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Partial Seizure Provoked by Hyperbaric Oxygen Therapy: Possible Mechanisms and Implications

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Summary: Hyperbaric oxygen treatment (HBO_2) is used commonly for treatment of bone and soft-tissue radiation necrosis. It may be a potential therapy for radiation necrosis seen after brain irradiation. HBO_2 risks include generalized tonic–clonic convulsions. We report a patient after resection of anaplastic astrocytoma and 5,580 cGy of total external-beam radiation treatments with brain radiation necrosis who underwent HBO_2 therapy and developed a partial seizure during treatment. Mechanisms and implications are discussed. **Key Words:** Hyperbaric—Radiation necrosis—Seizure.

Case series suggest that hyperbaric oxygen (HBO_2) therapy might slow radiation-induced brain necrosis (1). HBO_2 therapy is associated with an increased risk of generalized tonic–clonic (GTC) convulsive seizure in ~0.002–0.035% of patients undergoing treatment (2,3). To our knowledge, partial seizures (PS) have not been reported during hyperbaric treatment. This patient, while undergoing HBO_2 therapy for brain radiation necrosis, showed a PS. Mechanisms and implications for seizure provocation during HBO_2 treatment are discussed.

CASE REPORT

A 51-year-old, 61-kg man was first seen 1 year earlier with sialorrhea and left-sided tongue deviation. Brain magnetic resonance imaging (MRI) showed an extensive right motor strip tumor. A biopsy was performed, and the pathology showed anaplastic astrocytoma. The tumor was surgically debulked, followed by 5,580 cGy of external beam radiation therapy, temodar, and steroid chemotherapy.

Two months after resection, PS consisting of a protracted jacksonian march of convulsive movements up his left arm into his face and leg developed. These evolved over the next 8-month period to include ictal paresthesias and postictal hand paresis. PS proved refractory to phenytoin (PHT), valproic acid (VPA), and clonazepam (CZP). Interictal left leg and arm paresis worsened, as did dysarthria; seizure frequency increased to one per day. Repeated MRI suggested edema around prior surgical margins, so the patient underwent a second debulking. Pathologic changes consistent with radiation necrosis were found. Postoperatively, seizures remitted with unchanged therapy. Because of symptomatic worsening, he was advised to begin both warfarin and HBO_2 treatments.

PHT (15.1 μg/ml; therapeutic, 10.0–20.0) and VPA (33 μg/ml; therapeutic, 50–100) levels were measured before beginning HBO_2 during a 28-day postoperative period of seizure freedom. His planned regimen included 30 treatments in a multiplace chamber with pressurization to 2.36 atmospheres absolute pressure (atm abs), with 90 total min of 100% oxygen (O_2) given via O_2 hood (model 8891-010; Amron International, Escondido, CA, U.S.A.), delivered as four 20-min and one 10-min periods each, separated by 5 minutes of breathing air. Hood O_2 flow was 30 L/min.

While breathing O_2 at treatment pressure for 12 min in the second O_2 period of his initial HBO_2 treatment (32 min O_2 total), stereotyped convulsive movements and paresthesias in the left arm developed. O_2 administration was discontinued after 2.5 min, with prompt seizure resolution. Hyperbaric treatments were not continued.

DISCUSSION

HBO_2 therapy is effective treatment for many forms of bony or soft-tissue radiation necrosis (1). Efficacy in treating brain radiation necrosis is not as well documented, although some case series suggest benefit (4). To test this therapy, a prospective, randomized controlled trial sponsored by the National Institutes of Health is currently under way.

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CNS oxygen toxicity, as manifest by GTC seizure activity, is a rare but recognized side effect of HBO_2. This idiosyncratic reaction may occur in individuals without history of epilepsy or brain injury. In 20,328 routine hyperbaric treatments performed at 2.36 atm abs and delivering oxygen by hood in a multiplace chamber, six GTC seizures were noted, yielding a risk of ~1:3,300 treatments (0.03%) (2). The risk differs depending on treatment pressure, oxygen-delivery system (i.e., a mask has a lower incidence when compared with a hood), and underlying conditions (4). For example, ≤5% of patients treated with HBO_2 for acute carbon monoxide poisoning may show GTC activity (5). The risk of seizure provocation during HBO_2 in patients with epilepsy is not known, nor is it known whether seizure activity during HBO_2 begins characteristically as partial activity that secondarily generalizes.

The mechanism(s) for HBO_2-induced seizures probably vary. In hyperbaric conditions, oxygen inhibits glutamic acid decarboxylase, the critical enzyme for synthesizing the inhibitory neurotransmitter γ-aminobutyric acid (6). Additionally, changes in cerebral blood flow (CBF) observed during HBO_2 show increased flow immediately before signs of CNS toxicity and seizure (7). Epileptogenic zones also show increased CBF during seizure, a finding that underpins ictal SPECT imaging. HBO_2-induced CBF changes may be mediated by hyperoxia and hypocarbia, which initially act as potent vasoconstrictors. Regardless of HBO_2 therapy, CBF also is regulated by carbon dioxide (CO_2). Hypercapnia, for instance, increases CBF, whereas hypocarbia does the opposite. However, with prolonged HBO_2, vasodilation occurs, potentially mediated through fluctuating levels of generated free radicals and nitric oxide (8,9). In rat hyperbaric epilepsy models, altered levels of nitric oxide may play a role in repeated seizure generation, and repeated HBO_2 therapies may predispose to more convulsions (10,11).

Voluntary hyperventilation (HV) leads to respiratory alkalosis and hypocarbia. Interictal and ictal patterns, particularly involving generalized spike-and-wave discharges, may be seen with electroencephalography. However, adult patients with defined PS rarely precipitate seizures with HV (12). Furthermore, abortion of perceived seizures with deep breathing in adults with PS suggests a possible role for HV and hypocarbia in focal seizure inhibition (13). Similarly, patients with vagus nerve stimulators (VNSs) placed for focal seizure control show hypocapneic end-tidal CO_2 measurements during stimulation phases, but whether transient hypocapnea is responsible for VNS efficacy is unclear (14). Finally antiepileptic medications like topiramate, zonisamide, and acetazolamide inhibit carbonic anhydrase, effectively leading to a mild reduction in bicarbonate, a proxy measure of hypocarbia (15). Whether different medicines have different thresholds of seizure generation during HBO_2 remains unclear; in animal models, CZP may be more likely to increase seizure threshold than VPA or carbamazepine (16).

During HBO_2, a safe inspiratory CO_2 level is 15.2 mm Hg. This produces no minute ventilation (MV) increase and is tolerable for long periods. Maintaining CO_2 below this level inside a hyperbaric O_2 delivery hood requires gas flow ≥2.1 times the patient's resting MV. Because the normal adult resting MV is 6–8 L/min, the hood flow during hyperbaric therapy (30 L/min) is more than sufficient to prevent significant CO_2 accumulation and rebreathing.

If perfusion changes initiate seizures, then presumably the commonly reported cases of HBO_2-induced seizure manifest as GTC seizures, because the increased flow is global. In this case, a simple PS may have occurred because of a resumption of previously recognized seizure activity that coincided with his HBO_2. Alternatively, HBO_2 may have provoked an increase in regional blood flow through necrotic vasculature in which more specific alterations in perfusion, oxygenation, and/or hyper- or hypocarbia were also manifest. Although further work establishing how atmospheric pressure, oxygenation, and CO_2 regulation might provoke or prevent seizures is needed, the risk of seizure is likely heightened during HBO_2 in patients with known epilepsy, including those with PSs. HBO_2 is by no means clearly indicated for patients with brain tumors, let alone those with brain tumors and epilepsy. If such a patient is to undergo HBO_2 therapy, supervising staff should be prepared to manage acute seizure activity safely.

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