of examination were performed during the admission. Electroencephalography did not reveal epileptic discharges or slow waves. At the same time, nerve conduction studies showed no delay in distal latencies, and the conduction velocities and amplitudes of compound muscle action potentials in the median, ulnar, tibial, and peroneal nerves were normal. Electromyography of the right quadriceps muscle showed normal motor unit action potentials without signs of denervation. Brain magnetic resonance image (MRI) showed typical features of CO intoxication, including necrosis of bilateral globus pallidus (Fig. 1A) and periventricular white matter changes (Fig. 1B). T2-weighted MRIs of the lower extremities demonstrated a high signal intensity selectively involving the iliopsoas,

the tensor fascia lata, rectus femoris, sartorius, and quadriceps muscles (Fig. 1C). The plain film of the right pelvic region also showed calcification with more emphasis on the hip joint (Fig. 1D). A technetium-99m methylene diphosphonate (Tc-99m MDP) whole-body bone scan obtained three hours after injecting the radioactivity revealed a substantial increase in uptake in the areas adjacent to the lower pelvic bone and proximal femoral regions (Fig 1E). Biopsy of the right upper part of quadriceps muscle was performed. On microscopic examination, the excised tissue fragments showed marrow tissue and trabecular bones rimmed by osteoblasts, with interstitial fibrosis (Fig. 1G). Based on the above mentioned clinical and laboratory findings, HO was

diagnosed 3 months after CO intoxication.

One month after the diagnosis, surgery was arranged to remove the ectopic bone around the femoral joints. A marked improvement was observed in the gait after the operation. Although she still had difficulty in rising from a squatting position, she was able to walk without assistance. During the physical examination on follow-ups, the patient had no hip joint limitation and could bend her thigh toward the abdomen. Six months after the surgery, a Tc-99m MDP bone scan revealed that there was no recurrence of ectopic bone formation. (Fig. 1F). At the last follow-up three years post-CO exposure, the patient could walk without assistance.



**Figure 1.** A: Brain magnetic resonance imaging performed at 3 months after intoxication shows high signal intensity at the globus pallidus (arrow) at T2-weighted imaging  
 B: Periventricular white matter high signal intensity changes (arrow) at T2 FLAIR imaging  
 C: T2-weighted magnetic resonance imaging of the thigh performed at 3 months after intoxication shows high signal intensity involving bilateral anterior muscle compartments (arrows).  
 D: Plain film shows calcification in the right pelvic region (arrow).  
 E: Tc-99m technetium-99m methylene diphosphonate whole-body bone scan shows an increase in the uptake of the radioisotope in the pelvis (arrow) and upper thigh regions of both sides.  
 F: Follow-up Tc-99m technetium-99m methylene diphosphonate whole body bone scan shows no focal recurrence (arrow) of heterotopic ossification.  
 G: Hematoxylin-eosin staining of the specimens obtained by muscle biopsy shows trabecular bones (arrow) rimmed by osteoblasts with interstitial fibrosis. (bar= 0.1 mm)

## DISCUSSION

HO has been frequently observed in ischemia or reperfusion injuries occurring after orthopedic surgeries<sup>(4)</sup>. It is less commonly seen after nontraumatic neurological conditions, such as a prolonged coma or neuromuscular blockade in patients under prolonged mechanical ventilation<sup>(5)</sup>. Our patient showed none of the above mentioned clinical conditions and HO developed as a complication of CO intoxication that led to the ambulation problem in this patient. From this history, our patient had transient global hypoxia caused by CO intoxication. The gait disturbance observed in CO intoxication has been conventionally attributed to encephalopathy and peripheral neuropathy<sup>(6)</sup>; however, these conditions had been ruled out in our patient. Skeletal muscle necrosis has been known to occur occasionally in CO intoxication<sup>(6)</sup> which may be responsible for the unsteady gait found earlier in this patient; however, HO in the skeletal muscle leading to a motor deficit has not yet been reported.

In this patient, HO developed after rhabdomyolysis, suggesting the importance of ischemia and reperfusion in the pathogenesis of this condition. Previous reports have indicated that ossification is initiated by hypoxia; however, this mechanism has not been fully confirmed<sup>(7)</sup>. Both angiogenesis and osteogenesis are involved in HO pathogenesis; tissue hypoxia is believed to be critical for the commencement of the angiogenic cascade, while osteoblasts may be responsible for osteogenesis<sup>(8,9)</sup>. It is likely that a microenvironment of hypoxia induces the progenitors in the soft tissue to differentiate into chondrocytes or osteoblasts, thus leading to subsequent ossification. Bone scans have revealed that an increase in the osteoblastic activity leads to HO. Although the *in vitro* model demonstrated the early vascularization and bone formation leading to HO as early as three to five days after a hypoxic environment<sup>(10)</sup>, our consideration of gait disturbance in this patient was multifactorial in the early stage, more focused on the rhabdomyolysis and brain damage. HO may be considered as a later complication in CO intoxication in this patient.

The globus pallidus is the most commonly affected structure in CO intoxication because it has a high oxy-

gen demand and therefore, an increased vulnerability to hypoxia<sup>(11)</sup>. We also speculated that there may be a tissue-specific vulnerability to HO since in this case, HO selectively occurred in both iliopsoas and anterior compartments of thighs. The hypothesized connection between hypoxia and focal HO in our case was supported by the critical role of metabolic rate. According to the general principle of basal metabolic rate, body weight is among the chief variables influencing the basal metabolic rate. Given that the most frequently involved muscle compartment in HO is the quadriceps femoris, we hypothesized that a hypoxic microenvironment would be likely to develop in the quadriceps femoris because its metabolic rate<sup>(12)</sup> is relatively higher than that of all other muscle groups, which results in a tendency towards HO development.

The treatment option for HO is mainly excision. The available data do not support the belief that early excision triggers later recurrence<sup>(13)</sup>. In our case, no recurrence has been noted so far, as confirmed by the results of the follow-up bone scan. This is the first published case of HO after CO intoxication, excision might also be considered in such cases, as in HO resulting from other causes.

In summary, HO can be a cause of gait disturbances after CO intoxication, and it can be detected by noninvasive methods such as plain film or bone scans. CO intoxication and muscle injury may increase the risk of development of HO. In addition to the effects of HO, a subsequent decrease in muscle activity may adversely affect muscle power. Excision of HO may be a treatment option to correct the limitations in locomotion.

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