Controversies in Neuro-Ophthalmic Management

An Evidence and Case-Based Appraisal

Amanda D. Henderson
Andrew R. Carey
Editors

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Part I

Introduction

Introduction

1

Amanda D. Henderson and Andrew R. Carey

Neuro-ophthalmic diseases may be both sight- and life-threatening and often require expedient management for optimal clinical outcomes. However, due to the rarity of many of these conditions, both individual practitioners and the medical community at large may have limited experience, as well as imperfect scientific data, regarding their ideal management. Additionally, because of the high-stakes nature of many of these diseases (in which delayed or missed diagnosis or inappropriate treatment could lead to permanent vision loss, neurological disability, or even death), some eye care providers may feel nervous or inadequately prepared to handle these patients.

While patients with these disorders often initially present to ophthalmologists or optometrists, they also may present to primary care clinics, emergency departments, or the clinics of neurologists, endocrinologists, or otolaryngologists. Therefore, familiarity with the anatomy relevant for localization of these problems, as well as the clinical features that compel urgent or emergent testing or intervention, is valuable for a wide range of providers. While many of the neurologic pathways travel vertically, the visual pathways traverse predominantly in the anterior-posterior plane and involve or surround important intracranial structures including the cavernous sinuses, pituitary gland, brainstem, and third and lateral ventricles. Additionally, over a third of the cerebral cortex is dedicated to vision, making the neuro-ophthalmic examination crucial for localization of many neurologic disease processes.

In neuro-ophthalmology, as in many fields of medicine, expert opinions regarding optimal management of disease may differ, and newly published data that may change preferred practices frequently become available. Keeping up with the pace of relevant new publications can be daunting and, particularly for practitioners caring for a wide variety of ophthalmic conditions (e.g., residents, optometrists, and

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comprehensive ophthalmologists) and practitioners outside of the eye care field, nearly impossible. Therefore, we developed this book for medical practitioners who are likely to encounter patients with neuro-ophthalmic disease in their practices, with the goal of providing a concise, case-based resource that distills the evidence for evaluation and treatment of neuro-ophthalmic conditions into a readable format.

Written by experts in the field of neuro-ophthalmology, this book provides an evidence-based approach to controversial management decisions, presented in a digestible, case-based structure. We focus on topics that (1) historically have presented a dilemma regarding optimal management, (2) have undergone a recent shift in traditional management due to new scientific discoveries or novel therapies, or (3) require different management strategies depending on nuances of the case presentation. In situations in which the data are not adequate for strong support of a single management pathway, we present the available data, as well as expert opinion on management (highlighting controversies where they exist), thus providing a foundation for the clinical judgment of the practitioner in individual cases.

The format of this book was inspired by the manner in which we, as both clinicians and educators, think and teach on a daily basis in our own clinics, with our students, residents, and fellows. To start each chapter, we present one or more illustrative cases along with associated management dilemma question(s). Based on the case presentation(s), we then discuss the relevant diagnosis, evaluation, and treatment issues; the associated scientific evidence; and expert guidance regarding management recommendations to identify dangerous disease urgently and to provide the best available treatment for optimal patient outcomes. Additionally, we emphasize situations in which co-management with practitioners in other fields of medicine is advocated. By using this case-based approach, we provide a framework for clinical decision-making that is directly transferable to the patient care setting.

We hope that use of this resource will improve your familiarity and comfort level with the neuro-ophthalmic conditions presented, provide an efficient review of the available evidence to guide management of these conditions, and outline evaluation and treatment recommendations that will facilitate improved patient care.

Part II

Optic Neuropathies

Non-Arteritic Anterior Ischemic Optic Neuropathy

2

Amanda D. Henderson

Case 1

A 65-year-old man with diabetes and an otherwise unremarkable medical history presents with 3 days of decreased vision in the right eye, which he noticed upon awakening. He has no headache, scalp tenderness, jaw pain with chewing, shoulder or hip stiffness, fevers, or weight loss. Examination demonstrates visual acuity of 20/30 in the right eye and 20/20 in the left. There is a right relative afferent pupillary defect. Anterior segment examination is unremarkable. Dilated fundus examination demonstrates diffuse edema of the right disc with several peripapillary hemorrhages. The left disc is sharp and pink with a 0.1 cup-to-disc ratio. Humphrey visual field demonstrates an inferior altitudinal defect in the right eye, with a full visual field in the left.

What minimum workup is indicated for this patient?

(a) MRI brain and orbits with and without contrast
(b) Serum testing for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelets
(c) Lumbar puncture
(d) Serum testing for hypercoagulability
(e) Temporal artery biopsy

Assuming that the testing requested from the last question is unremarkable, what treatment should be offered to this patient for his vision loss?

(a) Intravenous steroids

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(b) Oral steroids
(c) No treatment
(d) Topical brimonidine
(e) Anti-vascular endothelial growth factor (VEGF) injection

Case 2

A 45-year-old woman with an unremarkable past medical history presents with vision loss in the left eye. Six days prior, she noticed that she could not see her keyboard out of that eye while typing at work. Aside from some mild left-sided headache, she has no other associated symptoms. On examination, visual acuity is 20/20 in the right eye and 20/40 in the left. There is a left relative afferent pupillary defect. Visual field shows an inferior altitudinal defect in the left eye. Anterior segment examination is unremarkable, and dilated fundus examination is remarkable for a right optic disc with cup-to-disc ratio of 0.15 and a swollen left optic disc.

What minimum workup is indicated for this patient?

(a) MRI brain and orbits with and without contrast
(b) Serum testing for ESR, CRP, and platelet count
(c) Lumbar puncture
(d) Serum testing for hypercoagulability
(e) Temporal artery biopsy

Management

In Case 1, an older patient with a known vasculopathic risk factor, diabetes, presents with acute onset of vision loss, associated with optic disc swelling and an inferior altitudinal defect. Additionally, he has a crowded disc or a "disc-at-risk" in the fellow eye. This clinical scenario is typical of non-arteritic anterior ischemic optic neuropathy (NAION). However, any patient age 50 or over presenting with an ischemic optic neuropathy must undergo evaluation for giant cell arteritis (GCA). His lack of other GCA symptoms, as described in the case presentation, makes GCA less likely. However, *(b) serum testing for ESR, CRP, and platelet count* remains an essential part of his evaluation. Since this case describes a typical presentation of anterior ischemic optic neuropathy (AION), further evaluation with MRI, lumbar puncture, and hypercoagulability testing is not required. If his serum inflammatory workup is abnormal, then a temporal artery biopsy is indicated for further evaluation for GCA. If his serum testing is unremarkable, then the NAION diagnosis may be confirmed. Unfortunately, there is *(c) no treatment* for NAION that has clearly shown improvement in visual outcomes.

In Case 2, a patient again presents with vision loss associated with disc swelling and an inferior altitudinal defect. Unlike the patient in Case 1, this patient is younger and has no known vasculopathic risk factors. Additionally, the time course of vision

loss is less clear, although it may have occurred acutely 6 days prior. Therefore, additional evaluation with *(a) MRI brain and orbits with and without contrast* is required, to evaluate for other etiologies, including inflammatory or compressive lesions. Because she is younger, GCA is less of a concern. Additional evaluation with lumbar puncture and/or hypercoagulability testing could be considered in this atypical case.

NAION is the most common acute unilateral optic nerve-related cause of vision loss in people over age 50 [1]. NAION is characterized by optic disc edema, often with peripapillary hemorrhages, in the affected eye (Fig. 2.1). The disc in the fellow eye often appears crowded [2–6], and the presence of this disc-at-risk is thought to be a predisposing factor to NAION, perhaps due to the propensity for development of a compartment syndrome when axoplasmic stasis occurs in the setting of this anatomic arrangement [7]. The most common visual field defect associated with NAION is an inferior altitudinal defect (Fig. 2.2), although other field defects may be present [8–11].

When evaluating a patient with AION, the most important initial determination is whether the cause is non-arteritic, or whether an underlying arteritic process, specifically GCA, is present. Since GCA carries a high risk of fellow eye involvement, frequently within 2 weeks of first eye involvement, and resultant devastating vision loss, it is crucial to identify and treat cases of GCA immediately [12]. A thorough history taken in all cases should address symptoms suggestive of GCA, including new headaches, scalp tenderness, jaw claudication, transient vision loss preceding permanent visual deficit, fevers, weight loss, malaise, and polymyalgia rheumatica [13–15]. Examination characteristics that may increase suspicion for arteritic AION (AAION) include severe vision loss and pallid disc swelling [12, 16]. Serum ESR, CRP, and platelet count should be checked in all patients age 50 or over with AION. If clinical suspicion remains, based on history, examination, and laboratory values, then temporal artery biopsy should be pursued. Steroid treatment

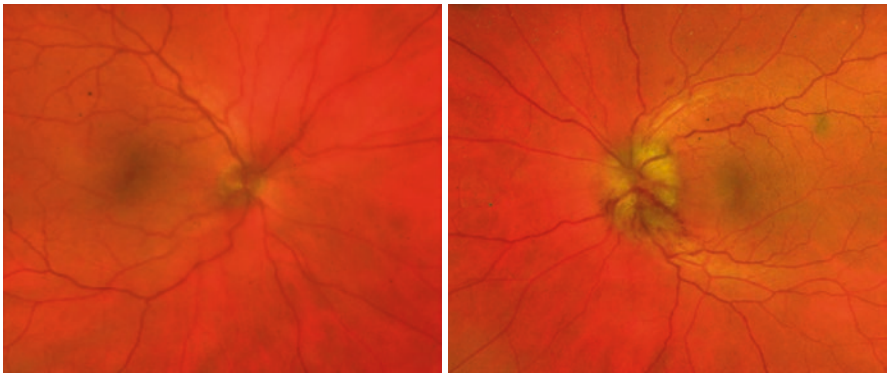

Fig. 2.1 Optic disc photos show an unaffected right optic nerve and a left optic nerve affected by NAION. The right optic nerve appears crowded with no visible cup, a so-called disc-at-risk, and the left optic nerve has 360-degree swelling and multiple hemorrhages. (© AD Henderson 2021. All Rights Reserved)

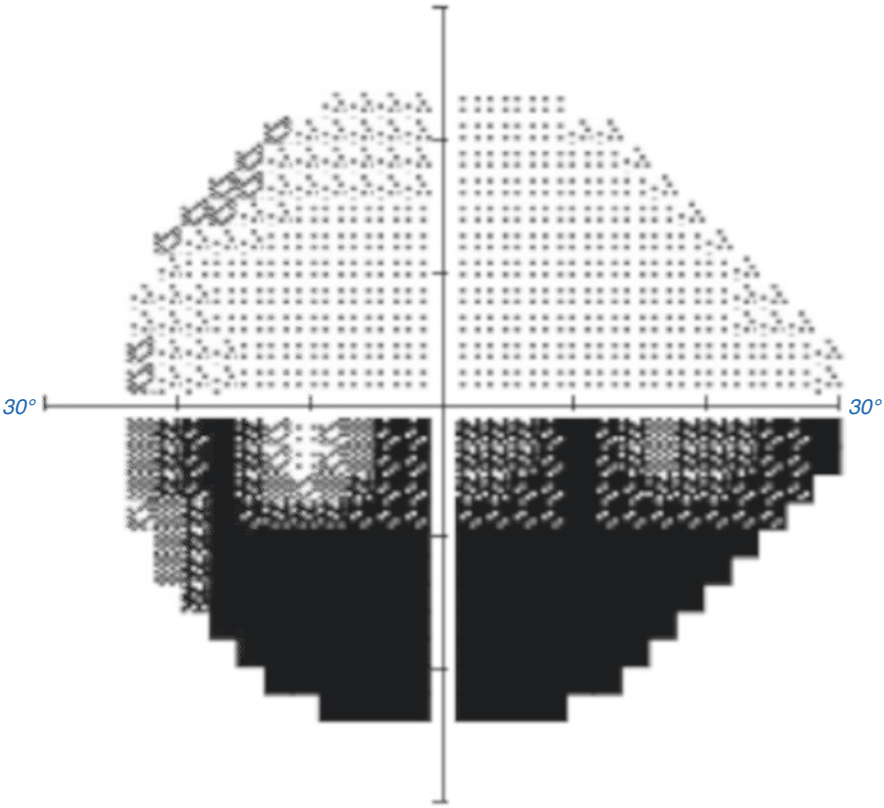

Fig. 2.2 Humphrey visual field 24-2 from a left eye affected with NAION demonstrates an inferior altitudinal field defect. (© AD Henderson 2021. All Rights Reserved)

should not be deferred for confirmation of the diagnosis; rather, patients undergoing temporal artery biopsy should almost always be placed on steroid therapy while awaiting biopsy results. GCA will be covered in more detail in Chap. 23.

After AAION has been excluded, and a diagnosis of NAION is established, then the primary concern becomes management of underlying systemic risk factors. All patients with NAION need a primary care evaluation, including assessment for and treatment of hypertension, diabetes, and hyperlipidemia. In any patient without known obstructive sleep apnea (OSA), a sleep study may be performed to evaluate for OSA. Not only is OSA associated with the development of NAION [17], but also untreated OSA has been identified as a risk factor for fellow eye involvement in NAION [18]. While it is accepted that a hypercoagulable workup is not indicated in typical cases of NAION in older patients with vasculopathic risk factors, it has been reported that underlying thrombophilic disorders may be more common in NAION patients aged 55 years and younger, with a personal or family history of prior thromboembolic events, or without any vasculopathic risk factors [19]. Therefore, it is reasonable to consider a workup for hypercoagulable conditions,

specifically serum testing for Factor V Leiden mutation, antithrombin III mutation, antiphospholipid antibodies, lipoprotein (a), protein C, protein S, MTHFR mutation, and homocysteine, in these cases [20]. While neuroimaging is not required in typical cases of NAION, if the presentation is atypical, then MRI brain and orbits with and without contrast may be considered to evaluate for a retrobulbar process, such as an optic neuritis or a compressive lesion.

Optic disc drusen are a risk factor for NAION, particularly in younger patients [11, 18, 21, 22]. However, like the disc-at-risk, optic disc drusen are nonmodifiable. Therefore, although the presence of optic disc drusen may increase the risk of fellow eye involvement, no specific treatment is recommended for patients with disc drusen.

Phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, vardenafil, tadalafil, and avanafil, are most often used to treat erectile dysfunction in men but also are used to treat pulmonary hypertension, and thus may be used by men and women. PDE-5 inhibitor use has been associated with the development of NAION within several days after drug ingestion, although the absolute number of NAION cases associated with PDE-5 inhibitor use likely is quite low [23, 24]. Therefore, it may be appropriate to ask any patient diagnosed with NAION about prior PDE-5 inhibitor use and counsel him or her regarding the potential for PDE-5 inhibitor use to contribute to increased risk for NAION in the fellow eye.

Nocturnal arterial hypotension, with resultant reduced perfusion pressure to the optic nerve, has been proposed as a contributing factor to NAION [25, 26]. However, there are conflicting data regarding this issue, and a clear link has not been established [27, 28]. While avoidance of the nighttime drop in blood pressure would address this potential issue, there are data to indicate that some patients who do not have the expected nocturnal "dip" in blood pressure could be at increased risk for cardiovascular events and mortality [29–31]. Therefore, any consideration for adjustment of antihypertensive medications, such as a recommendation to take them earlier in the day, should be undertaken with involvement of the patient's primary care physician.

Unfortunately, there is no treatment that has been proven to improve visual outcome in NAION. Aspirin has shown no benefit for visual outcome in the affected eye [32], and data have been inconsistent for a role in risk reduction for second eye involvement [33–35]. Overall, there is no convincing evidence that use of aspirin prevents future NAION [36]. The question often arises as to whether aspirin should be recommended to patients with NAION for prevention of other vascular events like stroke or myocardial infarction. While studies have shown that aspirin is effective as secondary prevention in patients with prior cardiovascular events [37], patients with NAION often do not fall into this group. The role of aspirin in primary prevention of cardiovascular events, even in the setting of known vasculopathic risk factors, is less clear, and recent reports have indicated an increase in major hemorrhage without any significant reduction in the risk of cardiovascular events [38]. Therefore, the potential benefits of aspirin in prevention of cardiovascular disease must be weighed against the risks of bleeding complications. While its use may be

considered on an individual basis, with the input of the patient's primary care physician, the routine use of aspirin in patients with NAION is not recommended.

The use of oral steroids in NAION is controversial. Hayreh and Zimmerman reported on a large cohort of 696 eyes with NAION, comparing those who received oral steroid therapy with those who did not. Notably, the patients themselves selected their treatment group, meaning that there was no randomization, masking, or true control group. The authors reported that among eyes with initial visual acuity of 20/70 or worse that were seen within 2 weeks of onset, visual acuity was more likely to improve in the steroid-treated group than in the group that received no treatment. They also reported that improvement in the kinetic visual field, by subjective assessment, was more likely in the treated group [39]. However, other studies have found no benefit from treatment with oral steroids but have shown an increased risk of complications related to steroid treatment [35, 40]. Therefore, we do not routinely recommend steroids for treatment of NAION.

The use of erythropoietin to treat NAION also is controversial, and the data are limited. One interventional case series reported visual improvement of at least three lines in 55% of eyes treated with intravitreal erythropoietin, although the trend was toward initial improvement with gradual decline of vision after 3 months [41]. There was no control group in this study, but the authors argued that the rate of visual improvement was superior to the rate of 39.5% previously reported in the natural history of NAION [42]. Another study evaluating treatment of NAION with intravenous erythropoietin showed no effect on visual outcomes [35]. Overall, there are no strong data to support the use of erythropoietin in NAION.

Optic nerve sheath fenestration was reported not only to lack benefit in the visual outcome of NAION but also potentially to increase the risk of harm in these cases [42]. Brimonidine, which had shown the promise of a neuroprotective effect on retinal ganglion cells in animal models [43–46], has not shown benefit in humans with NAION [47, 48]. While intravitreal anti-VEGF therapy, used widely for the treatment of ischemic conditions of the retina, initially was reported as a promising treatment for NAION [49], no benefit was demonstrated in a nonrandomized controlled trial [50].

A prospective, randomized, masked, controlled trial was performed in patients with acute NAION to evaluate the potential benefit of intravitreal QPI-1007, a small interference RNA designed to inhibit expression of caspase 2 [51]. The trial revealed no significant improvement in vision in participants who received the drug compared with participants who received a sham injection. Two other randomized, masked, controlled trials evaluating the use of subcutaneous RPh201, an extract of gum mastic with possible immunomodulatory and neuroprotective effects, in patients with optic nerve dysfunction from previous NAION, also failed to show any statistically significant benefit [52]. Additional interventions that have been studied and reported to be ineffective include phenytoin [53] and hyperbaric oxygen [54].

Case Resolution

The patient in Case 1, unfortunately, experienced further decline in his vision in the right eye to 20/200 in the 2 weeks after his initial presentation. His disc swelling resolved over 6 weeks, and he was left with right disc pallor. He underwent a sleep study, was diagnosed with moderate obstructive sleep apnea, and was started on continuous positive airway pressure (CPAP) when sleeping, after which he reported significant improvement in his overall energy level. His visual function stabilized and remained stable at follow-up 2 years later.

The patient in Case 2 underwent extensive medical workup, including testing for diabetes, hypertension, and hyperlipidemia; hypercoagulability workup; and sleep study, which revealed markedly elevated cholesterol but was otherwise unremarkable. MRI was performed and also was unremarkable with no optic nerve enhancement or compressive lesions. Disc edema resolved over a month, and she had residual superior segmental disc pallor. She was followed annually, and her visual function remained stable in both eyes 10 years after her NAION.

Conclusion

In conclusion, there is no strong evidence to support a treatment that improves visual outcomes in NAION. Management of patients with NAION focuses on evaluation for and treatment of underlying risk factors, which could place the patient at risk of NAION in the fellow eye, as well as other systemic complications, in the future.

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Radiation-Induced Optic Neuropathy

3

Amanda D. Henderson

Case

A 64-year-old man presents with decreased vision in the left eye for 2 weeks. His past medical history is significant for glioblastoma multiforme, diagnosed 1 year prior, for which he underwent surgical resection of a left temporal lobe lesion, chemotherapy with temozolomide, and whole-brain external beam radiation for a total dose of 60 Gy in 30 fractions. Examination demonstrates visual acuity of 20/20 in the right eye and counting fingers at one foot in the left eye. There is a left relative afferent pupillary defect. Anterior segment examination is unremarkable. Dilated fundus examination of the right eye is unremarkable, and left fundus examination shows optic disc pallor. Humphrey visual fields demonstrate temporal changes respecting the vertical midline in the right eye and a superior altitudinal defect denser nasally than temporally in the left eye (Fig. 3.1). Due to concern for radiation-induced optic neuropathy (RON) versus tumor progression, he underwent MRI imaging, which demonstrated left prechiasmatic optic nerve enhancement (Fig. 3.2). Additionally, MRI showed evidence of the prior left temporal craniotomy with areas of temporal lobe encephalomalacia, along with an adjacent focus of nodular enhancement. The surrounding parenchyma demonstrated T2/FLAIR hyperintensity.

What is the appropriate management plan for this patient?

(a) Intravitreal (IVT) steroids
(b) Intravenous (IV) steroids
(c) IVT bevacizumab
(d) IV bevacizumab
(e) Hyperbaric oxygen therapy

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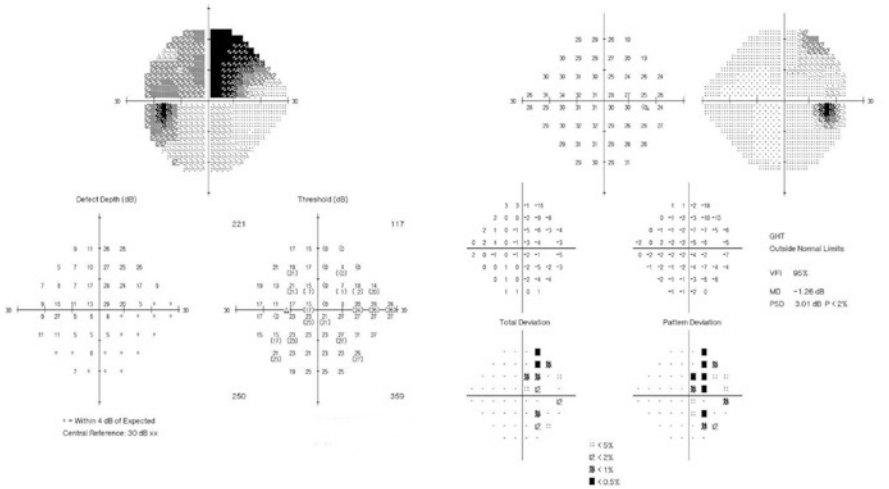

Fig. 3.1 Humphrey visual field 24-2, performed with a size III target in the right eye and a size V target in the left eye due to the poor acuity, demonstrates temporal changes respecting the vertical midline in the right eye and a superior altitudinal defect that is more dense nasally in the left eye. (© AD Henderson 2021. All Rights Reserved)

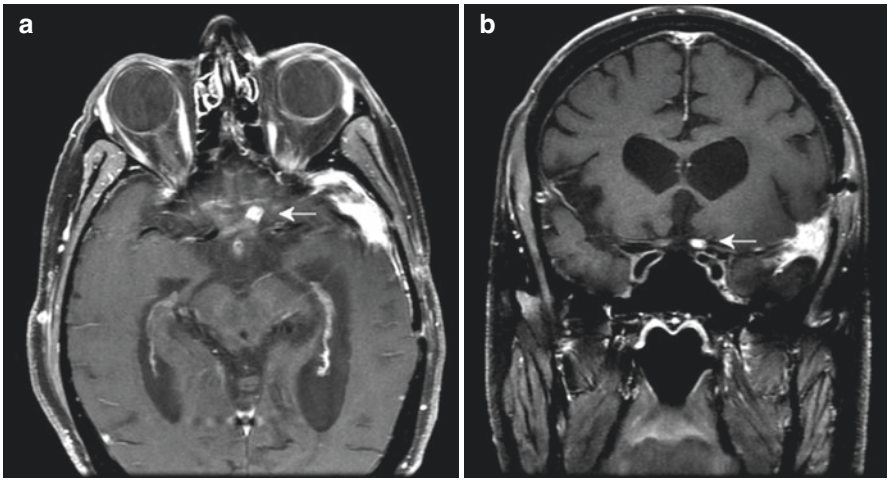

Fig. 3.2 Axial (**a**) and coronal (**b**) T1-weighted postcontrast MRI demonstrates a discrete region of left prechiasmatic optic nerve enhancement (arrows). (© AD Henderson 2021. All Rights Reserved)

Management

The likely diagnosis in this patient is RON of the left optic nerve. His presentation is concerning for early chiasmal involvement, which could explain the mild temporal visual field defect in the right eye. While there is no treatment for RON that is supported by level I evidence, the currently available data support *(d) IV bevacizumab* as the most appropriate treatment option to consider in this case.

RON is a delayed ischemic complication after radiation to the optic nerve and typically leads to severe, irreversible vision loss [1, 2]. The pathogenesis of central nervous system (CNS) radiation damage involves endothelial cell injury with increased capillary permeability, breakdown of the blood-brain barrier, and increased local vascular endothelial growth factor (VEGF) levels, as well as an inflammatory response and injury to glia and neural stem cells [3]. RON can be anterior, usually developing secondary to plaque brachytherapy or proton beam radiation for retinal or uveal tumors and presenting with optic nerve swelling, or posterior, usually occurring after radiation therapy to treat paranasal sinus or skull base tumors and presenting without swelling of the optic nerve [4]. Posterior RON typically appears as prominent postgadolinium enhancement of the involved optic nerve(s) on MRI. Enhancement and expansion of a discrete region of the affected prechiasmatic nerve, as seen in the case described, is most typical of RON [5, 6]. Time of onset is highly variable and has been reported from 1 month to 14 years after radiation therapy [7, 8]. When proton beam irradiation is used to treat parapapillary choroidal melanoma, rates of development of RON as high as 68% have been reported [9]. However, in a retrospective study of 400 patients treated with palladium-103 ophthalmic plaque brachytherapy, only 6% developed RON [10]. Risk of development of anterior RON increases with increasing radiation dose to the optic disc [11, 12]. Anterior RON may have more favorable outcomes than posterior RON [9]. The development of posterior RON also is dose dependent, with low risk in conventional radiotherapy with total dose of less than 50 Gy, risk of about 5% with 50–60 Gy total radiation dose, and risk increasing up to 30% with total radiation dose of greater than 60 Gy [4]. The size of each fraction also contributes to the risk, with a higher fraction dose associated with a higher rate of RON development. Parsons et al. reported a 15-year risk of RON among patients who received a total radiation dose of ≥60 Gy of 11% when fraction size was ≤1.9 Gy versus 47% with fractions ≥1.9 Gy [7]. With regard to stereotactic radiosurgery, recommended upper limits for optic pathway dose are 10 Gy in a single fraction, 20 Gy in three fractions, and 25 Gy in five fractions. At these levels, a <1% risk of development of RON has been calculated [13]. Additionally, other factors including increasing age, diabetes, chemotherapy treatment, acromegaly, and extrinsic optic nerve compression by tumor may lower the threshold for developing RON [2, 4, 6, 7].

While there are no randomized controlled trials (RCTs) addressing treatment of RON, multiple treatments have been evaluated in animal studies, case reports and

series, and retrospective studies. Systemic steroids are commonly used for treatment of radiation necrosis of the CNS and may provide benefit by decreasing edema and inflammation and preventing demyelination [1, 14]. Despite their role in the treatment of CNS radiation necrosis, steroids have shown no benefit for RON [1, 2]. Due to the lack of evidence for response, as well as the potential systemic side effects of steroid use, steroids are not indicated for the treatment of RON.

The angiotensin-converting enzyme (ACE) inhibitor ramipril has been proposed as a potential prophylactic treatment for RON in at-risk patients. This suggestion is based on studies in radiation-exposed rats, which demonstrated a protective effect of early, high-dose ramipril treatment on the later development of RON [15, 16]. Further study is needed in humans prior to recommending broad use of ramipril as prophylaxis against the development of RON.

Pentoxifylline is a methylxanthine derivative that was developed to modify blood viscosity and improve circulation [17]. In combination with vitamin E, its use has shown a decrease in production of reactive oxygen species and impaired fibrosis in vitro. Additionally, pentoxifylline has been shown to reduce necrosis in nonneural ischemic tissues in animals, possibly due to effects on the microcirculation and on the production of inflammatory mediators [18]. An RCT reported promising results for the use of the pentoxifylline and vitamin E combination, but neither alone, in radiation fibrosis in superficial nonneural tissues in humans [19]. However, the overall body of data is inconclusive [17]. Pentoxifylline has been postulated as a potential treatment for RON; however, scientific evidence is sparse. In a single case report, a patient treated with pentoxifylline in combination with vitamin E and dexamethasone had visual improvement in the affected eye [20]. Overall, there is no clear evidence of benefit of pentoxifylline for RON.

Hyperbaric oxygen has been explored as a treatment for RON. Case series have reported that treatment with hyperbaric oxygen (100% oxygen at 2.4–2.8 atm) may lead to clinically relevant visual improvement if started within 72 h of the onset of visual loss [21, 22]. However, hyperbaric oxygen therapy has not demonstrated efficacy when initiated outside of the 72-h time window [22, 23]. Practically speaking, it is uncommon for a patient to present within 72 h of vision loss secondary to RON, and it is even less common that arrangement of hyperbaric oxygen therapy is feasible within this time window. Therefore, hyperbaric oxygen is rarely a realistic treatment option for RON.

Increased VEGF expression has been demonstrated in animal models of CNS radiation necrosis [24]. Bevacizumab, a humanized monoclonal antibody to VEGF, has been suggested as a potential treatment for CNS radiation necrosis, with the rationale that blocking VEGF reduces endothelial leakage and resultant edema [25]. Bevacizumab IV has shown benefit for treatment of CNS radiation necrosis, in terms of clinical and radiographic response, in retrospective studies, a prospective study using historical data as a control, a systematic review, and RCTs [25–30]. In one RCT, Levin et al. reported that five out of five patients with CNS radiation necrosis treated with bevacizumab IV had clinical and radiologic improvement, whereas none of those receiving placebo improved. Subsequently, in a crossover arm, all seven patients who originally received placebo then received bevacizumab

IV, and all improved [28]. In another RCT that compared bevacizumab IV to corticosteroid treatment, Xu et al. reported that 65.5% of patients treated with bevacizumab improved, compared with only 31.5% treated with corticosteroids. However, the response was not sustained after cessation of the bevacizumab therapy [29]. Adverse effects of bevacizumab treatment, which include hypertension, hemorrhage, thromboembolism, headache, nausea and vomiting, bowel perforation, leukopenia, neutropenia, myalgias, and weakness, must be considered when making treatment decisions [1]. Rarely, treatment-related effects from bevacizumab can be fatal in cancer patients [31]. Three patients treated with bevacizumab in Levin's RCT had serious adverse events, including aspiration pneumonia, superior sagittal sinus thrombosis, and pulmonary embolism [28]. However, in the systematic review, only 2.4% of the 125 cases included were reported to have a serious adverse event, suggesting that the risk-to-potential-benefit ratio in patients with CNS radiation necrosis may be acceptable [27].

The rarity of RON limits the ability to evaluate treatment options using RCTs. While no RCTs are available for the use of bevacizumab in RON, case reports and series have reported clinical benefit, in a time window that is feasible for the arrangement of therapy. Bevacizumab IVT, both alone and in combination with triamcinolone IVT, has shown some promise for treatment of anterior RON in patients treated with plaque brachytherapy for uveal melanoma [12, 32, 33]. However, a recently published retrospective study evaluating patients with anterior RON after proton beam therapy for uveal melanoma demonstrated no benefit for bevacizumab IVT when compared with steroid IVT treatment and no benefit for IVT treatment of any kind when compared with observation alone [34]. Prophylactic use of IVT bevacizumab in patients treated with proton beam irradiation for choroidal melanoma has shown high rates of visual acuity retention over 2 years, with decreased rates of both radiation maculopathy and anterior RON in those with small/medium tumors [35]. However, prophylactic bevacizumab IVT after plaque radiotherapy did not demonstrate any effect on the rate of development of anterior RON [36]. As spontaneous visual improvement may occur in about one-third of patients with anterior RON, it remains unclear whether bevacizumab IVT offers any long-term benefit with regard to anterior RON, specifically [9].

While IVT drug delivery is a reasonable consideration for anterior RON, it is likely to be inadequate for RON involving the orbital or intracranial portions of the optic nerve. Therefore, IV delivery of bevacizumab has been evaluated in this setting. Dutta et al. reported a series of three cases of RON treated with bevacizumab IV 5 mg/kg initially, then 10 mg/kg every 2 weeks for a total of six doses, or until visual improvement occurred. Bevacizumab was initiated between 4 and 7 weeks after the onset of vision loss. All three cases demonstrated visual improvement [37]. Farooq et al. reported a case of bilateral RON, which was treated with bevacizumab IV 7.5 mg/kg every 3 weeks for a total of three doses. Bevacizumab treatment was initiated 4 weeks after vision loss. The patient also received dexamethasone and pentoxifylline. Acuity, color vision, and visual fields improved markedly over 4 weeks after the initiation of the bevacizumab treatment, and visual function remained stable over a 3-year follow-up period [38]. These reports, as well as author

experience with bevacizumab IV treatment in posterior RON, support the potential of this therapy in these cases, which otherwise have a dismal prognosis.

Case Resolution

The patient in the case was treated with bevacizumab 10 mg/kg IV every 2 weeks for a total of four doses. At his latest follow-up 13 months after presentation, his acuity was 20/40 in the right eye and counting fingers at two feet in the left. His visual fields remained stable in both eyes. Overall, since the time of initial presentation, his visual function remained largely stable with no improvement but also no significant progression of vision loss.

Conclusion

As the visual prognosis in RON typically is poor, and no other treatment has clearly demonstrated benefit, we recommend that bevacizumab IV be considered in patients with vision loss from RON. However, evidence for efficacy of bevacizumab IV in RON is limited to case reports and series, and the optimal treatment scheduling and dosing has not been defined.

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