Review Article

Hyperbaric Oxygen Therapy for Radiation-induced Optic Neuropathy

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Abstract

Introduction: Radiation-induced optic neuropathy (RON) is an infrequent but devastating consequence of radiation exposure to the visual pathways, usually following months to years after the treatment of paranasal or intracranial tumours. Hyperbaric oxygen (HBO) therapy is one of several therapies that have been tried for this condition. The purpose of this review is to describe the clinical characteristics of RON, the rationale for the use of HBO in this condition, and the available clinical data on its safety and efficacy. Methods: MEDLINE searches were performed on radiation optic neuropathy, hyperbaric oxygen therapy, and similar terms, and selected references were reviewed. The results were combined with the experience at our own institution. Results: RON typically follows a fulminant course with characteristic symptoms, examination findings, and imaging. The threshold for prior radiation exposure depends upon the delivery system used and patient characteristics. Therapy with anticoagulants or steroids has been unsuccessful. While there are case reports in the literature of successful treatment with HBO, therapy with HBO has to be initiated soon after the onset of vision loss, and even then yields variable results at best. Conclusions: There is still no consistently successful treatment for RON. HBO may be attempted in selected cases, but the prognosis for preservation of vision remains grim.

Ann Acad Med Singapore 2006;35:151-7

Key words: Optic chiasm, Optic nerve, Radionecrosis, Radiotherapy, Vision loss

Introduction

Radiation optic neuropathy (RON) is an infrequent but usually devastating consequence of radiation to the optic pathways. It is almost exclusively an iatrogenic phenomenon, occurring in patients who have undergone radiation therapy for tumours and other lesions in sites near the visual apparatus, such as the choroid, orbit, paranasal sinuses, nasal cavity and cranial fossae. Once RON begins, usually after a latency of months to years following radiation exposure, it typically follows a fulminant course, resulting in poor to no vision in one or both eyes. Although RON has been documented and studied for almost a century, no consistently effective treatment has emerged to restore or even preserve visual function once visual loss has begun. Hyperbaric oxygen (HBO), a therapy well established for a number of other conditions, has been reported to be of benefit in select patients with RON. This review will discuss the clinical presentation and pathophysiology of RON, the rationale for the use of HBO in RON, and the data to support its use.

The Clinical Presentation of RON

Radiation damages tissue by a variety of mechanisms, and the effects may be immediate or delayed. In neural tissue, 2 types of delayed responses are recognised. "Early" responses, which occur within several weeks of initiation of therapy, are characterised pathologically mostly by inflammation, and may be reversible, whereas "late" responses, which occur months to years after completion of therapy, are characterised by vasculitis and necrosis and generally are irreversible.[1] In humans, the early effects may be mild and clinically unrecognised; the late effects, however, are often devastating and may destroy any part of the nervous system. Late delayed radionecrosis most often affects white matter tracts, sometimes with striking sparing of the cerebral cortex, even when otherwise widespread involvement is present.[2]

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Radionecrosis isolated to the visual pathways was described in 1956 by Forrest et al,[3] who studied 27 breast cancer patients treated by injection of radon seeds into the pituitary gland. Although some of these patients experienced regression of the cancer, 4 (15%) experienced severe optic neuropathy, with the vision in 3 deteriorating to no light perception (NLP) in both eyes. Following publication of this paper, there was little in the literature other than a few scattered case reports until 1985, when the concept of RON was reintroduced into the ophthalmic literature by Kline et al,[4] who described 4 patients who had received external beam radiation (EBR) for pituitary adenomas and subsequently lost vision in one or both eyes. The descriptions of the findings in these cases are now considered the "classic" presentations of RON, and most reported cases since the publication of this article seem to follow a similar profile of signs and symptoms, imaging findings, and disease progression.

Although RON has been reported as early as 1 month following completion of radiation therapy,[5] it more often becomes manifest after a latency of 3 months to a few years.[4,6] Indeed, most patients present within 8 to 16 months of completion of radiation therapy, with very few presenting after 3 years.[7] Some patients present with stuttering symptoms before a constant visual defect is present;[8] however, most follow an unremitting course, with progressive vision loss over weeks to months. In patients in whom both optic nerves or the chiasm are exposed to radiation, an estimated 75% will have bilateral involvement,[5] with the second eye following within weeks of the first, although an interval of 7 months has been reported.[9] In the initial series reported by Kline et al,[4] all 4 patients presented with painless, progressive vision loss and had normal appearing discs that became pale over time; however, some patients have pallor at the time that vision loss first becomes symptomatic,[10] suggesting that the optic neuropathy has been present for at least 4 weeks, and a small percentage present with optic disc swelling,[6] particularly when a more anterior segment of the optic nerve has been irradiated.[11]

Magnetic resonance imaging (MRI) with gadolinium-DPTA enhancement is the preferred modality for establishing the aetiology of vision loss, in that it is necessary to differentiate RON from recurrent tumour. MRI shows segmental enhancement of the nerves, chiasm, or tracts, sometimes associated with enlargement of the affected region.[12-14] Interestingly, the characteristic MRI changes may precede the onset of clinical RON – in one report, changes were present on routine MRI in a patient who had normal visual function but who developed symptomatic vision loss 11 weeks later.[15] In most cases, however, patients in whom an MRI is performed before visual loss demonstrate no predictive imaging abnormalities. After vision reaches its nadir, and the optic disc or discs become pale, the MRI findings typically resolve.

The natural course of RON is usually devastating. Most affected eyes have a final visual acuity less than 20/200 and many are completely blind.[5,10] There have been a few scattered reports of spontaneous improvement following the onset of disease, but these occurred largely in patients who had received radiation to the anterior optic nerve from cobalt plaque therapy for choroidal tumours; these patients typically present with an anterior optic neuropathy characterised by disc swelling and even haemorrhage, and also have retinal exudates and cotton-wool spots.[11] It is therefore possible that this represents a special subset of RON, with a reversible inflammatory component. Lessell[9] reported a patient who became NLP in one eye from RON and who progressed to 20/70 in the other eye; despite treatment with corticosteroids, the patient's vision in the better eye initially remained 20/70 but after several months improved to 20/40 with simultaneous improvement in the visual field. Despite the spontaneous improvement in vision in this patient, other large series indicate that spontaneous improvement never or almost never occurs in patients with typical RON.[5,6]

Pathologic specimens of optic nerves from patients with RON reveal areas of necrosis with fibrin exudates, reactive astrocytosis, loss of myelin and axis cylinders, and an obliterative endarteritis characterised by proliferation of endothelial cells and thickened vessel walls.[4,16] Whether the primary insult occurs in the vasculature or in the parenchyma of the nerve has been a source of debate for decades. Early reports focused on damage to blood vessels, a logical approach given that radionecrosis in general is not limited to neural tissue. A more balanced theory subsequently emerged, however, in which damage to both endothelial and glial cells contribute to the final pathology.[1] In this scenario, both glial progenitor cells and vascular endothelial cells are damaged, so that there is a progressive depletion of glial cells, combined with a progressive inability of the vasculature to meet the metabolic demands of the damaged tissue. Support for this scenario comes from evidence that in both humans and animals, demyelination of white matter tracts precedes vascular insufficiency. More recent reports have returned the focus to the vascular origin of RON.[17] In fact, animal models of RON suggest that vasculitis precedes injury to neurons and glia;[17] in addition, pathologic specimens of irradiated optic nerves in humans demonstrate a relative depletion of endothelial cells.[18] Mirroring this emphasis on vascular changes, this phenomenon has been labelled an "occlusive vasculitis."[5]

With such a devastating, albeit rare complication, an obvious goal of radiation therapy is to limit the effective dosage to the visual apparatus. But what dose of radiation

should be considered safe? In the case of fractionated, external beam radiotherapy (EBR), a total dose of 50 Gy is often cited as the upper limit of a safe dose, with individual fractions not to exceed 2.0 Gy; however, these numbers are merely guidelines. They cannot be applied to every patient and certainly not to other forms of radiation therapy. In a series of patients who had received EBR for extracranial head and neck tumours, no optic neuropathy was noted with total dosages of less than 59 Gy, whereas doses higher than 59 Gy were associated with RON, with the risk increasing with increased doses.[19] The fraction size was also important in this series; patients who received fractions greater than 1.9 Gy were more likely to develop RON than patients receiving lower fractions. In another series of patients who received EBR for tumours of the nasal cavity and paranasal sinuses, no patient who was treated with 50 Gy or less developed RON, and again there was a significant increase in incidence of RON with increasing doses of radiation.[7] Nevertheless, in one series of 13 patients who received EBR for tumours near the optic chiasm, doses as low as 45 Gy were associated with RON.[6]

The dose of radiation that can cause RON may be affected by a number of factors. For example, diabetes mellitus, concomitant chemotherapy, and prior radiation exposure all appear to decrease the threshold dose for RON.[11] In 1 patient who received intrathecal chemotherapy for lymphoma, 24 Gy given in 12 fractions of 2.0 Gy was sufficient to produce RON.[20]

Although both the total dose of radiation and the size of the individual fractions are important in the development of RON, it is difficult to interpret these data with respect to newer forms of radiation therapy, such as stereotactic radiosurgery. For example, the total treatment dose in gamma knife radiosurgery (GKRS) is comparable to or may even exceed that of EBR, but the technique results in a marked reduction in radiation to neighbouring tissues. In a series of 159 patients receiving GKRS for cavernous meningiomas, there were 3 cases of RON, 1 of which appeared to reverse with corticosteroids.[21] In a series of 2400 patients receiving GKRS for perichiasmal tumours, 2 experienced RON.[22] Lastly, in a third series of 218 GKRS patients, 4 subsequently developed RON, although 3 of these patients had received prior EBR.[23] From these and other studies, it has been estimated that a safe single dose to the visual apparatus with GKRS is around 8 Gy to 10 Gy.[24,25] Conformal radiotherapy for optic nerve meningiomas, in which fractionated EBR is delivered to the orbit in a highly focused paradigm, also appears to be very safe; but this technique is relatively new, and data are limited by fewer patients and shorter follow-up periods.[26,27] Thus, although technologic advances have made it possible to deliver highly focused radiation to pathologic tissue, with relative sparing of the visual pathways, RON remains a real threat.

The treatment of RON is unsatisfactory to say the least. Corticosteroids are often used even though there are no controlled clinical trials demonstrating their efficacy, and multiple reports in the literature describe no beneficial effect. Indeed, a retrospective analysis suggests that steroids are not independently associated with any difference in outcome.[5] Anticoagulation with heparin and/or warfarin also appears to be without benefit. In one oft-quoted series, anticoagulation appeared to have a beneficial effect in patients with generalised radionecrosis of the cerebrum and/or spinal cord,[28] but a similar effect has not been demonstrated in patients with RON. In one study, a patient whose vision had declined to NLP despite being treated with corticosteroids was subsequently treated with anticoagulation using heparin followed by warfarin without any return of vision, although it was noted by the authors that anticoagulation was begun rather late in the course of the disease.[29] Stronger circumstantial evidence of lack of benefit from anticoagulation comes from several case reports describing patients who developed RON while they were taking warfarin for another condition such as a cardiac arrhythmia.[10,30,31] Whether or not these patients would have benefited from heparinisation at the time of initial visual loss is a matter for speculation, but the evidence is strong enough to suggest looking elsewhere for a treatment strategy.

Perhaps more promising data come from investigations in animals using inhibitors of angiotensin-converting enzyme (ACE) to reduce radiation-induced injury. For several decades, these agents have been investigated in the setting of experimentally produced radiation injury to healthy, non-neural tissues, such as lung and kidney. More recently, Kim et al[32] investigated the use of the ACE inhibitor ramipril in a rat model of RON. The investigators stereotactically irradiated the brains of adult rats with 30 Gy using a single collimated beam focused on the optic nerves and chiasm. Two weeks after radiation, rats were begun on chronic treatment with either ramipril or placebo, and after 6 months, they were assessed for optic nerve damage both functionally, using visual evoked potentials (VEPs), and histologically. The placebo group showed a three-fold increase in the mean peak latency in the VEP, whereas 75% of the ramipril group had VEPs that resembled those of normal rats. In addition, the optic nerves of the ramipril-treated rats appeared nearly normal on histologic examination, whereas there was significant demyelination in the optic nerves of the placebo-treated rats. This study represents the first demonstration of medical prophylaxis of radiation-induced optic neuropathy, at least in an animal model, and may provide a pharmacological strategy that

can be used in patients at risk for, or who develop RON.

The Potential Benefits of HBO Therapy

HBO therapy refers to the delivery of 100% (or nearly 100%) oxygen at greater than 1 atmosphere (ATM) of pressure, usually between 2 and 3 ATM. Although it can be delivered directly to the lungs via endotracheal intubation, it is usually administered in a pressurised chamber in a series of "dives" of variable duration, generally from 30 to 60 minutes. The rationale for the use of HBO in different conditions varies with the condition; for example, the hyperbaria may be useful in disorders involving other gasses dissolved in the bloodstream, whereas in patients with infections, the oxygen may be toxic to anaerobic pathogens. In the setting of radionecrosis, it is believed that in damaged tissues, oxygen levels are too low to support angiogenesis, and that an artificially produced higher oxygen tension therefore breaks the cycle of ischaemia and necrosis.[33]

In 1987, HBO was referred to as "a therapy in search of diseases";[34] however, it was subsequently found to be beneficial in a number of diverse settings, including carbon monoxide poisoning, decompression sickness, arterial gas embolisation, gas gangrene, and "problem wounds" such as diabetic foot ulcers.[35] Perhaps of more significance is that HBO has been shown to be useful in treating radiation-induced necrosis of non-neural tissues,[36] particularly bone.[37]

The efficacy of HBO in conditions more closely related to RON is less well established. Its efficacy in traumatic brain injury, for example, is a matter of debate.[38] Similarly, although a few small trials suggested that HBO may be of some benefit in the treatment of multiple sclerosis, a subsequent meta-analysis of available data found little evidence that it is of any real value in this setting.[39] Trials of HBO for the treatment of nonarteritic anterior ischaemic optic neuropathy (NAION) have also been disappointing.[40]

Although practitioners generally think of HBO as completely safe, it has common, albeit mild side effects as well as rare but serious complications. Ophthalmic complications are among the most common but, fortunately, the least serious. Dry eye, for example, is frequently experienced by patients undergoing HBO. There is also a high frequency of a reversible myopic shift that may or may not be symptomatic. In some cases, this shift may be as high as 6 diopters;[41] however, it is more often less than 1.5 diopters.[42] The development of visually significant cataracts during HBO was reported in one series,[43] but this complication occurred only in patients who had undergone 150 total hours of HBO.

Less common but more serious adverse effects of HBO include otic barotrauma, reversible bronchopulmonary toxicity, and seizures. Most HBO-induced barotrauma is mild (similar to that experienced while flying in an airplane), although tympanic membrane rupture can occur. Similarly, respiratory toxicity is usually limited to a transient cough or chest tightness[35] but may cause more significant pulmonary compromise. Seizures, while rare, are a well-documented phenomenon. In one series, the incidence of seizures was 0.5%, with the seizures occurring in patients with no known epileptic risk factors.[44] In another, larger series reported by Yildiz et al,[45] 2 of 80,679 patients (0.002%) experienced seizures after HBO. Although these percentages are small, the fact remains that HBO-induced seizures can be fatal. For example, one of the patients reported by Yildiz et al was a 22-year-old man who was undergoing his 30th session of HBO for a decubitus ulcer when he developed tonic-clonic seizures and subsequently died in status epilepticus. A computed tomographic (CT) scan was reported to be normal in this patient, although no postmortem examination was performed. Although seizures have not been reported in patients receiving HBO for RON, reports documenting seizures in patients undergoing HBO for other reasons are of particular concern because patients with RON have, by definition, a pre-existing CNS disease and could therefore be at a higher baseline risk for seizure development.

Lastly, HBO is costly. In the United States, a month-long course of HBO currently costs around $20,000. Then, there is the additional cost of the patient's time commitment, as well as his or her expectations for some treatment effect.

Reports of HBO for the Treatment of RON

In 1986, Guy and Schatz[8] reported a series of 4 patients with RON who were treated with HBO. All 4 patients had received EBR for intracranial masses, and all had received HBO at a pressure of 2.8 ATM. One patient developed vision loss to 20/50 with an associated field defect in one eye after a short period of nonspecific visual symptoms. HBO therapy was instituted within 48 hours of visual loss, and within 2 days of beginning treatment, the vision in the affected eye had returned to normal and remained so during 9 months of follow-up. A second patient had a complex ocular and neurologic history that included retinal oedema previously treated with laser photocoagulation, and CNS large-cell lymphoma with ocular involvement. Seven months after EBR, he developed 2 months of transient visual obscurations followed by progressive vision loss in one eye, from 20/30 to hand motions. Associated findings included enlargement of a previous central scotoma, disc haemorrhages, and a dorsal midbrain syndrome. MRI was reported to show changes only in the thalamus. HBO therapy was begun 3 days after the onset of vision loss, and vision subsequently returned to 20/40. Therapy was then stopped, at which point the patient's vision decreased to 20/300. Accordingly, HBO was restarted, but vision continued

to worsen to finger counting in that eye. The 2 other patients in the study had no benefit from HBO, although their treatments were begun later in the course of their disease. Even though one of the patients experienced only a transient response to HBO and 2 patients had no response at all, Guy and Schatz were encouraged by these results. They emphasised that if HBO were to be used to treat patients with RON, it should be given within 2 days of onset of visual loss, and they suggested that a controlled trial of HBO for RON might be warranted.

In 1990, Roden and coauthors[6] published a series of 13 patients treated for RON with HBO. None had an improvement in the condition, and in many, vision continued to deteriorate during the treatment. Notably, however, the majority of the affected eyes in these patients (19 of 26 eyes) had disc pallor by the time the patients were referred to the authors for evaluation, and the earliest that HBO was instituted after the onset of visual symptoms was 2 weeks rather than the 48 hours suggested by Guy and Schatz.[8] In addition, HBO in this study was administered at a pressure of 2.0 ATM, somewhat less than the optimum dose recommended by some authors.

Subsequently, Liu reported a series of 5 patients with RON, 2 of whom received HBO.[46] Both of these patients had received radiation for nasopharyngeal tumours, and both presented with unilateral vision loss. A CT scan demonstrated no tumour recurrence, electroretinography was normal, and VEPs showed an increased latency of the P100 peak on the affected side. Both patients had optic disc pallor at presentation but no other fundoscopic abnormalities. The first patient presented with vision of 0.3 in the affected eye (compared with 1.5 in the unaffected eye). She received HBO and her vision improved to 0.7 and remained stable during 21 months of follow-up. The second patient presented with vision of 0.6 in the symptomatic eye associated with temporal visual field loss and with vision of 0.9 in the contralateral eye. Within 10 days, the vision in the symptomatic eye had become further reduced to 0.2. The patient received HBO, and the vision returned to 1.0 but with a persistent field defect. One year later, the visual acuities were 1.0 in the affected eye and 1.5 in the contralateral eye. The report does not describe the exact timing of delivery of the HBO, the oxygen percentage or pressure, or the timing of visual recovery with respect to treatment.

In 1996, Borruat et al[5] reported a series of 5 patients with RON, 4 of whom received HBO at a pressure of 2.4 ATM. One patient (also described in a previous report[47]) lost vision first in one eye to NLP. He then began to experience blurred vision in the fellow eye and was found to have visual acuity of 20/20 with a temporal hemianopia. MRI revealed enlargement of the nerve and of the chiasm on the side of the newly symptomatic eye, with gadolinium enhancement of these areas. The patient was given intravenous corticosteroids, and HBO was begun. Four weeks later, at the end of HBO therapy, visual acuity in the eye with the temporal hemianopia was still 20/20 and the visual field had improved; 6 months later, visual acuity in the eye was 20/20 and the visual field was entirely normal. The other eye never recovered any vision.

A second patient reported by Borruat et al[5] presented 3 months after receiving 45 Gy for a pituitary adenoma with new onset of blurred vision in the right eye and severe vision loss in the left eye. Three weeks later, despite being treated with oral corticosteroids, the patient's vision had decreased to 20/40 in the right eye and 3/200 in the left eye. The patient now began HBO at a pressure of 2.4 ATM as well as intravenous corticosteroids. During the 31 days of HBO therapy, visual acuity and colour vision continued to decline in the right eye but acuity improved slightly in the left eye, so that by the end of treatment, vision was 20/200 in both eyes. Following this treatment, the patient's vision gradually improved in both eyes, such that by 3 months following the end of treatment, vision was 20/40 in both eyes with concomitant improvement in the visual fields. The 2 other patients in this series who were treated with HBO both had a continued decline in visual function despite treatment.

Although 2 of their patients had no response to HBO, Borruat et al[5] concluded that treatment with HBO was superior to the natural course of the disease because 2 of their patients improved, whereas their literature search revealed no cases of spontaneous improvement in the setting of RON. They also found that although the visual function in patients who received HBO might not improve, patients who received HBO at any pressure were more likely to experience a halt in the progression of their visual loss than patients who were not treated. Finally, they concluded that for HBO to be effective in the treatment in RON, it must be begun within 72 hours of the onset of vision loss and must be instituted at 2.4 ATM or greater.

The experience at our institution with HBO for RON has not been positive.[10] We have used HBO to treat over a dozen patients with RON and have no cases in which there was visual improvement regardless of when in the course of the disorder the treatment was begun. For example, in 1997, we evaluated a patient who, following treatment of nasopharyngeal carcinoma with surgery and radiation, developed a rapidly progressive, painless vision loss in one eye. At the time of examination, he had visual acuity of 20/400 in that eye but 20/15 in the other, with a full visual field in the eye with normal visual acuity and a normal-appearing optic disc on that side (the other optic disc was pale). The patient underwent MRI that demonstrated enhancement

and thickening of both optic nerves, and he was therefore immediately started on HBO therapy according to the protocol suggested by Borruat et al.[5] Despite this treatment, the patient progressively lost vision in both eyes until he was bilaterally NLP.

Conclusions

In summary, there are only a few patients in the literature with RON whose vision has improved following initiation of HBO. Based on the available data and our own experience, we only reluctantly and without enthusiasm refer patients with RON for HBO. Although the treatment is relatively safe, and its side effects are infrequent, it is expensive and time-consuming; and, perhaps most significantly, may offer false hope in the setting of a relentless disease process. In addition, we agree with those authors who believe that HBO should be limited to those cases where the literature supports a potential value to the treatment – specifically, where symptoms have begun recently and optic pallor has not yet developed – and should be administered at a pressure of at least 2.4 ATM. Despite the theoretical value of prophylactic HBO treatment, in the setting of MRI changes in an otherwise asymptomatic eye, our experience does not suggest such a benefit. If HBO is to be initiated, it should be emphasised to the patient that no good therapy exists for this condition, and that he or she is likely to have a poor outcome despite the treatment. Lastly, the small risks of HBO should not be ignored, particularly in a patient with pre-existing CNS or systemic morbidity.

At present, the best treatment for RON is prevention: that is, the further development of technology to minimise the effective dose of radiation to the visual apparatus. Until that time, however, even if there is some theoretical benefit of HBO in the treatment of RON, a more consistently beneficial therapy, possibly the use of ACE inhibitors, is needed.

Acknowledgement

We would like to acknowledge Qingliang Wang, MD, PhD for his assistance in translating the reference by Liu.

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