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# Treatment of cerebral radiation necrosis using hyperbaric oxygen therapy in a child: illustrative case

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**BACKGROUND** Cerebral radiation necrosis (RN) is an uncommon sequela that occurs in up to 25% of irradiated patients. This can occur 6 months to several years after therapy and create symptoms of headaches, focal neurological deficits, seizures, or behavioral changes. Management can involve corticosteroids, antiplatelet drugs, surgery, and hyperbaric oxygen therapy (HBOT). Currently, there is a paucity of literature investigating these therapies for routine use in the pediatric population.

**OBSERVATIONS** A 5-year-old male with a right frontal atypical teratoid rhabdoid tumor previously underwent craniotomy for tumor resection, followed by chemotherapy, radiation, and autologous stem cell transplant therapy. Progressive radiographic changes surrounding the resection cavity were noted on routine surveillance imaging 20 months after the initial craniotomy and 11 months after the completion of radiation therapy. A biopsy ultimately confirmed RN. Due to the patient's previous complications with steroid use, the patient underwent HBOT. This achieved a significant improvement in clinical and radiographic sequelae of RN.

**LESSONS** HBOT was utilized successfully for the management of this patient's RN. HBOT should be considered for pediatric patients with cerebral RN as a potential treatment strategy.

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**KEYWORDS** radiation necrosis; hyperbaric oxygen; pediatric neurosurgery; neuro-oncology

Cerebral radiation necrosis (RN) is a complication following radiation therapy (RT) of various central nervous system (CNS) pathologies that has been reported to occur in 1%–30% of patients and can be more common with re-irradiation.[1–5] It usually occurs in the region of the radiation field within 6 months to 1–2 years postirradiation but can occur years later. Symptoms of cerebral RN are variable and dependent on the site of the lesion, but they can include focal neurological deficits, seizures, headaches, and altered mental status.[6–9] Differentiation between RN secondary to treatment as pseudoprogression or true tumor progression can be difficult. This distinction can be made with the assistance of more advanced imaging techniques or through biopsy, which is the gold standard.[8]

Current management strategies for RN include corticosteroids, anticoagulants, antiplatelets, high-dose vitamins, bevacizumab, hyperbaric oxygen therapy (HBOT), laser interstitial thermal therapy (LITT), or surgery.[4,6,9–12] Corticosteroids are considered first-line therapy, as they are effective for symptom control and reduction of edema.[6,13,14] However, for many of these therapies, the optimal scheduling, dosage, and duration of therapy have yet to be standardized. Data are limited for newer treatment modalities and even more so in the pediatric literature. Additionally, many of these therapies, including corticosteroids, are not without adverse effects. Therefore, management strategies need to be customized for each patient and clinical scenario. To highlight this, we present a case of a complex pediatric patient who underwent successful management of his biopsy-proven RN with HBOT.

## Illustrative Case

A 5-year-old male with a complex medical history including Phelan-McDermid syndrome and ring chromosome 22 abnormality was found to have a new intraparenchymal mass in his right frontal lobe during workup of developmental delays at age 3 years. He underwent a right frontal craniotomy for gross-total resection of this atypical teratoid rhabdoid tumor and completed adjunct therapy per ACNS0333

**ABBREVIATIONS** CNS = central nervous system; HBOT = hyperbaric oxygen therapy; LITT = laser interstitial thermal therapy; MRI = magnetic resonance imaging; RN = radiation necrosis; RT = radiation therapy; VEGF = vascular endothelial growth factor.

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protocol, which included autologous stem cell transplants and proton RT (54 Gy over 6 weeks, completed 10 months after tumor resection). His adjuvant therapy was complicated by respiratory failure requiring a course of prolonged corticosteroid therapy. This resulted in the development of symptomatic lumbosacral epidural lipomatosis that was diagnosed 4 months after completing RT and required decompressive surgery. Postoperatively, the patient regained his leg strength and baseline ambulatory function. A corticosteroid wean was initiated.

Ten months after this, new changes were noted on routine surveillance imaging, raising concern for tumor recurrence versus RN, with progressive changes on close interval follow-up (Fig. 1). Throughout this, the patient remained at his neurological baseline; however, he developed progressively frequent and severe headaches. The patient underwent a stereotactic biopsy for diagnosis. Histopathological analysis confirmed RN. Several options were considered for management by our multidisciplinary team, including steroids, bevacizumab, surgery, LITT, and HBOT. Steroid risk was considered unacceptable given his recent epidural lipomatosis requiring surgical decompression. Bevacizumab was not recommended due to limitations in monitoring for complications of intracranial hemorrhage in a developmentally delayed child. Finally, LITT was not readily available.

Ultimately, given the risk profile of each modality, the patient's history, and after thorough discussions of each management modality with the patient's mother, the decision was made to pursue HBOT while he continued his corticosteroid wean. HBOT consisted of 90 total minutes at 100% $O_2$, diving at 2.4–2.5 atm. His treatment consisted of 3 30-minute intervals with 5-minute air breaks, for a total of 30 sessions. The patient completed the 30 sessions in 7 weeks, with 5 treatment days per week, on average. These sessions were well tolerated with no complications. Surveillance magnetic resonance imaging (MRI) after 14 HBOT therapy sessions showed a marked reduction in size and enhancement of the area of RN, with no new areas

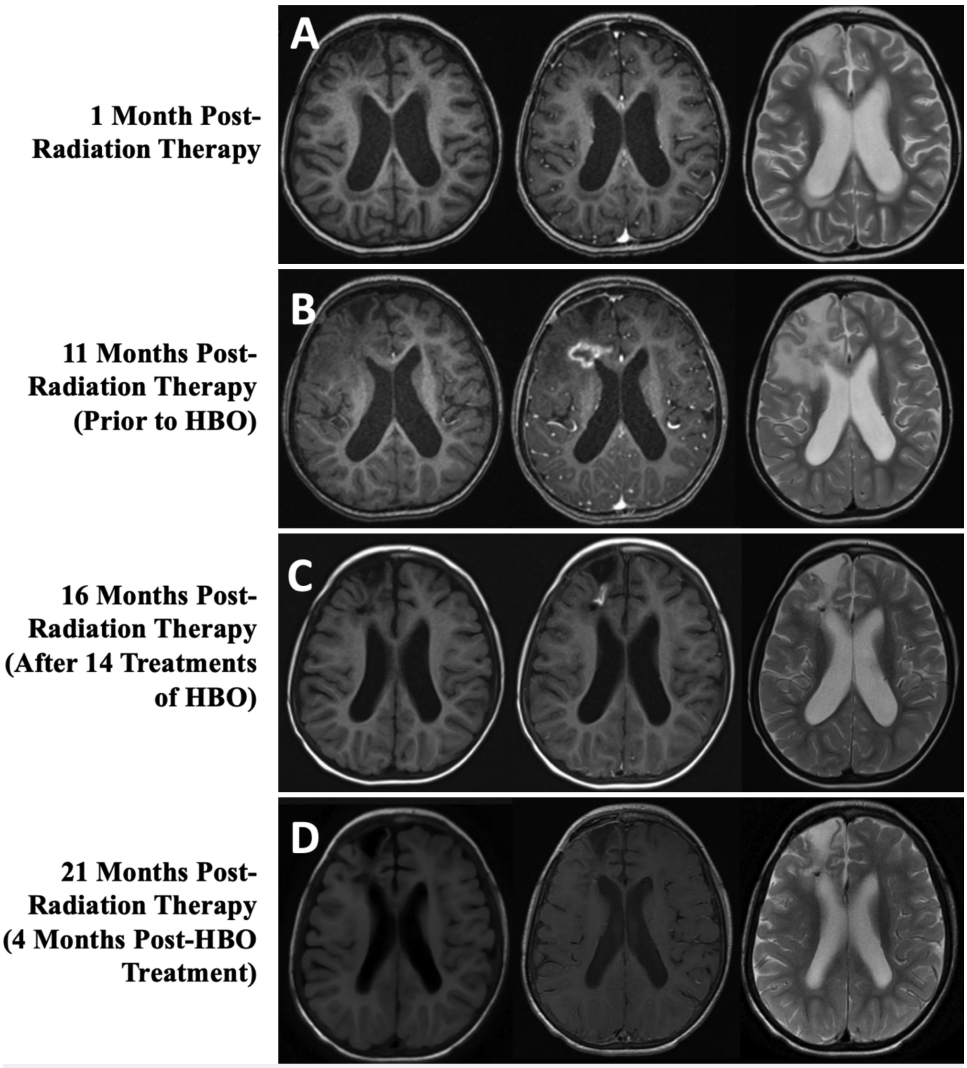


**FIG. 1.** Axial precontrast (*left*) and postcontrast (*center*) T1-weighted and precontrast T2-weighted (*right*) MRI at intervals preceding and following HBOT. **A:** One month post-RT. **B:** Eleven months post-RT. **C:** Sixteen months post-RT and after 14 treatments of hyperbaric oxygen (HBO). **D:** Twenty-one months post-RT and post-HBO treatment.

of concern (Fig. 1C). His headaches improved after approximately 15 sessions.

After 30 completed sessions of HBOT, it was decided to add 20 more sessions using the same schedule to see if there could be further reduction in the enhancement seen on MRI secondary to RN. Since he was tolerating the sessions well, a goal of complete resolution of MRI enhancement was sought in order to simplify ongoing surveillance imaging of his aggressive tumor. During the 33rd treatment, the session was stopped prematurely due to concerns about a seizure-like episode accompanied by an apneic event. The patient's clinical status rapidly normalized, with no clear etiology found for the event. The patient was discharged from the hospital after 5 days with no clinical sequelae.

Following this, the multidisciplinary clinical team and the patient's parents decided to discontinue any further HBOT. The patient was last seen in a follow-up 4 months after stopping HBOT, with a stable neurological examination and clinical status. Additionally, his MRI at that follow-up showed near resolution of the area of RN (Fig. 1D).

### Review of the Literature

A PubMed search through March 2024 was conducted using the search terms (cerebral) AND (radiation necro*) AND (hyperbar*) (Fig. 2). Papers were included if they were published in the English language and described pediatric patients (age < 21 years) who were treated with HBOT for the development of RN after treatment of a cerebral neoplasm. Articles were excluded if they reported on multiple concurrent treatment modalities, excluding corticosteroid use. Relevant demographic and clinical characteristics, as well as outcomes of the cases found in the literature review, are summarized and compared to our illustrative case in Table 1.

### Informed Consent

The necessary informed consent was obtained in this study.

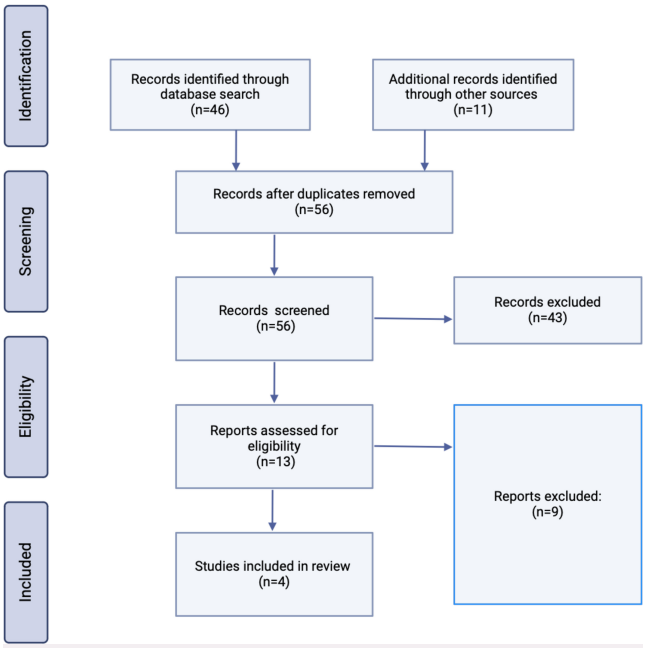


**FIG. 2.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses screening workflow for the utilization of HBOT in the treatment of pediatric cerebral RN.

## Discussion

### Observations

RN primarily arises from damage to the small arterioles and arteries, causing coagulative necrosis and endothelial thickening and impairing blood flow. This leads to an inflammatory response and the stimulation of new microvessels, which can lead to embolic events or bleeding. Thus, RN is an ischemia-reperfusion injury phenomenon caused by a coagulative and ischemic process leading to cellular death.[15]

Controlled clinical trials are limited. Optimal management of RN is inconsistent, and standardized guidelines or protocols are lacking.[10–12] Additionally, the utilization of HBOT for treating RN is inconsistent, even within single institutions (Table 1).[10–12] The true clinical impact of HBOT alone is difficult to quantify, as many cases utilize multimodal management strategies. However, there is a rational basis for HBOT, and good clinical results have been seen. The increased partial pressure of oxygen in HBOT correlates with better diffusion of oxygen.[16] Furthermore, HBOT improves angiogenesis, resulting in better tissue perfusion with more robust vessels. This aids in the restoration of cellular functions, repair of ischemic damage to tissues, and more normal reperfusion of damaged areas. HBOT is also believed to diminish neuroinflammatory responses, impacting neurogenesis and helping with neuronal and axonal integrity and synaptogenesis.[17] Additionally, the utilization of HBOT is not limited to RN, as it has been used in decompression sickness, carbon monoxide poisoning, and arterial gas embolism, to name a few.[18]

The true clinical impact of HBOT on RN is difficult to quantify, as the proton RT dosage can vary by tumor type and location and does not directly correlate with the extent of RN. One study reported that chemotherapy exposure after RT increases the incidence of RN by fivefold.[9] Another study reported that 20 HBOT treatments a week after RT saw a reduction of cerebral RN from 20% to 11%.[10]

HBOT has not been commonly used in the pediatric population. Most of the literature focuses on the adult population.[10–12,19,20] Barriers to care include its time-consuming nature, high costs, and accessibility. Younger patients can also have difficulty tolerating HBOT, as they are enclosed in a chamber for 90–120 minutes daily and often require at least 30 treatments. There is no minimum age requirement. Middle ear barotrauma is the most common HBOT-related complication, with incidence rates ranging from 2% to 82%, which may also be more challenging for children than for adults.[16]

The study by Chuba et al. is valuable in that it incorporates both adult and pediatric patients.[21] They found either clinical or radiographic improvement in all their patients who underwent HBOT. In addition, known complications of oxygen toxicity were not seen in any of their patients, most likely due to the short duration and relatively low pressure utilized in their treatment protocol. In 6 surviving patients, they found radiographic stability at the 3-year follow-up. Aghajan et al.[22] published a case series (n = 7) of pediatric patients ranging from 7 months to 16 years of age with primary CNS tumors in which they utilized HBOT. They found clinical and radiographic improvement in 4 of 7 patients after 40 sessions of HBOT, comprising 80 minutes under 2.4 atm per session. Additionally, they showed that this therapy is well tolerated and can be practically utilized in the pediatric population. The 2 adverse events reported during HBOT were anxiety and tachycardia. Patients showed either stable or resolved radiographic disease at a median follow-up of 5 years.[22]

In summary, our literature review of articles published between 1996 and 2024 (Table 1) shows the outcomes of HBOT for RN in 20 pediatric patients, to which we have included our data for comparison.

**TABLE 1. Literature review of pediatric studies utilizing HBOT in the treatment of cerebral RN**

| Authors & Year | No. of Pediatric Cases (age <21 yrs) | Pediatric Age Range | HBOT Protocol | Side Effects (no. of cases) | Resolution (no. of cases) |
|---|---|---|---|---|---|
| Aghajan et al., 2019[22] | 7 | 7 mos–16 yrs | Median 40 HBO sessions, 100% $O_2$ at 2.4 atm for 80 mins, 80-min dive (4 20-min dives w/ 5-min air break in btwn) | Anxiety (1), tachycardia w/ hypoxia (1) | Improved (4), stable (2), worsened (1) |
| Ashamalla et al., 1996[25] | 2 | 3.5–21 yrs | Median 30 HBO sessions 6×/wk, 100% $O_2$ at 2 atm, 120-min dive (2 60-min dives w/ 5-min air break in btwn) | None reported | Radiograph showed transient initial improvements in audiograph (1), no temporal bone erosion in FU (2) |
| Chuba et al.,1997[21] | 9 | 4–14 yrs | 20–40 sessions, 100% $O_2$ at 2.0–2.4 atm, 90- to 120-min dives | Ataxia (3), CN palsies (2), headache (4), dysphasia (1), hemiparesis (1), seizure (1), visual loss (1) | Stabilized initially (9), some were resolved, radiograph worsened (1) |
| Wanebo et al., 2009[26] | 1 | 16 yrs | 30 HBO sessions 5×/wk, 100% $O_2$ at 2.4 atm, 90-min continuous dive | None reported | CT 3 wks after demonstrated marked reduction of lt temporal lobe edema & mass effect |
| Present case | 1 | 5 yrs | 33 sessions, 100% $O_2$ at 2.4–2.5 atm (3 30-min dives w/ 5-min air break in btwn) | None reported | MRI showed improvement of RN |

CN = cranial nerve; CT = computed tomography; FU = follow-up; HBO = hyperbaric oxygen.

The youngest reported patient to undergo HBOT was 7 months of age. There was variability in the HBOT protocols utilized between studies, with many prescribing at least 30 HBOT sessions on average, using 100% $O_2$ between 2.0 and 2.4 atm, and lasting at least 60 minutes per dive session. Many of the pediatric patients reported stability of RN, if not improvement. The most common side effect reported was headaches, while the most severe reported events included seizures, hemiparesis, and visual loss.

Our patient experienced a seizure after the 33rd treatment. This could have been independently related to his Phelan-McDermid syndrome. However, HBOT can also cause CNS oxygen toxicity, which usually manifests as a generalized tonic-clonic seizure in 0.002%–0.035% of patients. Partial seizures have also been noted but are more rare.[23] The mechanism for hyperoxic-induced seizures includes the inhibition of glutamic acid decarboxylase, decreasing the inhibitory neurostransmitter γ-aminobutyric acid and increased cerebral blood flow to epileptogenic centers via chronic vasodilation from increased nitric oxide. While these effects are usually global, they can be partial if there is abnormal vasculature or perfusion in a tumor near a sensitive brain region. Our patient did not require any further treatment for his hyperoxic-induced seizure and has remained seizure free without antiseizure medications.

Besides the utilization of HBOT, other treatments to manage cerebral RN include glucocorticoid use, resection, laser interstitial thermal ablation, and anticoagulants. Most recently, bevacizumab, a humanized monoclonal antibody blocking vascular endothelial growth factors (VEGFs), has been utilized. A meta-analysis by Delishaj et al. showed that utilization of bevacizumab for RN resulted in improvements in clinical and radiographic responses, with a decrease in median T1 contrast enhancement by up to 64%.[24] Bevacizumab inhibits VEGF, which can pare down the abnormal vasculature (such as the injury-induced telangiectasias), while HBOT enhances VEGF to promote the formation of new normal blood vessels to replace the abnormal telangiectasias. Both can be used to treat RN via different effects on vasculature. However, like the other treatment therapies, there has yet to be a study that evaluates the optimal scheduling, dosage, and duration of therapy that is effective in treating RN.

### Lessons

Herein, we present the case of an irradiated pediatric neuro-oncological patient who underwent successful treatment of RN using HBOT. Limitations of this study include its retrospective nature and small sample size. However, given the paucity of available literature on this clinical scenario, more case reports need to be published for the pediatric population. Randomized controlled studies will be difficult to conduct, as symptomatic patients will not want to be randomized into a control arm of no treatment, and a sham control arm of HBOT over 30 sessions is also difficult to implement. HBOT has been discussed for use in a variety of pediatric brain injuries, from stroke to cerebral palsy, with mixed results due to some of these difficulties. From our review of the literature, this is one of the youngest patients to have undergone this therapeutic modality.

While not considered first-line therapy, HBOT should be considered earlier in the management of pediatric patients with CNS RN, especially in those who have comorbidities that may limit alternate management strategies. Providers should be aware of the potential adverse effects of oxygen toxicity or other respiratory events when considering its use. More data on individual and multimodality approaches may aid in mitigating the risks associated with any one modality and allow management strategies to be tailored to each patient. Until then, guidelines will largely be based on anecdotal case series.

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## Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

## Author Contributions

Conception and design: Ruge. Acquisition of data: Ruge, Jimenez, Li. Analysis and interpretation of data: all authors. Drafting the article: Jimenez, Mohiuddin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ruge. Study supervision: Ruge, Mohiuddin, Li.

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