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Letter to the editor

Is "delayed" hyperbaric therapy effective for "delayed" encephalopathy after carbon monoxide intoxication?

Dear Editor,

Carbon monoxide (CO) is a leading cause of accidental poisoning worldwide [1]. CO binds haemoglobin with higher affinity than oxygen, inducing hypoxemic hypoxia. The standard treatment is high-flow oxygen therapy, mainly hyperbaric therapy (HBOT), which accelerates the elimination of CO. Over half of the patients who survive CO intoxication can develop, after a lucid period of 3 days to 4 weeks, delayed neurological sequelae (DNS) [2]. This is a potentially permanent encephalopathy, characterized by subtle abnormalities up to severe cognitive and motor impairment. However, the risk of this delayed, adverse outcome of CO poisoning is not currently predictable on the basis of the clinical history or laboratory testing. According to a few studies, HBOT following CO poisoning might reduce the incidence and severity of DNS, although this effect was partial and not sustained [2].

Moreover, the pathophysiology of DNS is not yet completely understood and the beneficial role of HBOT in this clinical setting remains controversial. Some studies on animal models suggest that DNS may be the result of an adaptive immunological response to chemically modified myelin basic protein (MBP), with concomitant inflammatory reaction [3]. Specifically, CO poisoning causes adduct formation between MBP and malonyl aldehyde, a reactive product of lipid peroxidation, resulting in an immunological cascade [3]. Indeed, a complex interplay between systemic immune cells and resident cells has been observed in the brain of CO-poisoned rats, including an increased expression of MHC II and CD-40 markers on microglia, along with histochemical evidence for CD-4 T cell infiltration [3]. Activated microglia could mediate cognitive dysfunction, by impairing neurogenesis and by causing neuronal necrosis or apoptosis [4].

Since the therapeutic use of oxygen at supra-physiological pressures may increase systemic oxidative stress and/or cause overproduction of reactive oxygen species (ROS) [5], some authors have suggested the concurrent use of HBOT plus antioxidants and anti-inflammatory drugs for DNS treatment.

Herein we report a case of 63 year-old woman, with a transient confusional state after CO poisoning, who had apparent full recovery after HBOT therapy. However, 12 days later, she began developing a motor and cognitive decline, which progressed to a catatonic state. After being hospitalised in a Psychiatry Unit, the patient did not respond to antipsychotics or antidepressants. One month after poisoning, brain MRI showed increased signals in long-TR and DWI sequences in the periventricular white matter, basal ganglia and internal capsule, with a substantially symmetrical appearance. The same appearance was observed in the splenium of the corpus callosum, with a diffuse inhomogeneous enhancement after gadolinium (Fig. 1), leading to a delayed CO-encephalopathy diagnosis. Treatment with high-dose of N-Acetylcysteine (10 g die) and prednisone (37.5 mg die) was promptly started, whilst 10 HBOT sessions were carried out subsequently, at three months from the DNS onset, along with intensive physical rehabilitation. Steroid therapy was gradually tapered down over an 8 month period. She started a progressive clinical recovery: one year later, the Mini Mental State Examination score improved from 6/30 to 27/30, limb spasticity decreased and she was able to walked with assistance. Her MRI (Fig. 1) showed the disappearance of white matter alterations but a severe and diffuse cortical-subcortical atrophy become evident.

Our case suggests that early diagnosis and multi-target therapy (HBOT plus ROS-scavengers and steroids) may improve the clinical-neuroradiological outcome of DNS, most likely by reducing the inflammatory response. A combination of antioxidant and anti-inflammatory drugs may have a synergic effect and counterbalance the putative HBOT-induced oxidative stress. However, we can neither exclude a spontaneous recovery, nor evaluate the distinct role of each single component of this combined treatment.

Current literature on DNS treated with delayed HBOT plus ROS-scavenger drugs is scanty. One such report was by Spina et al., who reported the clinical-radiological follow-up of a DNS case treated with HBOT, N-Acetylcysteine and glucocorticoids, who had a progressive and sustained clinical and radiological improvement [6]. This case is strikingly similar to ours, as were the treatment modalities, including late HBOT. In both cases, the good clinical outcome was associated with a neuroradiological time course, where the white matter alterations turned into diffuse cortical-subcortical atrophy (Fig. 1). Indeed, the MRI provides clinicopathological information on brain damage after CO-poisoning [7]. Whilst the hypoxic-hypotension damage seems to be the underlying factor mainly for the basal ganglia alterations in DNS, the inflammatory process is most likely to be the pathological correlate of white matter alterations with progressive demyelination and cytoxic edema on MRI [7]. Choi et al. [8] reported on a large case series and stated that demyelination may be reversible within 1–2 years in about 70% of cases in the chronic phase, whereas the necrosis is associated with cortical-subcortical atrophy.

In our case, the question arises whether the clinical-radiological evolution might be due to the natural history of DNS or to the association of anti-inflammatory effect of N-Acetylcysteine and prednisone, even in the absence of HBOT treatment. However, although HBOT might induce oxidative stress, it does have pleiotropic effects on immunity and haemodynamics, including mechanisms of neuroplasticity and cellular repair, angiogenesis and even neurogenesis, as suggested by animal studies [9]. Although these data may provide a rationale for HBOT in the treatment of DNS, we wonder if it is strong enough to support the use of such an expensive resource, which may be also

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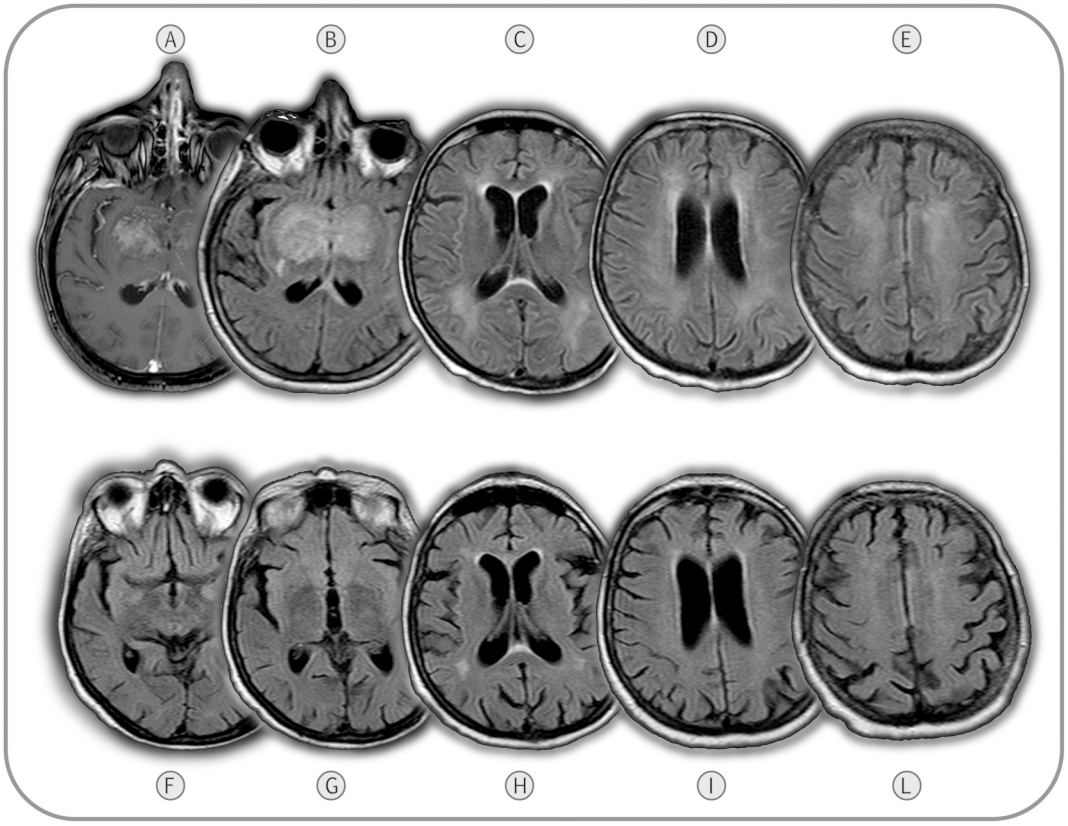

Fig. 1. Acute phase (one month after poisoning) (A–E): contrast-enhanced T1-weighted images: (A) hypointensity with bilateral patchy enhancement in the basal ganglia. FLAIR images: (B–E) extensive involvement of basal ganglia (B), slight hyperintensity signal in the periventricular zone (C) bilateral white matter at the corona radiata (D) and centrum semiovale (E).
Twelve months after DNS onset (F–L): disappearance of deep white matter hyperintensity and cortical atrophy.

harmful, like a kind of a "Janus Bifrons".

Moreover, on considering animal models, we wonder if an accurate and early investigation of the immunological status in patients with CO-poisoning would be useful in identifying prognostic markers, predictive of DNS development and of a positive response to anti-inflammatory treatment.

Further studies are needed to clarify the role immune response plays in the pathophysiology of DNS, as well as to investigate the efficacy of HBOT and antioxidant/anti-inflammatory drugs, together or alone, with the aim of providing better evidence and clinical guidance for the treatment of this severe complication involved in CO poisoning.

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