Controversies in Neuro-Ophthalmic Management

An Evidence and Case-Based Appraisal

Amanda D. Henderson
Andrew R. Carey
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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

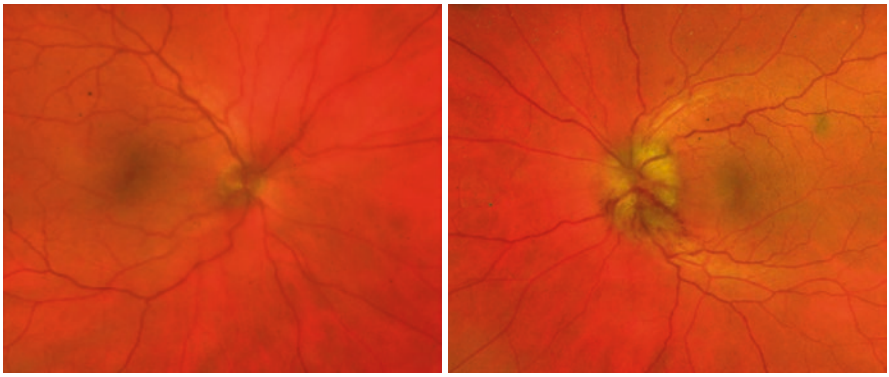

Fig. 2.1 Optic disc photos show an unaffected right optic nerve and a left optic nerve affected by NAION. The right optic nerve appears crowded with no visible cup, a so-called disc-at-risk, and the left optic nerve has 360-degree swelling and multiple hemorrhages. (© AD Henderson 2021. All Rights Reserved)

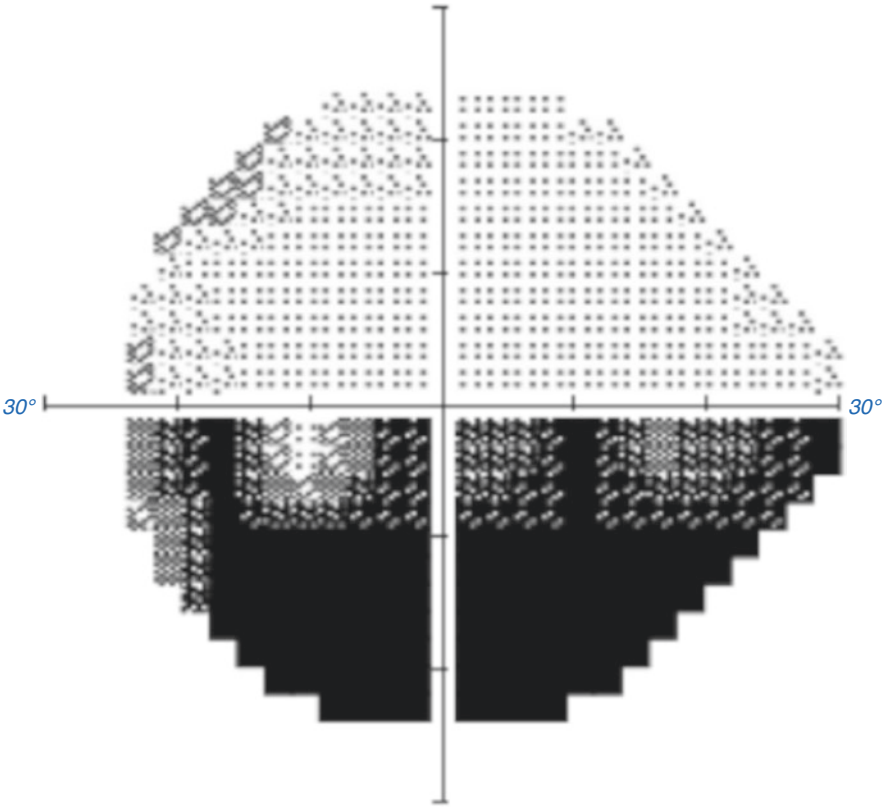

Fig. 2.2 Humphrey visual field 24-2 from a left eye affected with NAION demonstrates an inferior altitudinal field defect. (© AD Henderson 2021. All Rights Reserved)

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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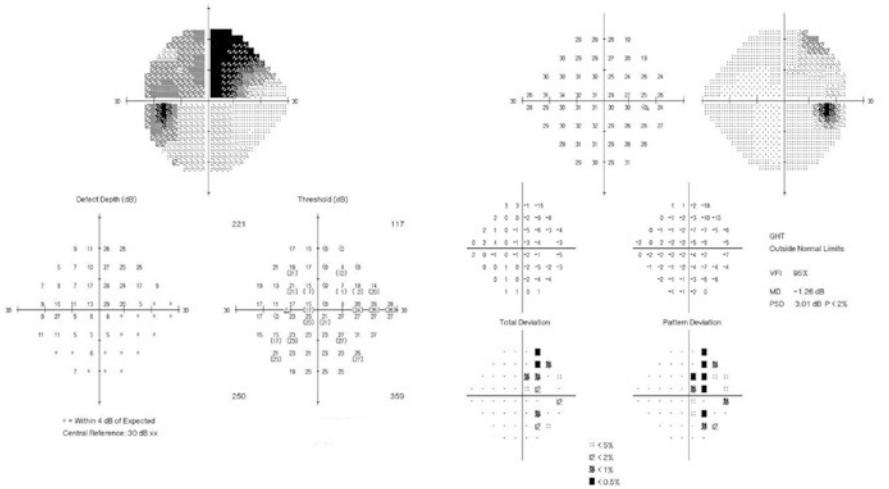

Fig. 3.1 Humphrey visual field 24-2, performed with a size III target in the right eye and a size V target in the left eye due to the poor acuity, demonstrates temporal changes respecting the vertical midline in the right eye and a superior altitudinal defect that is more dense nasally in the left eye.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

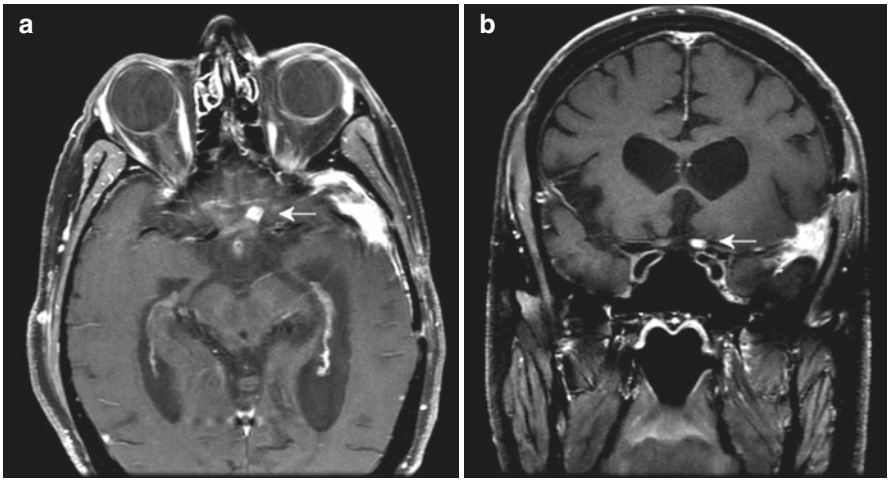

Fig. 3.2 Axial (**a**) and coronal (**b**) T1-weighted postcontrast MRI demonstrates a discrete region of left prechiasmatic optic nerve enhancement (arrows). (© AD Henderson 2021. All Rights Reserved)

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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Optic Neuritis

4

Amanda D. Henderson

Case 1

A 22-year-old woman with no significant past medical history presents with blurred vision and pain with eye movements in the right eye for 1 day. On examination, her visual acuity is 20/50 in the right eye and 20/20 in the left eye. There is a right relative afferent pupillary defect. Color vision is decreased in the right eye compared with the left eye. Anterior segment examination is unremarkable. Optic nerve appearance also is unremarkable (Fig. 4.1). MRI demonstrates a segment of right optic nerve enhancement, consistent with a unilateral retrobulbar optic neuritis (ON) (Fig. 4.2).

When managing acute unilateral retrobulbar ON, what is the minimum evaluation indicated to determine an underlying cause?

(a) No further workup required
(b) CT head with contrast, myelin oligodendrocyte glycoprotein (MOG)-IgG, aquaporin-4 (aqp4)-IgG
(c) MRI brain and orbits with and without contrast, MOG-IgG, aqp4-IgG
(d) MRI brain and orbits with and without contrast
(e) Lumbar puncture to evaluate for oligoclonal bands

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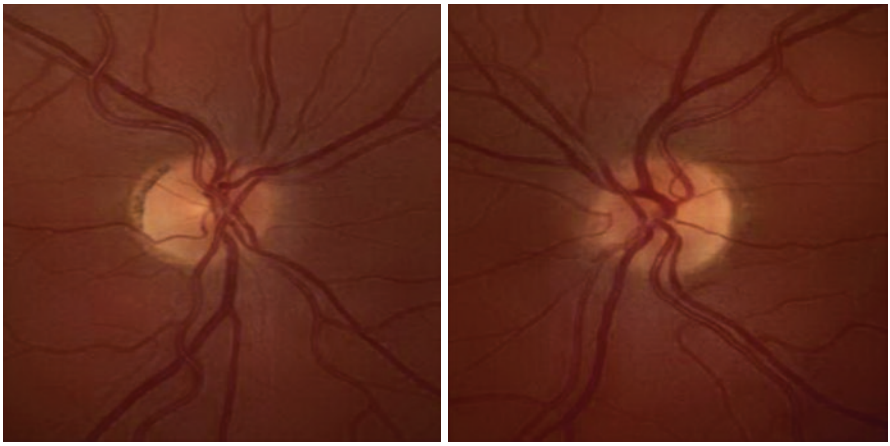

Fig. 4.1 Optic discs are sharp and pink in both eyes with no swelling or pallor (© AD Henderson 2021. All Rights Reserved)

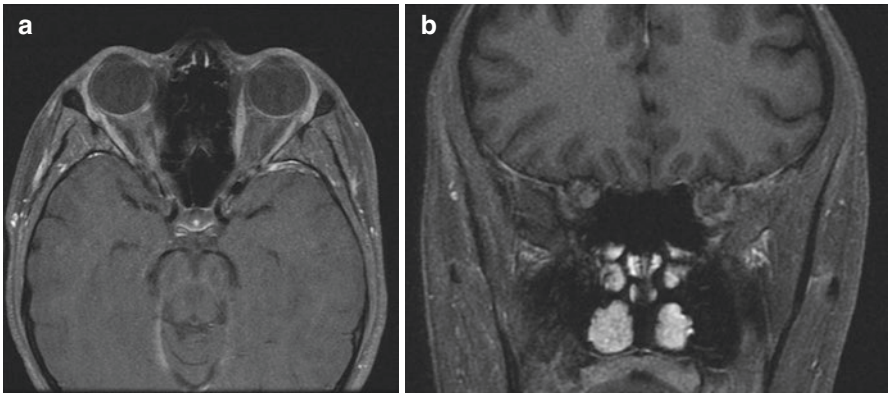

Fig. 4.2 (**a**) Axial and (**b**) coronal T1-weighted post-contrast MRI demonstrates enhancement involving the retrobulbar segment of the right optic nerve (© AD Henderson 2021. All Rights Reserved)

Case 2

A 27-year-old woman presents with 2 days of blurred vision in the left eye. On examination, her visual acuity is 20/25 in the right eye and counting fingers at one foot in the left eye. There is a left relative afferent pupillary defect. Anterior and posterior segment examinations are otherwise unremarkable. MRI demonstrates longitudinally extensive left optic nerve enhancement, involving the entire retrobulbar segment, the intracanalicular segment, and the prechiasmatic/intracranial segment (Fig. 4.3).

When managing acute unilateral ON with longitudinally extensive optic nerve enhancement that extends to involve the intracranial segment, what is the minimum evaluation indicated to determine an underlying cause?

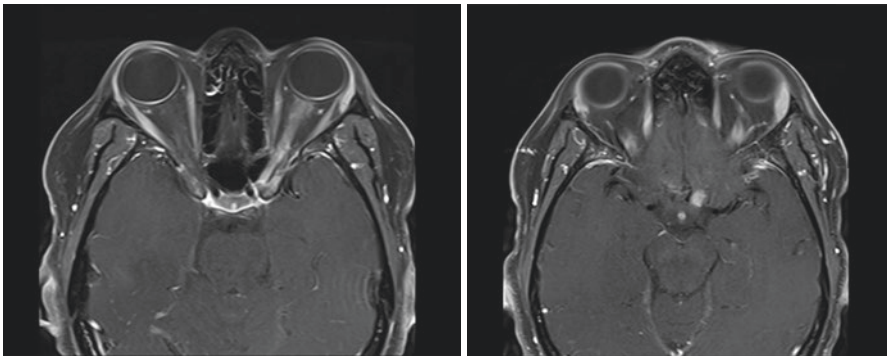

Fig. 4.3 Axial T1-weighted post-contrast MRI demonstrates longitudinally extensive enhancement of the left optic nerve including the retrobulbar, intracanalicular, and prechiasmatic (intracranial) segments (© AD Henderson 2021. All Rights Reserved)

(a) No further workup required
(b) CT head with contrast
(c) MRI brain and orbits with and without contrast, MOG-IgG, aqp4-IgG
(d) MRI brain and orbits with and without contrast
(e) Lumbar puncture to evaluate for oligoclonal bands

Case 3

A 49-year-old woman with no significant past medical history presents with 1 week of bilateral eye pain, worse with eye movements, and 2 days of bilateral blurred vision. On examination, visual acuity is 20/70 in the right eye and 20/50 in the left eye. There is no relative afferent pupillary defect. Anterior segment is unremarkable. Optic discs are swollen bilaterally (Fig. 4.4). MRI demonstrates longitudinally extensive retrobulbar enhancement of the optic nerves bilaterally (Fig. 4.5).

When managing acute bilateral ON, with disc swelling and longitudinally extensive optic nerve enhancement, what is the minimum evaluation indicated to determine an underlying cause?

(a) No further workup required
(b) CT head with contrast
(c) MRI brain and orbits with and without contrast, MOG-IgG, aqp4-IgG
(d) MRI brain and orbits with and without contrast
(e) Lumbar puncture to evaluate for oligoclonal bands

For Case 1, a typical case of unilateral, retrobulbar ON, the minimum acceptable workup is *(d) MRI brain and orbits with and without contrast*, specifically to evaluate for white matter lesions that would suggest underlying multiple sclerosis (MS)

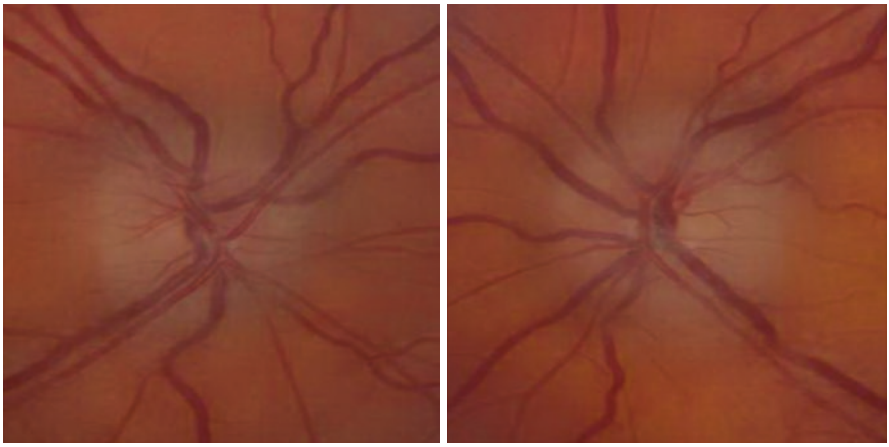

Fig. 4.4 Optic discs are swollen bilaterally (© AD Henderson 2021. All Rights Reserved)

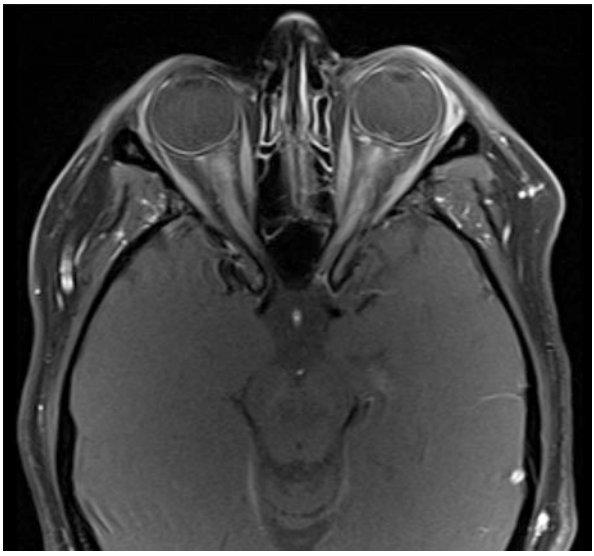

Fig. 4.5 Axial T1-weighted post-contrast MRI demonstrates longitudinally extensive enhancement of the optic nerves bilaterally (© AD Henderson 2021. All Rights Reserved)

(Fig. 4.6) [1]. However, for Cases 2 and 3, atypical ON cases, one with longitudinally extensive optic nerve enhancement involving the intracranial segment, and the other with bilateral involvement and disc swelling, further workup is required, including *(c) MRI brain and orbits with and without contrast, MOG-IgG, and aqp4-IgG* testing. Spinal cord MRI, additional inflammatory and infectious (including syphilis, bartonella, Lyme, and tuberculosis) workup, and lumbar puncture with cerebrospinal (CSF) fluid analysis likely are indicated, as well.

ON is the most common acute optic neuropathy in young adults, and this chapter focuses on ON in the adult patient. The incidence of acute ON ranges from 1.1 to 5.1 per 100,000 per year [2, 3]. Females are affected more commonly than males.

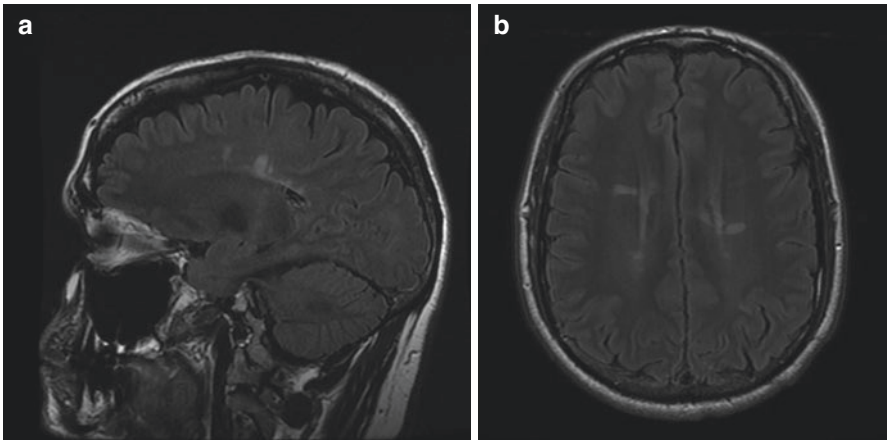

Fig. 4.6 (**a**) Sagittal and (**b**) axial T2-weighted FLAIR MRI demonstrates typical distribution of periventricular white matter lesions in MS, oriented perpendicular to the lateral ventricles, and involvement of the corpus callosum (© AD Henderson 2021. All Rights Reserved)

Table 4.1 Comparison of characteristic clinical and MRI findings of optic neuritis in multiple sclerosis (MS), seropositive neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein-IgG-associated disorder (MOGAD)

Underlying condition	Optic nerve appearance acutely [13, 23–25, 35]	Unilateral or bilateral involvement [13–15, 19]	Lesion length [9, 13, 15, 19]	Lesion location on MRI [9, 13, 14, 23, 25]
MS	Normal	Usually unilateral	Short segment	Retrobulbar/ intracanalicular segment
Seropositive NMOSD	Usually normal	Commonly bilateral	Longitudinally extensive	Extension to posterior segments (prechiasmatic, chiasm, tracts)
MOGAD	Commonly swollen	Commonly bilateral	Longitudinally extensive	Retrobulbar segment

ON can be isolated but often is associated with an underlying systemic disease, including MS, neuromyelitis optica spectrum disorder (NMOSD), MOG-IgG-associated disorder (MOGAD), and other conditions like connective tissue disease, granulomatous disease, and infection. ON typically presents in a young female with acute vision loss and associated pain that is exacerbated by eye movement, although clinical presentation can vary depending on the underlying cause. Unless the process is bilateral and symmetric, a relative afferent pupillary defect is expected. Visual fields classically demonstrate a central or cecocentral scotoma. Overall, among adults with ON, disc appearance is normal in two-thirds of cases and swollen in one-third, although disc appearance also varies depending on the underlying condition. Table 4.1 presents characteristic clinical and MRI features of ON associated

with MS, seropositive NMOSD, and MOGAD. While a complete discussion of ON in children is beyond the scope of this chapter, pertinent differences in presentation include higher rates of bilateral involvement and optic disc swelling acutely, as well as lower rates of ocular pain, in pediatric patients with ON compared with adults [4–7].

Multiple Sclerosis

ON secondary to MS, which is considered a "typical" ON, usually presents with a normal-appearing optic disc, and acute involvement generally is unilateral [8]. Most commonly, optic nerve involvement is focal and limited to the intraorbital portion of the visual pathways [9]. In all cases of optic neuritis, including typical cases, MRI of the brain with and without contrast is indicated to evaluate for lesions that may elucidate an underlying disease. MRI of the cervical spine also is indicated in many cases. Based on the Revised McDonald Criteria, diagnosis of MS in the setting of a patient presenting with a clinically isolated syndrome, such as an optic neuritis, requires: (1) dissemination in space, which may be demonstrated clinically or radiologically on MRI by one or more T2 hyperintense lesions in at least two out of four central nervous system areas, including periventricular, cortical or juxtacortical, infratentorial, and spinal cord, and (2) dissemination in time, which may be demonstrated clinically; radiologically by a new T2 and/or gadolinium-enhancing lesion with reference to a baseline MRI, or by the simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or by the demonstration of CSF-specific oligoclonal bands [10]. While MS is the most common underlying disease in patients presenting with optic neuritis, it is important to rule out mimickers.

Neuromyelitis Optica Spectrum Disorder

In atypical ON cases, as well as cases that do not have neuroimaging evidence of MS, further evaluation should be pursued. Previously considered a variant of MS, NMOSD now has been characterized as a distinct disease, often associated with the presence of aqp4-IgG. In the setting of aqp4-IgG seropositivity, diagnosis of NMOSD requires at least one core clinical characteristic, including (1) ON, (2) acute myelitis, (3) area postrema syndrome, (4) acute brainstem syndrome, (5) symptomatic narcolepsy or acute diencephalic clinical syndrome with typical MRI lesions, and (6) symptomatic cerebral syndrome with typical MRI lesions [11]. Aqp4-IgG causes an autoimmune astrocytopathy, in which central nervous system demyelination occurs due to a primary destruction of astrocytes. The aqp4-IgG serum test has a sensitivity of 33–91% and specificity of 85–100% for NMOSD, depending on the assay used for detection [12]. As cell-based assays have the highest sensitivity, their use has been recommended for detection of aqp4-IgG whenever possible [11]. ON in the setting of NMOSD with aqp4-IgG antibodies presents with

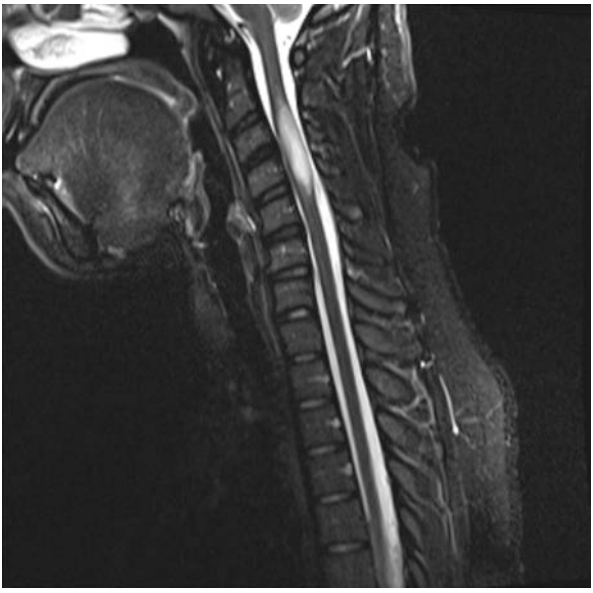

Fig. 4.7 Sagittal STIR MRI demonstrates longitudinally extensive demyelinating lesion of the cervical spinal cord, with associated central expansion of the cord, typical of an NMOSD-associated lesion (c) AD Henderson 2021. All Rights Reserved)

bilateral involvement in 30–82% of cases [13, 14]. Longitudinally extensive optic pathway enhancement is characteristic of this disorder [9, 15]. Intracranial optic pathway involvement also is common [9, 13, 14]. In addition to aqp4-IgG seropositivity, patients with NMOSD often have demyelinating lesions of the spinal cord. In contrast to MS, in which cord involvement usually is limited to peripheral white matter tracts and spans one or fewer vertebral segments, cord involvement in the setting of aqp4-IgG is longitudinally extensive, spanning three or more vertebral segments, and involves predominately the central gray matter, with expansion of the central cord (Fig. 4.7) [11, 16]. While aqp4-IgG accounts for a small percentage of ON cases overall in the United States (e.g., 3% in a predominantly Caucasian population in Minnesota), it has been reported to be more common in Asia [17, 18].

Myelin Oligodendrocyte Glycoprotein-Associated Disorder

MOGAD may present as (1) isolated optic neuritis, (2) relapsing optic neuritis, (3) NMOSD with transverse myelitis and ON, or (4) acute disseminated encephalomyelitis [19]. Although MOGAD can clinically resemble NMOSD secondary to aqp4-IgG, it has been shown to be a separate entity [15]. Notably, MOG-IgG has been associated with a significant portion of cases previously characterized as chronic relapsing inflammatory optic neuropathy (CRION), an optic neuropathy that responds to steroid administration and relapses upon steroid withdrawal [20, 21]. Although typical ON (i.e., that related to MS), presents most often in young adults, MOGAD has a broader age distribution, with onset ranging from infancy to advanced age [15]. Like MS-associated optic neuritis, MOG-IgG-associated ON

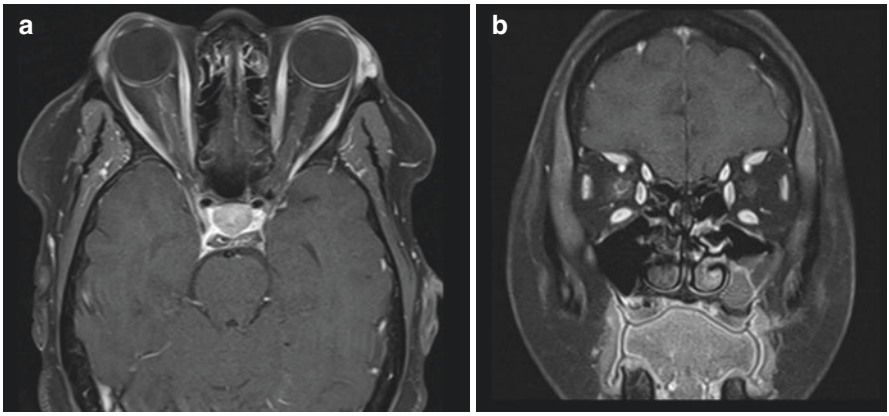

Fig. 4.8 (**a**) Axial and (**b**) coronal T1-weighted post-contrast MRI demonstrates right perineural enhancement, with sparing of the optic nerve itself, in the setting of a relapse in a patient with known MOGAD (© AD Henderson 2021. All Rights Reserved)

usually presents with painful extraocular movements [19]. MOG-IgG-associated ON presents with optic disc swelling in 46–94% of cases, and involvement is commonly simultaneously bilateral [13, 15, 19, 22–25]. On MRI, coexisting nerve and perineural enhancement is common, although perineural enhancement even can be seen in isolation (Fig. 4.8) [19, 20, 24, 26]. Nerve enhancement usually is longitudinally extensive (with >50% of the nerve involved in 80% of cases in one report), and the enhancement usually involves the retrobulbar segment of the optic nerve [13, 19, 23]. When blood samples from 177 patients from the Optic Neuritis Treatment Trial (ONTT) were examined, only three of them were MOG-IgG seropositive. Of these three, all had optic nerve swelling at ON presentation, two developed recurrent optic neuritis during the follow-up period, and none developed MS [22]. With regard to CSF analysis, patients with MOGAD may demonstrate pleocytosis and elevated protein, but they rarely demonstrate the intrathecal synthesis of oligoclonal bands that frequently is present in MS [19, 20, 27, 28]. While the analysis of serum from the ONTT indicates that MOGAD may be a relatively rare cause of ON in the United States, it may be a more common cause in certain populations. For instance, a recent report including 531 cases of optic neuritis in Japan indicated that 10% of these were MOG-IgG positive [29].

Management

It is crucial to discriminate between MS, NMOSD secondary to aqp4-IgG, and MOGAD, as prognosis and effective treatments differ for these diseases. Presence of aqp4-IgG predicts a worse visual outcome than MOGAD or MS [13–15, 21, 23, 25, 29–33]. While each ON episode has a better prognosis of visual recovery in MOGAD, presence of MOG-IgG predicts a higher risk of relapse than aqp4-IgG or MS [21, 34].

For treatment of acute ON, the ONTT-evaluated therapy with high-dose IV steroid (methylprednisolone 250 mg IV every 6 h for 3 days) followed by a moderate-dose oral steroid (prednisone starting at 1 mg/kg daily) taper, versus moderate-dose oral steroid alone, versus placebo. The study reported that high-dose IV steroid sped recovery from an acute ON episode but did not affect the ultimate visual outcome [8, 35]. Additionally, although high-dose IV steroid decreased the risk of developing MS within the first 2 years after the ON episode, this benefit did not persist beyond that time frame [8]. Interestingly, the authors also concluded that low-dose steroid treatment should be avoided in the treatment of acute ON, as it may increase the risk of ON recurrence when compared with treatment with high-dose steroid and with placebo [35]. While the ONTT delivered high-dose steroid IV and did not compare the relative efficacy of high-dose steroid administered orally versus IV, more recent studies have demonstrated similar outcomes, tolerance, and relapse rates when typical ON is treated with equivalent doses of IV and oral steroid [36, 37]. Since oral steroids offer potential advantages over IV steroids, including lower cost, greater convenience, and at times more rapid access, oral treatment is a reasonable option for many cases of typical ON [37]. Of note, due to the concern for gastrointestinal side effects with high-dose oral steroids, concomitant administration of a proton pump inhibitor (e.g., omeprazole) or H2 blocker (e.g., famotidine) during high-dose oral steroid treatment is prudent. While treatment with high-dose oral steroids (e.g., prednisone 1250 mg daily for 5 days) is an acceptable choice for typical ON related to MS, high-dose IV steroid treatment (with methylprednisolone 1 g daily for 5 days) is indicated in seropositive NMOSD, with oral steroid taper thereafter [38]. Additionally, the early use of plasma exchange, rather than its use only as a rescue therapy after poor response to steroids, may improve visual outcomes in ON secondary to NMOSD [39]. In this setting, early plasma exchange may be used concomitantly with IV steroid treatment.

Following acute treatment of ON, long-term management of the underlying disease process often is indicated, and accurate identification of the causative condition is necessary for treatment planning. There now are many effective disease-modifying therapies available to treat MS, and choice of treatment can be tailored to individual cases [40]. However, not only are MS treatments ineffective for NMOSD and MOGAD, but they may cause worsening in these conditions [41–45]. Since the morbidity and duration of NMOSD relapses are typically severe, long-term immunosuppression is required. Any patient with aqp4-IgG seropositivity should be presumed to be at risk for relapse indefinitely and, therefore, maintenance of immunosuppression is recommended. Rituximab, a monoclonal antibody to CD20 that causes B-cell depletion, has been considered the first-line treatment agent for NMOSD and has been demonstrated to reduce relapse rate and disability in this condition with an acceptable level of safety and tolerability [38, 46, 47]. However, in 2019, eculizumab, a C5 complement inhibitor, became the first drug approved by the US Food and Drug Administration for the treatment of NMOSD with aqp4-IgG seropositivity, after it was shown to decrease relapse rate in a randomized, controlled trial [48]. Shortly thereafter, in 2020, inebilizumab (an anti-CD19 antibody) and satralizumab (an anti-interleukin-6 receptor antibody) were approved [49, 50].

MOG-IgG is associated with an even higher rate of relapse than aqp4-IgG, although some patients never have a second episode. Persistent MOG-IgG seropositivity may be associated with risk for relapse [51]. Because some cases of MOGAD behave phenotypically like CRION, with relapse of the optic neuritis when steroids are withdrawn, a slow oral steroid taper (over 1–3 months) following the acute high-dose treatment has been recommended [52]. Prophylactic long-term immunosuppressive treatment should be considered in MOGAD, specifically in the setting of poor visual recovery from an episode of optic neuritis [27, 52]. However, patients who become seronegative for MOG-IgG may be at low risk for relapse and may not benefit from immunosuppressive therapy [51]. Commonly used immunosuppressive/immunomodulatory agents include rituximab, azathioprine, mycophenolate mofetil, and intravenous immunoglobulin (IVIg) [52]. Tocilizumab also has been reported to be effective in refractory disease [53]. Optimal choice of immunosuppression for MOGAD is not clear, although IVIg may be more effective at preventing relapse than other agents [54]. Importantly, disease-modifying therapy that is effective in MS may lead to increased disease activity in patients with MOGAD and, therefore, should be avoided [27, 54].

Case Resolution

Circling back to the cases, the patient in Case 1 ultimately was diagnosed with MS, the patient in Case 2 with seropositive NMOSD, and the patient in Case 3 with MOGAD. As demonstrated by these cases, all cases of ON require neuroimaging with MRI brain and orbits with and without contrast, unless there is an absolute contraindication to this procedure.

Conclusion

As described above, neuroimaging characteristics of the ON, including lesion location, length, and presence of associated perineural enhancement, as well as the characteristics of any associated brain or spinal cord lesions, can be used to guide clinical suspicion for underlying causes. It could be argued that further testing is not indicated in cases of optic neuritis that present in a typical fashion, with unilateral involvement, pain with eye movements, normal-appearing disc acutely, and a short segment of optic nerve enhancement on MRI, especially if white matter lesions typical of MS are seen on the brain MRI. In the case of atypical features, including bilateral involvement, optic disc swelling, lack of pain, longitudinally extensive optic nerve enhancement, perineural involvement, or brain or spinal cord lesions not suggestive of MS, then additional workup including MOG-IgG and aqp4-IgG testing is required. However, in our opinion, it is not unreasonable to check aqp4-IgG and MOG-IgG in all cases of ON, since the potentially debilitating outcomes of NMOSD and high recurrence rate of MOGAD, as well as the different treatment regimens for the conditions, make identification of these conditions crucial.

Additionally, the cell-based assays have very high specificities; therefore, the chance of false-positive results is low. Overall, we agree with others who have addressed this topic that the risk of recurrent attacks due to lack of treatment outweighs the risk of a false-positive test result [55]. Finally, exclusion of mimickers, as well as underlying infections that could be exacerbated by immunosuppressive treatments, is often advisable. Depending on the clinical context, workup for infectious conditions such as Lyme disease, bartonella, syphilis, and tuberculosis; paraneoplastic syndromes; and inflammatory processes such as IgG4-related disease and sarcoidosis may be appropriate in addition to the studies discussed in detail in this chapter.

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Traumatic Optic Neuropathy

5

Neil R. Miller

Case

A 25-year-old healthy man was injured in a motor vehicle accident earlier in the day. He lost consciousness at the time of the accident and remained unconscious for several hours thereafter. He was taken to the hospital where a CT scan was normal except for a fracture of the right optic canal. Upon awakening, the patient complains of decreased vision in the right eye. The examination reveals vision of light perception with the right eye and 20/15 with the left eye. There is a right relative afferent pupillary defect (RAPD). The ocular fundi are normal in appearance, with no evidence of optic disc swelling.

How should this patient be managed?

(a) Observation without intervention
(b) "Mega-dose" systemic corticosteroids
(c) High-dose systemic corticosteroids
(d) Decompression of the optic canal

Management

The likely diagnosis is traumatic optic neuropathy (TON) involving the right optic nerve. TON can be classified as anterior, i.e., the result of injury to the part of the nerve in the anterior or mid-orbit; or posterior, i.e., the result of injury to the posterior orbital, canalicular, and/or intracranial parts of the nerve. Anterior TON is

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characterized by optic disc swelling in the setting of other evidence of an optic neuropathy (e.g., decreased acuity, poor or absent color vision, a visual field defect, and a relative afferent pupillary defect (RAPD) if the injury is unilateral or asymmetric). It usually is accompanied by injury to associated vasculature. This, in turn, can lead to retinal ischemia or infarction, central retinal vein occlusion, anterior ischemic optic neuropathy, or a combination of these phenomena. Posterior TON also is characterized by clinical evidence of an optic neuropathy except that the optic disc appears normal on ophthalmoscopy. Regardless of the site of damage, the treatment of TON is aimed at improving outcome by mitigating secondary rather than primary damage. Patients who experience direct (i.e., penetrating) trauma to the optic nerve have a poor visual prognosis as do patients who experience indirect (i.e., blunt force, non-penetrating) trauma, regardless of the timing or type of intervention, although a possible exception to this pessimistic prognosis is the association of an anterior TON with evidence of a hematoma in the subarachnoid or subdural space surrounding the anterior orbital portion of the optic nerve on neuroimaging. In such a setting, an urgent optic nerve sheath fenestration may be of benefit [1].

Current management paradigms for posterior TON due to blunt trauma (i.e., posterior indirect TON) include observation without intervention, use of oral or intravenous systemic corticosteroids of various doses, surgery, or a combination of surgery and steroid therapy [2]. None of these options has been studied in any large, prospective, randomized clinical trials [3, 4]. Thus, the optimum management of a patient with TON is unknown [5–7].

Observation

Observation without intervention is a valid management option for patients with TON. Many patients (>50% in some series) improve spontaneously [8–11], and even patients with well-documented no light perception may improve to useful vision without treatment [9, 12–14]. Indeed, there is no convincing evidence that any medical or surgical intervention is superior to observation. Observation without intervention is a particularly good choice when the patient is unconscious or unable to consent. Given that an RAPD can be present in the setting of 20/20 vision and that an RAPD could be caused not by optic nerve damage but by damage to the contralateral optic tract or even the brainstem, even its presence does not necessarily indicate that a patient with a normal-appearing fundus has an optic neuropathy nor does it indicate the level of visual function unless the pupil is nonreactive to direct light but reacts normally consensually, in which case one can be certain that the affected eye has no light perception. Studies investigating observation have been small and retrospective or plagued by selection biases, i.e., patients with better initial visual acuities tended to be observed and also might be more likely to recover regardless of treatment [8, 10, 11, 14, 15].

Corticosteroids

Corticosteroid therapy came into vogue for the treatment of posterior TON in the early 1980s as it was thought that it could reduce edema and secondary inflammation following the injury [16]. Since then, varying dosing regimens of steroids have been suggested, ranging from "low-dose" (1–2 mg/kg/day) oral or intravenous administration, to "high-dose" (1000 mg/day) methylprednisolone in single or divided doses, to "mega-dose" (30 mg/kg of methylprednisolone as a bolus, followed by 5.4 mg/kg/h for 24–48 h) [8, 11, 17, 18].

Almost all data regarding the potential efficacy of steroid therapy in patients with TON come not from studies of TON itself but from treatment trials in patients with acute injury to another central nervous system (CNS) white-matter tract: the spinal cord [19]. The results of the first National Acute Spinal Cord Injury Study (NASCIS I), a prospective, randomized study designed to evaluate methylprednisolone in the treatment of acute spinal cord injury, were published in 1984 by Bracken et al., who compared the neurological effects of a 1000 mg bolus of methylprednisolone daily (i.e., "high-dose" steroids) with the effects of a dosage of 100 mg/day [20]. These investigators found no difference in neurological outcomes between the two groups of patients. In addition, there was a statistically significant higher rate of wound infections in patients who received the higher dose.

The Second National Acute Spinal Cord Injury Study (NASCIS II) was a prospective randomized placebo-controlled trial to evaluate the effects of methylprednisolone in the treatment of acute spinal cord injury [18]. In this study, patients were given either a bolus of 30 mg/kg of methylprednisolone within 8 h of spinal cord injury followed by infusion of 4 mg/kg/h for 23 h or placebo. The patients treated with so-called "mega-dose" methylprednisolone were found to have slightly better neurological outcomes at 6 months.

A third study (NASCIS III) also suggested benefit with mega-dose steroids in acute spinal cord injury, but it was not placebo controlled [21]. Despite the lack of a placebo group, many viewed this study as a further reinforcement and clarification of the use of mega-dose steroids in acute spinal cord injury (and by inference in TON) [19].

After the results of the NASCIS trials were published, a number of authors reported individual or small retrospective case series that indicated that steroids were efficacious in the treatment of TON. Unfortunately, these studies generally were not scientific and tended to be plagued with multiple forms of bias. To settle the question, the International Optic Nerve Trauma Study (IONTS) was conceived.

The IONTS was designed to be the largest study to investigate prospectively the treatment of TON, involving 76 investigators in 16 countries. The original study design was that there would be two arms: "high-dose" steroids (1000 mg/day) versus surgery consisting of optic nerve decompression by unroofing the optic canal. There was no control (i.e., observation) arm because it was thought by the designers of the study that nonintervention would be unethical. Unfortunately, after 2 years, it became clear that enrollment of patients would not be sufficient to power the trial, even if it were to be continued for several more years. The study therefore was

converted to an observational study of treatment paradigms of indirect posterior TON treated within 7 days of injury. One hundred thirty-three patients were included in the study, of whom 127 (95%) had unilateral injuries. Of the 133 patients, nine received no treatment, 85 were given steroids of varying doses, and 33 underwent optic canal decompression by several techniques, with 32 of these patients also receiving various doses of steroids. The primary outcome measure was last-measured visual acuity at least 1 month after treatment, with an improvement of at least three lines of acuity considered significant. One hundred four patients (78% of the cohort) were able to be assessed at least 1 month after treatment, at which time the authors found no statistically significant difference in visual improvement among the three groups. Specifically, with respect to steroid treatment, 52% of patients who received steroids alone improved at least three lines of acuity, whereas 57% of patients who were observed showed such visual improvement [8].

A more recent surveillance study of patients with TON in the United Kingdom would appear to confirm the findings of the IONTS. Of the 121 patients with TON in this study, 20% of those who received no treatment experienced improvement in visual acuity of at least three lines, compared with 24% of those who received any form of treatment [10].

In 2000, shortly after the IONTS was published, the results of another prospective, randomized, placebo-controlled trial designed to compare treatment with "mega-dose" steroids with no treatment for patients with acute spinal cord injury were published [22]. This trial, which enrolled 106 patients in France, reported no difference in neurological outcomes in those receiving mega-dose steroids (per NASCIS II guidelines) compared with patients who received no steroids. In addition, there was an increased rate of complications in the group of patients who received mega-dose steroids. The authors therefore suggested that the treatment of acute spinal cord injury with mega-dose steroids be revisited. At around the same time, increasing controversies regarding earlier reported results of the NASCIS trials were published. Concerns were expressed that statistical artifact, retrospectively induced bias, and even withholding of data compromised the validity of the results of the trials, and it was recommended that steroids not be used to treat patients with acute spinal cord injury [23, 24].

Soon thereafter, the effects of mega-dose steroids (in this case, a loading dose of 2 g methylprednisolone vs. a placebo followed by a maintenance dose of 0.4 g methylprednisolone per hour for 48 h) were studied in the treatment of head trauma in the Corticosteroid Randomization After Significant Head Injury (CRASH) trial. This trial, the largest of its kind, enrolled 10,008 adults with head injury and a Glasgow coma scale of $\leq$14. All patients were allocated randomly to a 48-h treatment period, with treatment beginning within 8 h of injury. The initial goal was to recruit 20,000 patients, but the trial was stopped early when it became clear that the group receiving methylprednisolone had a significantly increased mortality, regardless of the severity of the injury [25, 26].

Due in part to the results of the French [22] and CRASH trials [25, 26], the Congress of Neurological Surgeons published a statement in 2013 decrying the use of mega-dose steroids in traumatic spinal cord injury, downgrading much of the

evidence supporting the use of mega-dose steroids from class I to class III because of concerns of "omission of data from publication" and "retrospective post hoc analysis" [19]. The authors also cited concerns regarding data from these studies that showed a trend toward increased complications and mortality in those subjects who received higher doses of corticosteroids.

In 2013, an exhaustive Cochrane review found only one small prospective, randomized, placebo-controlled trial investigating the effects of systemic corticosteroids in the treatment of TON [3]. This trial, performed by Entezari et al. [15] reported the visual outcome in 31 eyes of 31 patients with TON who were randomly assigned to either a treatment group (16 eyes) or a placebo group (15 eyes) within 7 days of initial injury. The treatment group received 250 mg of intravenously administered methylprednisolone every 6 h for 3 days followed by 1 mg/kg/day of oral prednisolone for 14 days. The placebo group received 50 ml of normal saline intravenously every 6 h for 3 days, followed by placebo for 14 days. An increase of at least 0.4 logMAR in final visual acuity measured at 3 months was considered visual improvement. Although both groups showed significant improvement in final visual acuity compared with initial visual acuity ($p < 0.001$ and 0.010, respectively), there were no significant differences in final acuity between the two groups. Indeed, 68.8% of the steroid-treated group had significant improvement in visual acuity compared with 53.3% of the placebo group ($p = 0.38$) [15].

Based on currently available evidence, there appears to be no role for "mega-dose" steroids in the treatment of TON, and there also is little evidence for the use of "high-dose" methylprednisolone.

Surgery

The results of surgery for TON have never been studied in a prospective, randomized, placebo-controlled fashion [3]. Certainly, visual loss from direct optic nerve trauma, in which the axons have been transected, cannot be reversed by any current surgical technique. Similarly, anterior indirect TON usually will not benefit from surgery, a possible exception being when there is compression of an otherwise intact optic nerve by a subdural or subarachnoid hematoma that can be evacuated via an optic nerve sheath fenestration [1].

Posterior indirect TON can be caused by a wide range of mechanisms. Diffuse orbital hemorrhage as well as more localized orbital or posterior optic sheath hematomas and orbital emphysema all are well-recognized although uncommon indirect mechanisms of injury to the optic nerve. Nevertheless, in such cases, particularly when there is evidence of delayed or progressive loss of vision, surgery, via nerve sheath fenestration, local evacuation of the blood or air, lateral canthotomy, or orbital decompression, via a lateral or medial approach depending on the presumed mechanism of damage, should be performed [1, 27, 28].

Unfortunately, the most common site of injury to the optic nerve in posterior indirect TON is within the optic canal. The canalicular portion of the nerve is the region most vulnerable to trauma due to its being fixed via the dura to the

periosteum of the canal. This portion of the nerve also is theoretically vulnerable to compressive and/or lacerating forces from fracture, hematoma expansion, swelling, etc. For this reason, optic canal decompression sometimes is advocated when a surgical lesion appears to be involving this portion of the nerve. If such surgery is thought to be appropriate, it probably should be performed immediately or no later than 48 h after the injury [29]; however, there are no convincing studies to date showing any clear benefit to optic canal decompression [8, 10]. The IONTS showed that 32% of patients with unilateral TON who underwent optic canal decompression had improvement of visual acuity of three lines or more compared with 57% in the untreated group and 52% in the steroid-treated group [8]. The differences among groups were not significant. In addition, as this was not a randomized study, there almost certainly were intrinsic treatment biases, as patients with more severe visual loss and patients who were otherwise neurologically intact may have been more likely to receive surgery than patients with less severe visual loss and those who had other neurologic deficits. In a non-randomized study, Fukado reported dramatic improvement in a high percentage of individuals with TON who underwent optic canal decompression [30]; however, his results are not consistent with the results of most other authors. Similarly, other non-randomized studies that have reported marked improvement in vision in patients with TON who have undergone decompression are likely less tenable given potential selection bias, timing bias, and other methodological errors [31–33].

Given the unclear benefit of optic canal decompression, it may be prudent to pursue this treatment only in instances in which the patient's vision is clearly normal immediately after the injury and then deteriorates or clearly is progressively worsening, the site of injury is clearly the optic canal based on imaging that shows a canalicular fracture or involvement of the posterior ethmoid and/or sphenoid sinuses adjacent to the damaged nerve, and, perhaps most importantly, the patient can consent to treatment even though he or she understands both the unproven benefit and the potential risks (e.g., further visual loss; damage to other neural or vascular structures) [34]. As noted above, unconscious patients should not be considered surgical candidates as they cannot give consent and there is no way to assess their vision. A possible exception may be when the affected pupil does not react at all to direct light but reacts consensually when light is shined in the opposite eye. Alternatively, however, one could argue that in such a setting, the vision is so poor that no surgical measures should be attempted. In addition, if surgery is performed in this setting and the patient awakens completely blind in the eye, the patient and family may question the appropriateness of the treatment even though consent was obtained from a relative. In such instances, preoperative visual evoked potentials (VEPs) may be of benefit in that a flat VEP in one eye with a normal VEP in the opposite eye would lend credence to the belief that the patient truly is blind in the affected eye.

There are a number of techniques by which the optic nerve can be decompressed within the optic canal, the most commonly used being the transethmoidal route [29, 35], usually either endonasally [36] or via an external ethmoidectomy or transcaruncular approach [37]. Using this approach, the inferomedial wall of the canal is removed

[38]. The advantage of this approach is that it is the least invasive of the surgical approaches. Another option is the supraorbital sub-frontal approach. In this approach, the roof of the canal is removed. This approach is most useful when the anterior clinoid process is fractured and also allows opening of the falciform dural fold [39].

Sofferman provided criteria for adequate optic canal decompression, indicating that (1) at least 50% of the circumference of the osseous canal should be removed, (2) bone along the entire length of the canal should be removed, and (3) there should be total longitudinal incision of the dural sheath including the annulus of Zinn [40, 41]. We do not necessarily endorse the third recommendation.

Conclusion

Given the current deficiencies in knowledge regarding how to best manage TON, it is appropriate to observe any and all patients with TON, regardless of the level of vision in the affected eye. In addition, it is inappropriate to argue that "steroids can't hurt," particularly "mega-dose" steroids. Although there is no evidence that "high-dose" steroids (e.g., 1000 mg/day of methylprednisolone) are harmful to visual recovery in human TON, there certainly is no evidence that they are helpful. As far as surgery is concerned, in rare cases of a clear-cut compartment syndrome within the orbit or optic nerve sheath, particularly when new and/or progressive, immediate optic nerve fenestration should be performed. In select cases of known or presumed injury to the canalicular portion of the optic nerve, particularly when there is clear-cut delayed visual loss or vision is worsening, immediate decompression of the optic nerve within the canal may be reasonable, but only after a well-documented discussion with the patient and family. No treatment should be the default with unconscious patients with the possible exception of those in whom the pupil does not react directly but reacts consensually. In such cases, VEPs may play a role as absence of any response from the affected eye with a normal response from the contralateral eye will indicate not only that the affected eye truly is blind but also that treatment is unlikely to improve vision [42–45].

The search for neuroprotective agents for various mechanisms of traumatic and ischemic CNS injury is the holy grail of the neuroscience. Unfortunately, despite decades of research and a better understanding of the pathways of apoptosis and cell death, there are no clinically proven neuroprotective or regenerative therapies for traumatic CNS lesions, including TON [46, 47]. In addition, different types of injury may respond to different types of treatment. Unfortunately, a large, prospective, randomized, placebo-controlled trial designed to determine optimum therapy for TON is unlikely to be forthcoming, as demonstrated by the technical difficulties designing and conducting such a trial as evidenced by the failure of the IONTS. Nevertheless, I am hopeful that novel management strategies will emerge as more is understood about the converging pathways of various primary, secondary, and even tertiary mechanisms of cell injury and death at play in TON. Until then, the abiding theme in the treatment of traumatic optic neuropathy should be "primum non nocere."

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Papilledema

6

Andrew R. Carey

Case

A 19-year-old gentleman was referred for papilledema. He had severe daily headaches, which started 1 month after beginning minocycline for a skin rash. Headaches were pulsing-throbbing and associated with nausea and vomiting. He denied pulse-synchronous tinnitus, transient visual obscurations, and diplopia. His body mass index (BMI) was 36.8. Visual acuities were 20/20 in both eyes (OU), color vision normal, automated visual fields showed enlarged blind spots (Fig. 6.1), and his optic discs showed Frisen grade 4 papilledema OU (Fig. 6.2).

What is the most important next step?

A. Color fundus photography
B. Lumbar puncture with opening pressure and cerebrospinal fluid (CSF) analysis
C. Neuroimaging with angiography protocol
D. Optical coherence tomography (OCT) of the optic disc
E. Medication for headache

Management

While the history for this patient is classic for medication-induced intracranial hypertension, the patient is also obese, suggesting he may have underlying idiopathic intracranial hypertension, and other secondary causes need to be excluded. The correct answer is *(C) neuroimaging with angiography protocol*, which is the recommended first step in the evaluation of papilledema, to evaluate for space-occupying lesions,

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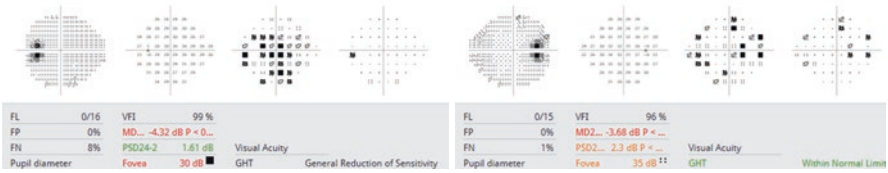

Fig. 6.1 Automated visual fields of right eye (on right) and left eye (on left) showing bilateral enlarged blind spots and generalized depression in the left eye. (© AR Carey 2020. All Rights Reserved)

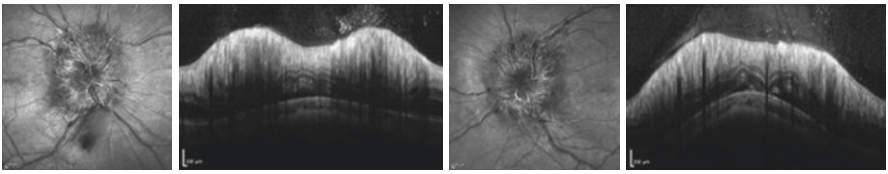

Fig. 6.2 Heidelberg OCT of the optic nerves with infrared image of the right eye (on the left) and left eye (on the right) showing bilateral severe optic disc edema and severe diffuse peripapillary retinal nerve fiber layer thickening. (© AR Carey 2020. All Rights Reserved)

venous sinus thrombosis, and signs of increased intracranial pressure (ICP). Neuroimaging should be performed expeditiously; in patients with chronic symptoms, mild disc edema, and typical demographics for idiopathic intracranial hypertension this can often be performed on an outpatient basis within 1–2 weeks as compared with a referral to the emergency room. The patient underwent magnetic resonance imaging (MRI) brain with and without contrast and MR venogram, which demonstrated a transverse dural sinus thrombosis. Hypercoagulability workup was negative, and the thrombosis was felt to be secondary to medication-induced intracranial hypertension.

Pseudopapilledema

It is important to distinguish pseudopapilledema from true papilledema to determine which patients require extensive evaluations. One series of 34 children referred for possible optic disc edema found that pseudopapilledema was present in 94% and true papilledema in only 6% [1]. Pseudopapilledema can be due to tilted optic discs, gliosis, myelinated nerve fiber layers, and optic disc drusen. Diagnosis of disc drusen is discussed in Chap. 17. Clinical clues suggestive of pseudopapilledema include the presence of spontaneous venous pulsation; absence of disc hemorrhage, vessel obscuration, and Paton lines; a small optic disc; normal peripapillary retinal nerve fiber layer thickness, and particularly nasal sector thinning on OCT, suggestive of tilted disc with temporal shifted peaks; and absence of clinical symptoms of elevated ICP; however, even in this setting, some patients may have early papilledema difficult to distinguish from a normal variant and may warrant close observation or neuroimaging to rule out intracranial mass and signs of elevated ICP (Fig. 6.3). OCT and/or color disc photographs can be valuable for monitoring change, as well as for grading papilledema (Fig. 6.4).

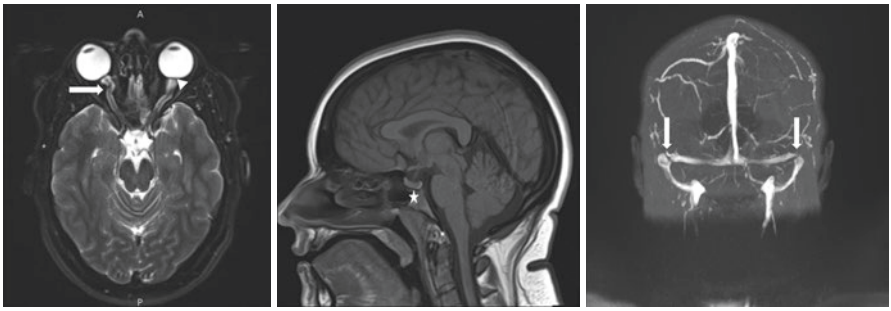

Fig. 6.3 MRI findings of elevated intracranial pressure. (Left) T2 fat-saturated axial image showing dilated and tortuous optic nerve sheaths (arrow) and posterior globe flattening (arrowhead). (Middle) T1 sagittal image showing concave pituitary gland as a forme fruste manifestation of empty sella (star). (Right) Coronal MR venogram showing bilateral transverse venous sinus stenosis (arrows). (© AR Carey 2020. All Rights Reserved)

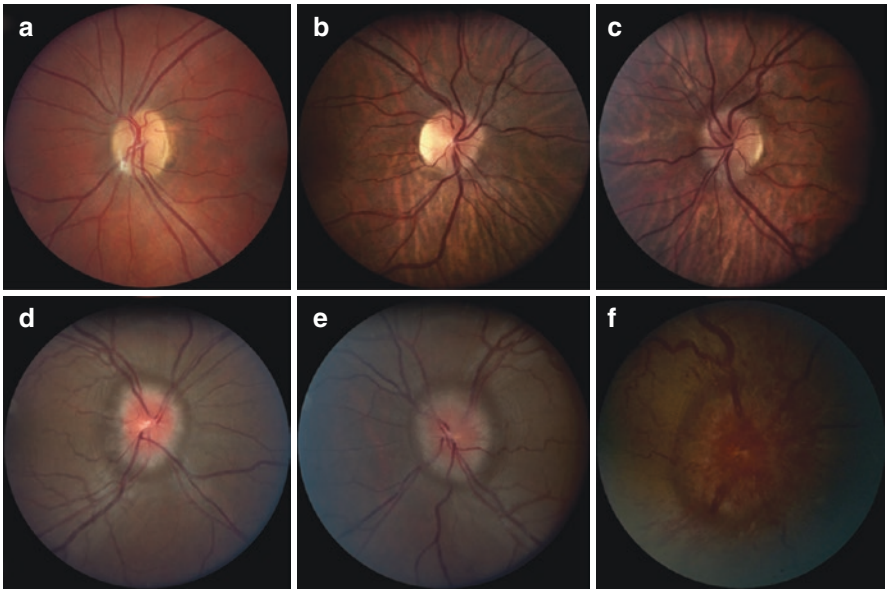

Fig. 6.4 Color fundus photos of optic discs with various Frisen grade levels of papilledema. (**a**) Grade 0: nasal mild blurring. (**b**) Grade 1: 270 degrees of margin blurring with temporal sparing. (**c**) Grade 2: 360 degrees of margin blurring but no vessel obscuration. (**d**) Grade 3: 360 degree margin blurring and obscuration of small vessels and large vessels in one quadrant crossing the disc margin. (**e**) Grade 4: 360 degree edema with obscuration of large vessels in multiple quadrants or vessels on the disc. (**f**) Grade 5: obscuration of all vessels overlying the optic disc. (© AR Carey 2020. All Rights Reserved)

In addition to physiologic mimickers, an important non-physiologic mimicker of papilledema is bilateral anterior optic neuritis. Optic neuritis is commonly bilateral in children (up to 72% of pediatric cases), and children also are more likely to present with optic disc edema (~50% of children vs. 33% of adults) [2]. While pain on eye movement is found in 93% of adults with optic neuritis, it may occur in only 33% of children [2]. Further complicating the picture is that 28% of children with optic neuritis may have an opening pressure >28 cm H_2O [3]. Therefore, optic neuritis should be a differential diagnostic consideration in children presenting with bilateral optic nerve swelling. Important clinical distinguishing features of optic neuritis are decreased visual acuity and color vision, which are much later findings in papilledema [2]. Management of optic neuritis is discussed in Chap. 4.

Ventricular Etiologies

A number of congenital issues can cause elevated ICP and papilledema, most commonly with hydrocephalus (HCP) [4]. Congenital HCP most typically is due to a malformation of the cerebral aqueduct and is treated by ventriculoperitoneal shunting. Chiari 1 malformation can also present with HCP and papilledema, and is often treated by suboccipital decompression. Both HCP and Chiari 1 malformation may have delayed presentation even into adulthood with unclear factors for late onset. A third condition that can present with childhood HCP is craniosynostosis, which is often treated by cranioplasty [5]. Papilledema in pediatric HCP has a variable incidence that may depend on age (in patients under age 1 year, as low as 25%) [5] as well as etiology [6]. If papilledema persists after cranioplasty (as it does in 1–5% of cases [5]), then CSF shunting is indicated.

Acquired pediatric HCP is most commonly due to intracranial tumor (59%), congenital anomaly (19%), intracranial hemorrhage (13%), or infection (9%) [7]. Papilledema may resolve after treatment of brain tumor; however, it persists in up to 66% of patients, presumably from postoperative debris clogging CSF outflow, and may require shunting [8].

Tumors in adults can lead to elevated intracranial pressure via multiple mechanisms: space occupation from tumor and secondary cerebral edema, HCP from compression of the ventricular system or cerebral aqueduct, compression of the venous outflow system, and clogging of the arachnoid villi impairing CSF resorption. HCP in these situations may be treated by shunting or third ventriculostomy, particularly if the tumor is cancerous, thus raising concern about seeding the abdomen.

Vascular Etiologies

Dural venous hypertension impairs CSF reabsorption leading to elevated ICP and can be caused by thrombosis, stenosis, arteriovenous fistulas, external compression or invasion of the venous system, or rarely from extracranial venous sinus thrombosis/stenosis (jugular vein/superior vena cava).

Children have higher rates of dural venous sinus thrombosis (DVST) compared with adults, likely owing to increased susceptibility to otitis media, complicated by propagation of inflammation through the temporal bone at the petrous apex and into the adjacent sigmoid sinus [9]. In one study from Turkey, DVST was present in 30% of children with intracranial hypertension [10]. Occult DVST mimicking IIH can occur in 14% of pediatric cases [11]. Children may present acutely with headache, blurred vision, esotropia, or double vision and can have profound papilledema. Notably, 40% may occur in neonatal period and present with fever, seizure, and depressed level of consciousness [9]. Hyperacute presentation can include seizures, loss of consciousness, cerebral hemorrhages, and brain herniation, and these patients have a 10% risk of permanent severe disability and 33% risk of death [12].

Additional risk factors in adults include puerperium, hematologic malignancies, anemia, and skull fracture [12, 13]. Radiologic clues for DVST can be seen on MRI and CT scans, but MR and CT venograms have higher (and equal) sensitivity. Conventional angiography is not needed for diagnosis [12].

Acute treatment for DVST involves anticoagulation [12]. Anticoagulation should be continued for 3–12 months [12]. Concurrent otitis media requires antibiotics. While steroids have not been shown to improve outcomes in the absence of an inflammatory cause, they are indicated in neuro-Behçet disease, which can be complicated by DVST in 89% of cases [12, 14]. Lumbar drains and CSF shunting have not been shown to improve outcomes in patients with severe presentation from DVST; however, patients with advanced vision loss from papilledema may need lumbar drain or shunting, and patients with impending brain herniation require calvarial decompression [12]. Endovascular treatments with intra-arterial thrombolysis and venous thrombectomy are experimental and may be considered for patients with clinical deterioration despite intravenous anticoagulation [15]. Similar to IIH, DVST patients with grade 3+ papilledema have increased risk of permanent vision field loss [16] and, therefore, also may require treatment with ICP-lowering medications.

Dural venous sinus stenosis occurs bilaterally in 94% of patients with IIH versus only 3% of the normal population. It most commonly affects the transverse sinus and transverse-sigmoid junction [17]. Transverse sinus stenosis has also been identified in patients with Chiari 1 malformation and correlates with worse pituitary flattening, suggesting an association with ICP [18]. However, bilateral transverse sinus stenosis may be seen in 34–100% of patients with chronic headaches, and in one study only 14% of these headache patients had opening pressure >25 cm H_2O, and 43% had borderline opening pressure [19]. In cases of high ICP, it remains unclear whether venous sinus stenosis is a preexisting condition, the inciting factor, or secondary to extrinsic compression from arachnoid granulations due to elevated ICP. In some patients, more than one factor may exist. Regardless of the etiology of the stenosis, venous manometry studies often confirm significant pressure gradient across the stenosis, with resolution post-stenting. Additionally, simultaneous ICP monitoring during stenting procedures [20, 21] demonstrates a near-instantaneous reduction in ICP following stenting [22]. Meta-analysis of patients undergoing stenting shows 50% achieving resolution of papilledema with an additional 20%

having improved papilledema [22]. Forty-nine percent have normalization of peripapillary RNFL measurements on OCT, 80% have visual field improvement, and 73% have improvement in headache [22]. Patients undergoing stenting require treatment with dual antiplatelet therapy starting ideally 1 week before the procedure and continuing for 3–6 months post-stenting, followed by aspirin monotherapy for an additional 6 months or more to prevent stent thrombosis [22]. Complications can include a new type of headache occurring in 14% of patients, stent thrombosis (which can be fatal) in 1%, in-stent stenosis in 2%, and stent-adjacent stenosis (requiring additional treatment) in 9–32%. There are rare reports of stenting in pediatric IIH. Successful treatment of fulminant papilledema from IIH has been described with stenting, with six of seven cases improving [23, 24]. There are additional reports of successful stenting for extrinsic stenosis from meningiomas [25]. Stenting has been reported for both acute and chronic DVST, with 20% procedure complication rate and 40% failure rate among 5 acute cases and 12% complication rate among the 17 chronic cases, one of which was fatal [26, 27].

Dural arteriovenous fistulae (DAVF) make up to ~15% of intracranial arteriovenous malformations, with an incidence of ~0.15–0.3 per 100,000 per year, and are a rare cause of elevated ICP and papilledema [28]. Acquired fistulae are more common among men and related to head trauma. Elevated ICP can be multifactorial, as arterial pressures are transmitted into the venous system, and dural sinus stenosis and/or thrombosis may occur [28]. Noninvasive vascular imaging with CT or MR may demonstrate hemorrhages, cerebral edema, and venous congestion, stenosis, or occlusion. Conventional angiography remains the gold standard and gives crucial information regarding arterial feeders, flow, and venous drainage [28]. While DAVF without cortical vein drainage (Borden type 1) have a benign course in 98.5% (excluding those with cavernous sinus drainage), those with cortical drainage (Borden type 2–3) can have a more aggressive course with intracranial hemorrhage and clinical presentations varying based on location [28]. Treatment may involve stenting, stereotactic radiosurgery, and embolization [29].

Medication Etiologies

Medications can cause secondary intracranial hypertension, although the exact mechanism is unclear. Some frequent offenders are acne medications: tetracycline (and its derivatives doxycycline and minocycline) and vitamin A derivatives (retinoic acid) [30]. Additionally, cyclosporine, an immunosuppressive medication commonly used for bone marrow and organ transplants, and lithium, a mood stabilizer, have been implicated in papilledema [31]. Some patients may have rapid recovery after discontinuation of medication, but others have a chronic course. Those patients with severe symptoms, visual field loss, or high-grade papilledema warrant treatment with ICP lowering medications. One challenge is determining causality. In patients without other risk factors and an abrupt onset of symptoms after beginning medication, a strong case for causality can be made. However, some patients may have underlying mild IIH, with medication as an exacerbating factor,

and other patients may have frank IIH and be incidentally placed on a high risk medication.

CSF Etiologies

As previously mentioned, the arachnoid granulations (and, thus, the CSF resorption they perform) may be impaired by clogging due to neoplastic or inflammatory debris (e.g., cells, protein, and blood). CSF analysis is the gold standard for ruling out these processes before arriving at a diagnosis of IIH. While a bacterial meningitis typically presents acutely, lyme, syphilis, and cryptococcus can cause a more indolent process. Treatment of these conditions is discussed in Chap. 8. Chronic inflammatory meningitides require treatment of the underlying disease and may require additional management for elevated ICP.

Adult IIH has a female predilection with ~95% occurring in women. Ninety percent of adult IIH patients are overweight or obese, and the risk of vision loss is proportional to BMI. Peak age of presentation is 33 years [32, 33]. The incidence of IIH in adults is 0.9 per 100,000 among the general population and 19 per 100,000 in obese women [11]. The presenting symptom is headache in 65–85%, followed by incidental papilledema in 30–48%. Papilledema is typically bilateral, and unilateral optic disc edema should raise suspicion for an alternative diagnosis. However, papilledema may be markedly asymmetric, with a difference in Frisen grading by 2 or more in 4% of patients [34]. The modified Dandy criteria for diagnosis of IIH were established in 1985 and include: signs and symptoms of elevated ICP, no localizing neurologic deficits (except sixth nerve palsies), elevated CSF pressure (>25 cm H_2O in adults) with normal CSF studies, normal neuroimaging except for signs of elevated ICP, and normal mental status. Additionally, in 2002 Friedman and Jacobson called for ruling out vascular lesions and medications discussed above, in addition to evaluation for Addison disease and medical conditions causing hypercarbia as secondary causes [35].

Weight loss alone has been demonstrated to be an effective treatment for IIH with a goal of 6–10% loss of starting body weight over 6–12 months [33]. Patients have a twofold rate of achieving weight loss goals when enrolled in a lifestyle modification program with at least 14 sessions over 6 months [33]. FDA-approved weight loss medications have not been studied specifically for IIH. A systematic review in 2016 identified 65 cases from retrospective studies treated with bariatric surgery (67% roux-en-y bypass) and reported 100% resolution of papilledema and 90% improvement in headache [36]. A randomized controlled trial of bariatric surgery versus community weight loss program for IIH is currently underway, with plans for enrolling 64 subjects with 5-year follow-up and a primary outcome of opening pressure at 1 year [37].

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was a double-masked placebo-controlled randomized study comparing acetazolamide + intensive weight loss interventions to intensive weight loss interventions alone in adult patients with IIH and mild to moderate visual field loss (mean deviation −2 to −7

decibels). One hundred sixty-five subjects were enrolled (98% women, mean age 29 years, mean BMI 39.9, 100% overweight, 88% obese; 65% white, 25% black, 10% other race) [38]. At baseline, 84% had headache, 68% had transient visual obscurations (TVOs), and 52% had pulse synchronous tinnitus, which was bilateral in two-thirds of cases [38]. Acetazolamide was titrated as tolerated to a maximum dose of 4 g per day with 44% tolerating this dosage. The mean tolerated dose was 2.5 g per day, with 8% of patients discontinuing medication due to intolerance and 2% due to pregnancy (per protocol) [39, 40]. No patients with Frisen grade 2 papilledema or less lost vision in either group over 6 months. Risk factors for vision loss included: grade 3 papilledema or higher (OR 9), more than 30 TVOs per month (OR 11), male gender (OR 26), and reduced visual acuity at baseline [41]. The acetazolamide group had greater improvement in mean deviation on visual field testing at 6 months, although the difference was less than 1 dB, and there was no statistical difference in percent of visual fields that were improved, stable, or worse at 6 months between the two groups [39, 42]. The acetazolamide group had more weight loss and improved quality of life [43], although there was no difference in headache improvement between the two groups, with one-third of patients still having significant impairment from headache at 6 month follow-up [44]. Therefore, patients with significant headache may need additional treatment separate from ICP lowering therapy. One percent of patients in the acetazolamide group had renal impairment requiring hospitalization, 5% had mild hypokalemia, and 1% had a significant drop in white blood count and exited the study (as acetazolamide in rare cases can cause aplastic anemia occurring in one in 18,000 patient-years) [40, 45].

Other medications have been studied for IIH but have less rigorous evidence supporting their use. Topiramate is an antiepileptic with carbonic anhydrase activity similar to acetazolamide and is FDA-approved for migraine and for weight loss in combination with phentermine. An open-label randomized prospective study comparing topiramate 100–150 mg daily with acetazolamide 1000–1500 mg daily found similar improvements in the primary outcome of visual field, as well as secondary outcomes including headaches, TVOs, diplopia, and papilledema, while the topiramate group had more weight loss [46]. In patients with low-grade papilledema with good visual fields whose primary symptom is headache, topiramate may be an ideal first-line option for medical therapy. Furosemide and other loop diuretics are used as second- or third-line medical therapy but require laboratory monitoring for renal impairment and hypokalemia (which can lead to cardiac arrhythmia) [47]. Subcutaneous octreotide was first described as a potential treatment in three cases in 1993, which reported rapid improvement in headaches as well as improved papilledema, visual fields, and CSF pressure [48]. This report was followed by a prospective open-label study in 26 patients, which showed rapid improvement in 92% of patients, mean reduction in CSF pressure by 21 cm H_2O, and no recurrence of papilledema up to 3 years after discontinuing treatment [49]. A third report described five patients with IIH refractory to medical therapy who were successfully treated with octreotide [50]. Further studies are needed to determine the risk-benefit profile of octreotide therapy. Topiramate is pregnancy risk category X and can reduce effectiveness of oral contraceptives; therefore, women of childbearing age should

be counseled regarding importance of effective contraception while taking topiramate. Furosemide and acetazolamide are pregnancy risk category C, although reports and our clinical experience suggest acetazolamide is safe in pregnancy [7, 51, 52]. Octreotide is pregnancy risk category B, making it of greater interest for further research.

For patients unable to tolerate medical therapies, with progressive vision loss, or with uncontrolled symptoms despite maximal medical therapy, surgical options exist. Optic nerve sheath fenestration may be an ideal option for a patient with minimal headache and asymmetric papilledema/vision loss. However, patients with bilateral vision loss would likely require bilateral surgeries, and non-vision-related symptoms are unlikely to be relieved by nerve sheath fenestration alone, with headache improvement occurring in only 44% [53]. Lumbar shunting has been performed but has higher failure rates than ventricular shunting, which on average still requires two revisions over 7 years. There are no randomized controlled trials comparing surgical options. A meta-analysis of case series comparing outcomes for optic nerve sheath fenestration, shunting, and dural venous sinus stenting in 2015 suggested stenting had superior outcomes for vision and papilledema, with fewer minor complications and similar outcomes for headache compared with shunting, with reoperation and major complication rates comparable to optic nerve sheath fenestration [53]. For patients with fulminant papilledema, lumbar drain has been described as a successful temporizing measure while awaiting the onset of medical therapy or surgical intervention [54].

Patients undergoing CSF shunting have a low risk of over-drainage resulting in iatrogenic intracranial hypotension, which can cause a glaucomatous-like optic neuropathy with reversal of the translaminar gradient, optic disc cupping, and peripheral field loss, in addition to postural low-pressure headache and sixth nerve palsies [55]. Patients typically have severe headaches worse with standing and cognitive impairment, but young children and patients with baseline cognitive impairment as seen in traumatic brain injury may not report these symptoms [55]. Characteristic findings include sunken globes and expansion of sphenoid and paranasal sinuses on imaging [55].

The most common cause of papilledema in children is likely pediatric IIH with one study reporting IIH in 42% of cases, compared with 18% from craniosynostosis, 16% from tumors, 5%, from primary hydrocephalus, and 3% from transverse sinus thrombosis [56]. Pediatric IIH occurs in 0.6 per 100,000 children [11] and can be divided into two cohorts: prepubertal and pubertal [11]. Obesity and gender do *not* appear to be significant factors in prepubertal IIH, while cases among adolescents follow the typical demographics seen in adults [11]. Additionally, prepubertal children are less likely to have headache (which may be absent in 14%) and may totally asymptomatic in 5–31%; therefore, not surprisingly many patients are identified incidentally on eye exam or present with blurred vision or diplopia [11]. Opening pressure cutoff in children has been adjusted based on a number of studies: in obese children or those requiring sedation, the upper limit of normal is 28 cm H_2O. While there are no prospective randomized controlled trials in children, acetazolamide is used first line beginning with a total

daily dose of 20 mg/kg divided in two to three daily doses and can be titrated as needed to a maximum dose of 400 mg/kg/day (not to exceed 4 grams per day), although this dose is rarely needed [11]. In the prepubertal nonobese patients, weight loss may not have a role, while in obese patients, weight loss goals are similar to adults [11]. However, in children, family lifestyle interventions are often required for successful weight loss, and it is important not to trigger an eating disorder. Furosemide (0.3–0.6 mg/kg/day) and topiramate (1.5–3 mg/kg/day) have been less studied in children than in adults for IIH but may be useful medical alternatives to acetazolamide [11]. Surgical interventions for children include shunting and optic nerve sheath fenestration [11]; however, children may have higher late shunt failure rates than adults (as they grow). Due to their reduced rate of symptoms, children may present with more advanced vision loss and be less likely to notice a treatment failure, both of which may contribute to worse visual outcomes [11]. There is an 18% recurrence rate among children, usually within the first year of remission [57].

Case Resolution

The patient was started on subcutaneous enoxaparin injections and transitioned to oral apixiban for the acute DVST, which was continued for 6 months, in addition to acetazolamide. His papilledema resolved over 3 months. Acetazolamide was tapered, and his headache recurred, although papilledema did not recur. Repeat MR venogram demonstrated resolution of thrombosis, but lumbar puncture showed persistently elevated opening pressure at 30 cm H_2O. Acetazolamide was restarted and headaches resolved.

Conclusion

There are a number of causes of papilledema. The first step in management is to identify the underlying cause. Treatments can involve lifestyle modification, cessation of offending factors, medications, and/or surgery, depending on etiology and severity of vision loss. Depending on the clinical situation, more than one treatment modality may be needed.

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Leukemic Infiltration of the Optic Nerve

7

Emma C. McDonnell and Amanda D. Henderson

Case

A 62-year-old man with a history of chronic myelomonocytic leukemia was admitted with fever, altered mental status, and nausea. Lumbar puncture showed an opening pressure of 55 cm H_2O with >3000 polymorphonuclear leukocytes and 70 monocytes. Flow cytometry demonstrated 63% myeloid blasts, confirming acute myeloid leukemia (AML) conversion with central nervous system (CNS) involvement. He was treated with intrathecal (IT) cytarabine. Two days following his first IT treatment, he complained of vision loss in the right eye, progressing over a 24-hour period. Ophthalmology was consulted for evaluation.

Visual acuity was no light perception (NLP) in the right eye and 20/70 in the left. He had minimal pupil reactivity and a right relative afferent pupillary defect. Confrontation visual fields were full on the left, and he correctly identified nine of ten color plates with the left eye. Extraocular movements were full. Hertel exophthalmometry measured 21.5 mm on both sides. Fundus examination was remarkable for optic discs with the appearance of Frisen grade 2 swelling in both eyes. At that time, retrolaminar optic nerve infiltration by leukemic cells was suspected.

What is the most appropriate treatment option?

(a) Systemic chemotherapy with an agent that crosses the blood-brain barrier
(b) Urgent radiation within 1 week

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(c) Emergent, same day radiation
(d) Continue current course of IT chemotherapy
(e) Continue IT chemotherapy, but switch to an agent with less CNS toxicity

Management

While this case is suspicious for papilledema secondary to increased intracranial pressure (ICP) from CNS leukemic involvement, in the setting of a high opening pressure of 55 cm H_2O, the degree of papilledema described would not account for this patient's level of visual compromise. Therefore, this case is also concerning for direct infiltration of the optic nerves by leukemic cells, which would be expected to present with rapid, severe vision loss. For treatment of leukemic infiltration of the optic nerve, the first recommended treatment is *(c) emergent, same day radiation*, with continued treatment of the systemic and CNS disease thereafter.

Leukemia affects the globe and orbit via three main mechanisms: (1) direct infiltration of ocular structures including the retina, nerve, and choroid; (2) consequences of anemia or thrombocytopenia, largely manifested as retinal hemorrhages; and (3) changes secondary to hyperviscosity syndromes [1–3]. Direct infiltration of any ocular structure is a poor prognostic indicator and often leads to severe vision loss [4].

Clinical studies have reported ocular involvement in 35–64% of patients with leukemia, [1, 5–7], whereas histopathologic studies have shown even more frequent ophthalmic involvement. In a large histopathologic study, Kincaid and Green evaluated all autopsy eyes from patients who died of leukemia at the Johns Hopkins Hospital between 1923 and 1980 and found that 82% of patients with acute leukemia and 75% of patients with chronic leukemia had ocular involvement. Optic nerve involvement was less common, present in 18% of those with acute leukemia and 16% with chronic leukemia [8]. Despite the frequency of ophthalmic involvement, clinically evident optic nerve infiltration is rare, occurring only in 0.3–1.1% of patients with leukemia [5, 7].

Leukemic infiltration of the optic nerve has been reported as the presenting sign of leukemia, the initial sign of disease relapse in patients who have achieved systemic remission, and in patients with known disease and CNS involvement [9–13]. Infiltration of the optic nerve by leukemic cells can affect the optic disc as well as the retrolaminar portion of the optic nerve. Infiltration of the optic nerve head may mimic papilledema clinically (Fig. 7.1), and infiltration just posterior to the lamina may cause true disc edema. Magnetic resonance imaging (MRI) may demonstrate thickening of the optic nerve posterior to the globe, as well as optic nerve or perineural sheath enhancement (Fig. 7.2). Nerve edema in a patient with leukemia has several potential etiologies and does not necessarily indicate leukemic infiltration. In addition to optic nerve infiltration, causes of optic nerve swelling in the setting of leukemia include papilledema from leukemic infiltrates in the CNS causing increased ICP, papilledema from increased ICP secondary to chemotherapeutic treatment (specifically with all-trans retinoic acid (ATRA) commonly used for acute

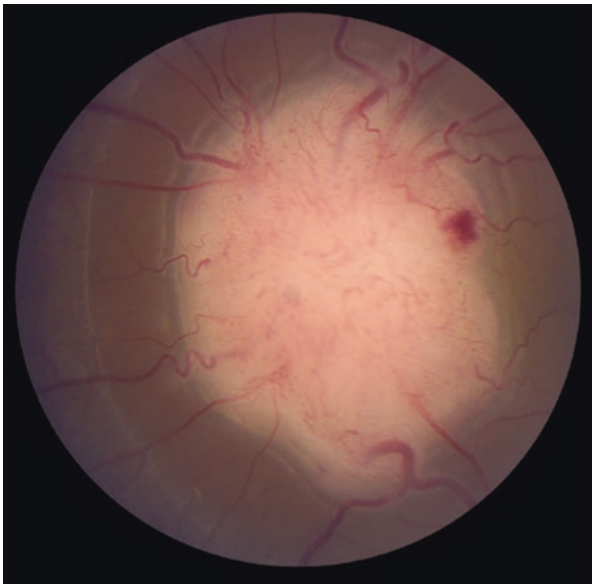

Fig. 7.1 Optic nerve photograph demonstrates leukemic infiltration of the optic nerve causing diffuse elevation of the optic nerve head. (© NR Miller 2021. All Rights Reserved)

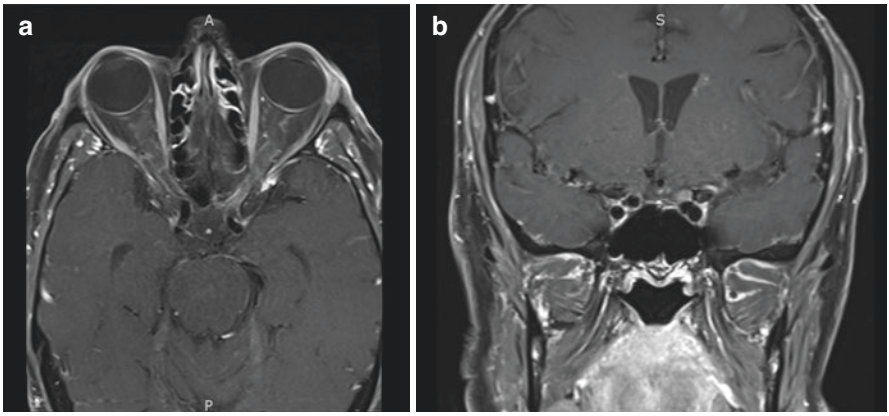

Fig. 7.2 T1-weighted post-contrast (**a**) axial and (**b**) coronal MRI images demonstrate bilateral optic nerve sheath enhancement and left optic nerve enhancement, consistent with leukemic infiltration. (© AD Henderson 2021. All Rights Reserved)

promyelocytic leukemia), discrete tumors of the orbit, ischemic optic neuropathy, and perivascular retinal infiltrates leading to venous engorgement and swelling of the optic nerve head [8, 14, 15]. Correct determination of the cause of the optic nerve swelling is important since the urgency and type of treatment vary depending on the etiology. Specifically, leukemic infiltration of the nerve requires swift intervention to prevent permanent blindness.

Thorough history and ophthalmologic examination, MRI, and lumbar puncture with CSF evaluation may assist in determination of the etiology of optic nerve

swelling in patients with leukemia. Perivascular retinal infiltrates may be seen on ophthalmoscopic evaluation and can lead to optic nerve swelling due to venous stasis [15]. Additionally, these retinal infiltrates also can occur in conjunction with direct infiltration of the optic nerve head [8]. Notably, severe, acute vision loss is unlikely to occur as a result of mild papilledema. Among patients with papilledema associated with pseudotumor cerebri, it has been shown that the amount of vision loss correlates with the severity of disc edema [16], and low grades of papilledema do not typically cause vision loss. Specifically, among 151 patients with pseudotumor cerebri enrolled in the Idiopathic Intracranial Hypertension Treatment Trial, none of those with Frisen grade 2 or lower papilledema had significant visual decline [17]. Therefore, in a case with mild optic disc edema, such as the one presented at the beginning of this chapter, it should be recognized that increased ICP and resultant papilledema alone do not account for severe visual compromise. Rather, another underlying cause, like direct optic nerve infiltration, should be strongly suspected.

In a patient with leukemia, vision loss can be caused not only by optic neuropathy, but also, and much more commonly, by retinopathy [5]. Vision loss secondary to leukemic retinopathy may be self-limited and resolve with time, as in the setting of macular hemorrhages caused by thrombocytopenia. Vision loss due to direct invasion of the optic nerve by leukemic cells, however, is an ophthalmologic emergency that may result in severe and permanent vision loss within a short period of time, due to loss of blood flow to the nerve and resultant tissue necrosis [18–20].

Although incidence and prevalence of leukemic infiltration of the central nervous system have increased as treatment for leukemia has improved and long-term patient survival has become more common, direct infiltration of the optic nerve remains rare [8]. This may, at least in part, be due to efforts to eliminate CNS leukemic involvement early in the disease course. Patients with ALL receive routine CNS prophylaxis with IT chemotherapy, even in the absence of apparent CNS involvement, with the aim of eliminating leukemic cells that may be harbored in the CNS, thus decreasing the risk for CNS recurrence [21]. While CNS radiation was commonly performed prophylactically in the past, radiation no longer is typically recommended for CNS prophylaxis in patients with ALL, due to the risk for side effects such as brain necrosis. However, radiation may be appropriate for those with known CNS leukemic involvement, particularly when IT chemotherapy already has failed to control the disease [22]. CNS involvement in AML is thought to be less common than in ALL; therefore, routine IT chemotherapy is not performed in patients with AML. However, standard use of systemic cytarabine, which crosses the blood-brain barrier, in the chemotherapeutic regimen for AML has been thought to eliminate leukemic cells in the CNS, although this assertion has recently been brought into question [23, 24].

Like the CNS in general, the eye and optic nerve are immunoprivileged and can sequester leukemic cells. Even IT chemotherapy, with chemotherapeutic delivery designed to bypass the blood-brain barrier, may be inadequate for elimination of these cells. Ellis and Little reported a case of optic nerve infiltration in the setting of CNS leukemia, in which postmortem evaluation demonstrated complete resolution

of leukemic involvement in the brain and retrobulbar optic nerve following IT chemotherapy; however, there was persistent involvement of the optic nerve anterior to the termination of the subarachnoid space just behind the globe, suggesting that the IT chemotherapy did not reach the most anterior portion of the optic nerve [18]. Additionally, anatomic study of the optic nerve has shown that the subarachnoid space is heterogeneous, filled with septae and trabeculae, rather than an empty chamber filled by fluid [25]. These findings may explain the barriers preventing IT chemotherapy from reaching the entirety of the optic nerve, even under normal circumstances. This issue may be perpetuated in a pathologic state. For instance, increased ICP due to leptomeningeal leukemic invasion, as well as expansion of the retrolaminar optic nerve in the setting of leukemic infiltration, would be expected to affect the dynamics of CSF flow, thus further inhibiting the dissemination of IT chemotherapeutic agents throughout the subarachnoid space surrounding the optic nerve. The effect of radiation therapy, in contrast, would not be affected by these dynamics and, thus, could be a better acute treatment option in these cases.

One concern regarding the use of radiation therapy is that, due to shielding of ocular structures to reduce the risk of radiation toxicity, a therapeutic radiation dose may not be delivered to all parts of the optic nerves [21, 26]. Changes to patient positioning during radiation delivery also may decrease the dose of radiation to orbital structures [27]. Recent recommendations for use of radiation to treat known CNS leukemic involvement have emphasized the need to include spaces known to harbor leukemic cells, including the posterior two-thirds of the globe, within the radiation field [22]. Clearly, this recommendation for radiation planning is particularly important in the setting of established optic nerve involvement.

There are no randomized controlled trials evaluating the treatment of leukemic infiltration of the optic nerve. However, retrospective studies and case series have shown that a combined approach of radiation and IT chemotherapy may result in the best overall outcomes, in terms of minimizing permanent vision loss and attaining remission of the underlying leukemia [3, 9–13, 18, 19, 28–31]. Cases of leukemic infiltration of the optic nerve have been reported to respond well to radiation targeted to the optic nerve, even after failure of the optic nerve involvement to respond to IT chemotherapy [19, 28, 29]. The optic nerve itself is less sensitive to radiation than leukemic cells, which are highly radiosensitive [18]. The radiation targets the leukemic cells infiltrating the nerve and destroys them, allowing for restoration of blood flow. This return of blood flow helps to salvage neural cells that are not yet necrotic and prevents additional neural cell death. Further penetration of the tissue with chemotherapy agents likely occurs once blood flow is restored [19, 20, 29]. Thus, the radiation and IT therapies may work synergistically, and both may be necessary to attain control not only of the optic nerve disease but also of the CNS and systemic disease. The additional use of steroids may decrease swelling that can occur with both chemotherapy and radiation, thus reducing tissue damage [32].

As we have described, IT chemotherapy alone may not be sufficient to treat infiltration, especially of the anterior portion of the optic nerve. Additionally, the time course of response to IT chemotherapy may not be adequate to preserve vision in cases of optic nerve infiltration presenting with severe vision loss. Notably,

concomitant IT chemotherapy and radiation increases the risk of toxicity, and at least 2 weeks of separation between the last IT chemotherapeutic infusion and the delivery of CNS radiation is preferred; however, an interval as short as 2 days is recommended for urgent cases needing radiation [22]. From the standpoint of preserving vision, ophthalmologists and neuro-ophthalmologists must advocate for the urgency of radiation treatment in patients presenting with vision loss secondary to leukemic infiltration of the optic nerve, to assist our oncology and radiation oncology colleagues with the treatment planning for these patients.

Case Resolution

Returning to the case, emergent radiation to the optic nerves, as well as neuroimaging with MRI of the brain and orbits with and without contrast and MRV, were recommended by the consulting neuro-ophthalmologist. In this instance, it was emphasized that radiation was of a higher priority than obtaining the MRI. While this may not always be the case, in this patient with known CNS involvement, proven by the CSF cytology, and severe visual compromise out of proportion to the exam, optic nerve infiltration was highly likely, and treatment delay to obtain neuroimaging confirmation was not deemed appropriate. However, due to patient and other treating physician preference, radiation was deferred in this case. The patient continued his IT cytarabine regimen. Five days after his initial evaluation, vision remained NLP in his right eye; however, he improved to 20/20 in the left. He remained on systemic chemotherapy with weekly IT chemotherapy, as per his oncology providers. Unfortunately, 3 months later, he experienced loss of vision to NLP in the left eye. MRI demonstrated an increase in leptomeningeal disease burden. On exam, his acuity was NLP in both eyes, pupils were nonreactive bilaterally, and he had new ptosis and significant decrease in extraocular motility. His fundus exam was notable for severe optic nerve pallor on the right and disc edema with moderate pallor on the left. At this point, he received emergent, same-day whole brain and optic nerve radiation; however, he had no visual recovery and remained NLP. Due to worsening overall condition, he was discharged to home hospice and passed away shortly thereafter.

Conclusion

Leukemic infiltration of the optic nerves is one of the few true emergencies in both neuro-ophthalmology and radiation oncology. Not only is it vision threatening, it is also a poor prognostic indicator for survival. While in any individual case it is difficult to determine whether emergent radiation will change clinical outcome, there are multiple reports of patients treated with radiation who have achieved visual improvement [28, 30, 31, 33, 34]. Therefore, we recommend treatment with emergent, same-day whole brain and optic nerve radiation, in addition to IT

chemotherapy, and systemic chemotherapy as deemed appropriate by an oncologist, for patients with leukemic infiltration of the optic nerves.

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Infectious Optic Neuropathy

8

Andrew R. Carey

Case 1

A 66-year-old woman living in Maryland presents with a 1-week history of three episodes of left eye (OS) transient vision loss lasting 3–5 minutes, followed by persistent inferior field loss described as "fuzzy". She reports a 4-week history of neck stiffness, cervical lymphadenopathy, and daily headache present in the morning, responsive to acetaminophen, aspirin, and caffeine combination (Excedrin), improved over the past 2 weeks. She recalls an episode of fever and chills that developed after eating red meat 3 weeks prior. Her eye exam is significant for bilateral visual acuity of 20/25, left relative afferent pupillary defect (RAPD) of 0.6 log units (LU), normal color vision, OS enlarged blind spot on automated visual field, and OS nasal disc edema with flame hemorrhage (Fig. 8.1). She recalls 6 weeks prior she had a tick bite.

What is the most appropriate next step for this patient?

1. Check Bartonella titers and start oral trimethoprim-sulfamethoxazole if positive
2. Check Borrelia titers and start oral doxycycline immediately
3. Check syphilis IgG and start an oral beta-lactam antibiotic immediately
4. Check Toxoplasma titers and start oral clindamycin if positive
5. Get urgent lumbar puncture and start intravenous (IV) antibiotics if evidence of infection

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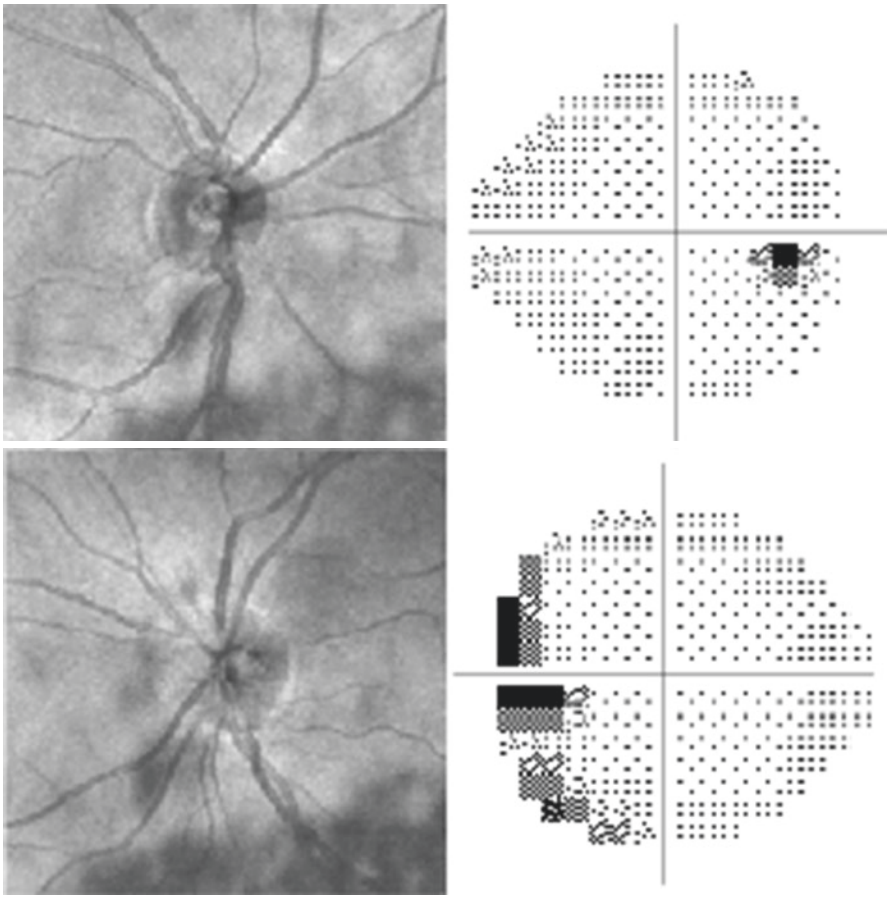

Fig. 8.1 Paired OCT fundus images of OD (top) and OS (bottom) and Humphrey visual field 24–2 demonstrate normal results for OD and OS with mild optic disc edema and enlarged blind spot and temporal rim scotoma. (© AR Carey 2020. All rights reserved)

Management

The most likely diagnosis is neuro-Lyme (Lyme neuroborreliosis). This patient falls in the acute phase, and titers may be falsely negative. Therefore, treatment should not be delayed while waiting for positive titer results, as delayed treatment could result in further neurologic complications and vision loss. If negative, titers may need to be repeated in 6 weeks to confirm disease. Recent studies have shown efficacy of oral treatment for neuro-Lyme; therefore, option *(b) check Borrelia titers and start oral doxycycline immediately* is a reasonable and cost-effective option. In patients with a more chronic course of neuro-Lyme, such as papilledema with good vision, lumbar puncture as the first step is appropriate.

Lyme

Sibony et al. put forth strict criteria for diagnosing Lyme-related optic neuritis based on experience with 361 retrobulbar optic neuritis cases, 55 papillitis cases, and 24 neuroretinitis cases in New York State. Of these cases, 28 had positive Lyme enzyme-linked immunosorbent assay (ELISA) screens, but only one – a patient with papillitis – had positive western blot. Only in this single patient was it thought that neuro-Lyme was the cause of the optic neuritis. Therefore, they concluded that there was insufficient evidence to connect Lyme with retrobulbar optic neuritis or neuroretinitis [1]. A study out of Sweden found optic disc edema in 3 of 48 eyes in patients with ophthalmologic manifestations of Lyme [2]. A review by Traisk and Lindquist found disc edema in 90% of patients with optic neuropathy and strong association with Lyme based on Sibony's criteria, while retrobulbar pain was present in only one case, and all cases had decreased visual acuity [3]. Rothermel reported four cases of children with optic nerve involvement: one with optic papillitis with negative MRI, two with papilledema from elevated intracranial pressure (ICP), and one with bilateral retrobulbar optic nerve enhancement on MRI as well as persistently elevated ICP despite treatment [4]. Long-term follow-up of some patients with optic neuritis initially attributed to Lyme prior to the development of western blot has revealed they actually had multiple sclerosis [5].

Current diagnostic criteria for Lyme is based on two-tier titer testing, with ELISA followed by confirmatory western blot test requiring five out of ten specific IgG bands or two out of three specific IgM bands [6]. There have been concerns about the sensitivity of this approach during acute Lyme infection due to the time necessary to develop antibodies. In the acute phase (erythema migrans), sensitivity has been estimated at 55% in Europe and 46% in the United States, increasing to about 90% with serum testing for Lyme neuroborreliosis in early disseminated disease, and over 90% in late disseminated stage, with specificities >99% [6]. Some finer points regarding serologies include isolated positive IgM 6 weeks or more after tick bite is considered a false positive, negative IgG in late disseminated stage should suggest alternative diagnoses (as false negatives are very rare), and persistently high antibodies years after appropriate treatment should not be considered recurrent infection [6]. Cerebrospinal fluid (CSF) CXCL-13 is a promising new test for confirming neuroborreliosis [6]. A modified two-tier testing algorithm using two different ELISA tests, rather than western blot, appears to improve sensitivity in early disease while maintaining specificity compared to traditional two-tier testing using western blot [6]. Notably, history alone is not sufficient to rule out Lyme disease. For instance, among 68 cases of definite neuro-Lyme (neurologic signs / symptoms, CSF pleocytosis, + CSF western blot), only 60% had an observed tick bite and 41% had erythema migrans [7].

Oral doxycycline has been shown to have equivalent efficacy to IV beta-lactam antibiotics, and a 14-day treatment course is sufficient for early neuro-Lyme. Fourteen to 21 days of treatment is sufficient for late/chronic neuro-Lyme [8].

Syphilis

Twenty-five percent of patients admitted for syphilis infection may have ocular involvement [9]. Optic nerve involvement in ocular syphilis is seen in 29–78% of cases, with bilateral involvement in two thirds [9–11]. Patients can present with optic disc edema, often with vitritis with or without a placoid chorioretinitis, neuroretinitis, papilledema from meningitis, or posterior optic neuropathy (optic neuritis with decreased visual acuity or perineuritis with preserved visual acuity) that may be gradually progressive [12]. HIV coinfection may occur in 29 to 34% of ocular syphilis cases and increases the risk of ocular involvement [13, 14]. Patients with HIV are less likely to have vitritis and may have a more slowly progressive course [12]. Ocular syphilis, particularly with optic nerve involvement, should be treated as neurosyphilis with IV penicillin for 10–14 days according to Centers for Disease Control and Prevention (CDC) guidelines if the CSF is normal [15]. If CSF is abnormal [pleocytosis, elevated protein, or positive venereal disease research laboratory test (VDRL)], repeat lumbar puncture is recommended 6 months after treatment to confirm negative VDRL (and, thus, adequate treatment). There is some evidence for treatment with an additional three doses of weekly IM penicillin to cover latent syphilis in other tissues [15]. Patients with penicillin allergy may be treated with intramuscular (IM) or IV ceftriaxone daily for 10–14 days; however, pregnant patients must be desensitized and treated with penicillin [15]. If diagnosed and treated promptly, patients may have full recovery of visual function, with up to 92% improving in a large series [16, 17].

Patients diagnosed with ocular syphilis should also be tested for HIV due to high coinfection rate. The use of steroids is of unclear benefit. Alternative treatment options include daily IM penicillin with oral probenecid for 10–14 days [15].

HIV

In addition to opportunistic infections and central nervous system (CNS) lymphoma, HIV can cause a primary optic neuropathy of variable presentation. Patients may develop chorioretinitis with papillitis, a steroid-responsive optic neuritis that may mimic neuromyelitis optica spectrum disorder (NMOSD), or slowly progressive vision loss akin to HIV dementia, sometimes referred to as "neuroretinal disorder" [12, 18–20]. One study looking at neuro-ophthalmic manifestations in HIV patients found that 23% of optic neuropathies were from HIV alone with a ratio of four cases of papilledema: two neuroretinitis: two papillitis: one retrobulbar optic neuropathy [21]. A study in South Africa looking at NMOSD showed 40% aquaporin-4 seropositivity in HIV-positive compared with 85% in HIV-negative patients [22]. HIV neuroretinal disorder has been defined as reduced contrast sensitivity below 1.5 log units in the absence of opportunistic infections or media opacities. It has a prevelance of 16% among patients with HIV infection overall and 51% by 20 years after AIDS diagnosis [23]. While many patients still have good acuity (mean 20/20), the visual field mean deviation is typically reduced, and there is a

6.5-fold rate of visual acuity 20/50 or worse and 5.9-fold rate of visual acuity 20/200 or worse compared with HIV patients without neuroretinal disorder [23]. HIV neuroretinal disorder is slightly more common among patients with lower CD4 counts, not on HAART, and with longer duration of AIDS, while the greatest risk factor is coinfection with hepatitis C (32% vs. 22%) [23]. Primary HIV optic neuropathy and neuroretinal disorder are diagnoses of exclusion. HIV-associated NMOSD has been treated with steroids and occasionally steroid sparing immunosuppression.

Fungus

Cryptococcus is an encapsulated fungus that most commonly comes from bird droppings, with some species having tropical and subtropical climate predominance [24]. Infections are seen more often in immunocompromised patients and can lead to vision loss from meningitis, which leads to elevated ICP from impaired CSF resorption due to arachnoiditis, compartment syndrome of the optic canal, and direct invasion of visual pathways [25–27]. Diagnosis of CNS involvement is made by lumbar puncture with measurement of opening pressure and CSF analysis for cells, protein, and Cryptococcus antigen, which has higher sensitivity compared with India ink stain [28]. Cryptococcal meningitis has 10– 50% 10-week mortality [29]. Treatment has multiple facets including antifungal treatment, management of ICP, minimizing drug toxicities, and managing inflammation [29]. Antifungal treatment has three phases: induction to rapidly clear the CSF, consolidation, and maintenance [29]. Induction usually involves amphotericin. The addition of 5-flucytosine has been shown to clear infection faster with improved survival rates, and adjunctive use of interferon-gamma increases clearance rate. If flucytosine is unavailable, fluconazole can be substituted [29, 30]. The second phase of treatment is consolidation with high-dose fluconazole or voriconazole and is followed by 6- to 12-month maintenance therapy with fluconazole or voriconazole [24, 29].

Elevated ICP may require lumbar drain when it persists for more than 2 days [26]. Ventriculoperitoneal shunting has shown benefit for ICP-related symptoms and hospitalization time [31]. Acetazolamide is not recommended due to worse outcomes [32]. Patients may have persistently elevated ICP as part of the immune reconstitution syndrome, which may also require VP shunting [29].

In AIDS patients, starting HAART may worsen CNS inflammation by inducing immune reconstitution inflammatory syndrome [29]; however, dexamethasone has been shown to slow fungal clearance with increased adverse events and no improvement in mortality when given acutely [33].

Aspergillus can manifest with a number of different clinical pictures [34]. Most commonly it causes fungal sinusitis in immunocompetent hosts, which can cause ethmoidal or sphenoidal bony expansion and resultant optic nerve compression. Noninvasive cases can be treated with surgical drainage and decompression [35]. In more aggressive CNS disease, particularly in immunosuppressed patients, elastase production by Aspergillus organisms leads to digestion of the internal elastic lamina of arteries, dissemination of fungal organisms, and resultant ischemic

complications. Neuro-ophthalmic involvement may include optic neuritis, orbital apex syndrome, and cavernous sinus syndrome. Presentation of invasive fungal infections can mimic optic neuritis with acute vision loss and normal fundus exam. Patients may initially respond to steroid treatment with worsening days later [36, 37]. Fungal sinusitis may be missed on MRI, and CT scan can be more sensitive for sinus opacification [38]. Biopsy and histopathologic examination are crucial for making a diagnosis. ELISA testing for galactomannoprotein and galactomannan can aid in identifying invasive disease with specificity of 98–99%, but sensitivity lags at 47–56% [39]. Voriconazole has long been felt to be first-line treatment, while amphotericin is second line [40]. A 2016 randomized controlled trial showed a new medication, isavuconazole, was noninferior to voriconazole, and may be better tolerated [41]. Fluconazole and fluorocytosine are ineffective [40]. Adjunctive treatments such as hyperbaric oxygen and local irrigation are of unclear benefit [42].

Mucormycosis (also known as zygomycosis) can present similarly to invasive aspergillus, although it may have a higher rate of infection among immunocompetent patients, particularly in the setting of poorly controlled diabetes, which is the primary risk factor in 40%, followed by hematologic malignancies. The sinuses are the most common site of invasion [43]. Symptoms usually begin with sinusitis and periorbital cellulitis and can progress rapidly to orbital apex syndrome. A black eschar is felt to be a specific finding indicating the ischemic vasoinvasive nature, although the sensitivity of this finding is unclear, and laryngoscopy may be required to identify it [43]. Early diagnosis is crucial as mortality even with aggressive treatment can be as high as 40% [43]. Diagnosis of Mucor cannot be made with 1,3-beta-D-glucan tests, but Mucor-specific T cells can be detected with immunospot testing during active infection [44]. PCR for 18S ribosomal DNA can aid in diagnosis as well, particularly when culture is inconclusive [44]. Treatment for Mucor differs from Aspergillus, as Mucor is resistant to voriconazole [44]. Surgery strongly improves survival and should be combined with amphotericin as first-line treatment and rescue therapy with posaconazole, with some suggestion that combination therapy may be helpful [44]. The 2016 VITAL study, an open-label Phase 3 trial, showed similar 42-day mortality rates with primary treatment with isavuconazole compared with amphotericin B; therefore, isavuconazole is now considered a first-line option, particularly in patients who are considered too high risk for amphotericin B [41]. Strict control of diabetes and treatment of ketoacidosis are also crucial [44].

Herpetic Disease

Human herpes viruses (HHV) 1–3 (simplex and zoster), in addition to causing ulcers of the skin and mucus membranes, uveitis, and retinitis, can present with CNS disease including optic neuritis. Optic neuritis may develop 6 to 30 days after rash and may be isolated papillitis or retrobulbar optic neuritis [45]. Optic disc edema may be the presenting feature of acute retinal necrosis and worsen with steroids [46]. CNS involvement and bilateral disease are more common in the immunosuppressed population. The mechanism of optic neuritis may be direct infection or postviral

autoimmune inflammation. Lumbar puncture with viral PCR is helpful for confirming CNS involvement. An anterior chamber paracentesis with viral PCR can be helpful for identifying intraocular viral replication [47]. Patients are traditionally treated initially with intravenous acyclovir [45], and intraocular infection can be treated with intravitreal injection of foscarnet [47]. If intraocular inflammation is present, topical steroids can be added as long as corneal epithelial infection is not present. Once infection is controlled, oral or IV steroids are often added. Oral valacyclovir has demonstrated equivalent efficacy to IV acyclovir for acute retinal necrosis but has not been studied for optic neuritis [48]. Epstein-Barr virus (HHV4) and cytomegalovirus (HHV5) less commonly cause optic neuritis. HHV5 is treated with valganciclovir, but there is no antiviral therapy for EBV.

Bartonella

Bartonella infections classically cause neuroretinitis with optic disc edema and macular exudates [49]. However, macular exudates may take up to 2 weeks to develop, so patients may not have exudates at initial presentation [50]. Other presentations of ocular Bartonella include anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, retinochoroiditis, vitritis, and peripheral choroidal granuloma [49]. Treatment is debated due to rarity of infections and lack of clinical trials. Antibiotics have not been shown to improve the cure rate for lymphadenopathy, although azithromycin has been shown to reduce lymph node volume [51, 52]. Some patients improve without treatment [53]. Reported treatment regimens for ocular disease include doxycycline, rifampin, macrolides (azithromycin), and fluoroquinolones, and some authors have recommended dual agent therapy, which is used for more complicated systemic infections [49, 51, 54]. One retrospective study showed 88% of eyes treated with antibiotics plus steroids (either oral or IV) gained at least three Snellen lines of vision compared with 50% treated with antibiotics alone, although the authors noted patients with more severe vision impairment were more likely to be treated with steroids and, therefore, had more room for improvement [55]. There was no difference in visual acuity outcome with or without antibiotic treatment [55].

Anti-Infective Medications

A number of medications used for infection may lead to optic neuropathy, which may confound the clinical picture. Linezolid, often used for vancomycin-resistant Gram-positive infections, such as Staphylococcus aureus and Enterococcus, may lead to toxic optic neuropathy with greater than 90% occurring in patients on therapy more than 28 days, with a dose-duration correlation [56, 57]. Doxycycline and other tetracycline derivatives, often used to treat zoonotic infections such as Lyme and Bartonella, used as second line for early and latent syphilis, and commonly prescribed to treat acne, can lead to secondary intracranial hypertension with papilledema with a hazard ratio of 1.8–1.9 and may portend a higher risk for vision loss

than idiopathic intracranial hypertension [58, 59]. Ethambutol, used for mycobacterial infections, can cause an optic neuropathy / chiasmal syndrome (decreased acuity and color vision with bitemporal hemianopia) with dose-dependent risk (18% >35 mg/kg daily dose, 5% >25 mg/kg, and <1% for 15 mg/kg or less), chronic kidney disease, hypertension, and older age [60–63]. In rat models, lutein as well as caffeic acid phenethyl ester were individually shown to be protective against ethambutol toxicity and could be considered as prophylaxis in high-risk patients [64, 65]. There are a handful of case reports of isoniazid-associated optic neuropathies without concomitant ethambutol use [66–70]. Additionally, certain HIV medications (nucleoside reverse transcriptase inhibitors, most famously ziduvodine – AZT) are known to cause mitochondrial toxicity and could potentiate other mitochondrially toxic disease or trigger vision loss in patients with genetic predisposition [71]. There are no proven treatments for visual recovery in these situations, so early recognition and cessation of the offending medication are crucial. In many cases, patients can recover vision. While a trial of steroids is often used for other causes of toxic optic neuropathy, steroids are typically avoided in the setting of active infection. In cases of elevated ICP, patients should also be started on ICP lowering medication, such as acetazolamide, until resolution of papilledema.

Case Resolution

The patient was started on doxycycline 100 mg twice daily for 3 weeks. She had resolution of her fevers, chills, neck pains, and lymphadenopathy, with improved vision. Her eye exam showed visual acuity of 20/20 in both eyes with resolution of optic disc edema and improved visual field (Fig. 8.2).

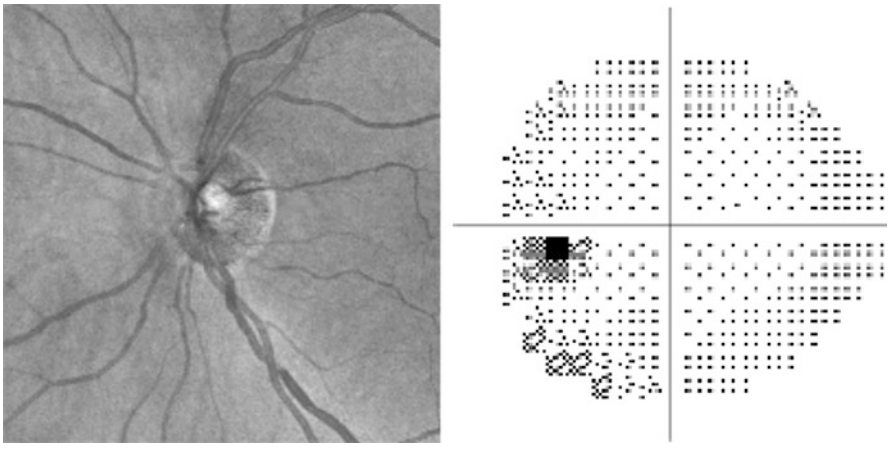

Fig. 8.2 OCT fundus image shows resolution of optic disc edema OS, and Humphrey visual field 24–2 shows improvement in both blind spot and temporal field defect. (© AR Carey 2020. All rights reserved)

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Hereditary Optic Neuropathy

9

Andrew R. Carey

Case

A 16-year-old male presents for second opinion regarding bilateral vision loss. He had painless, simultaneous vision loss 6 months prior. He felt he could drive for the first week, but vision loss progressed over a period of 3 months. His visual acuity was counting fingers in both eyes with central scotomas, color vision was gross colors only, pupils were slightly sluggish with no RAPD, and his ocular exam was significant only for 3+ diffuse pallor of both optic discs and mildly attenuated retinal vessels. His family ocular history was negative. Outside workup included an MRI of the brain and orbits with and without contrast which was negative for compressive lesions and optic neuritis, as well as normal thiamine, folate, and B12.

Which of the following is the most appropriate test to order?

(a) B12 level
(b) Mitochondrial panel
(c) mtDNA 3460 testing
(d) Nuclear optic atrophy panel
(e) *OPA1* sequencing

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Management

This presentation with sequential painless vision loss in a teenage male with unremarkable MRI is classic for Leber hereditary optic neuropathy (LHON). The most appropriate confirmatory test is genetic testing for a mutation in the mitochondrial genome with a *(b) mitochondrial panel*.

Hereditary optic neuropathies can be separated into mitochondrial and nuclear inheritance patterns. While there are exceptions, mitochondrial optic neuropathies typical present with acute to subacute vision loss while nuclear optic neuropathies have either poor vision from birth/early childhood or slowly progressive vision loss. Either group can have associated neurologic, cardiac, and metabolic disorders. A common pathway in mitochondrial dysfunction is either due to a primary error in mitochondrial DNA, an acquired error in mitochondrial DNA due to a primary error in a nuclear gene important for mitochondrial DNA maintenance, or a primary error in nuclear DNA for a protein that is important for mitochondrial function. Toxic and metabolic insults can also cause mitochondrial dysfunction mimicking a hereditary optic neuropathy. A French study from 2013 reviewed 184 patients from 127 families over 21 years with hereditary optic neuropathies and found 50% were dominant, 9% recessive, 24% sporadic, and 16% maternal, although a number of the sporadic cases may represent LHON with no family history. A molecular diagnosis was achieved in 46.5% of cases [1]. The same study found syndromic presentations in 9% of dominant cases, 67% of recessive cases, and 22% of sporadic cases [1].

Mitochondrial diseases are marked by maternal inheritance, incomplete penetrance, and delayed onset. Mitochondrial optic neuropathies were initially described as LHON or LHON like if they did not fit the classic picture. Typical LHON occurs in a male in his teens or twenties with painless sequential vision loss, MRI negative for enhancing or compressive lesions, and a positive family history in a maternally connected male. In this classical picture, three mitochondrial mutations, often called the primary mutations, make up 95% of LHON cases in patients of western European descent: G3460A in *mtND1* (~10%), G11778A in *mtND4* (~75%), and T14484C in *mtND6* (~10%), all of which are part of complex 1 in the electron transport chain of oxidative phosphorylation for ATP genesis [2]. A meta-analysis from 2012 estimated prevalence in European populations at 1:45,000 [3], and the carrier rate for the primary mutations in the UK is estimated at 1 in 300 [4]. The allelic frequencies vary by population with G11778A occurring in 36% of Han Chinese affected with LHON, 74–87% among Japanese, 56% among Koreans, and 10% in Indians [5, 6]. Among Middle Eastern patients who do not fit the classic picture—usually lacking family history—these primary mutations may only make up 17% of cases [7]. LHON penetrance may vary by underlying genotype but is reported at 50% for men and 10% for women with the 11778 variant and less with others [8]. Certain environmental factors may increase penetrance or "conversion" to vision loss from carrier status, such as exposure to mitochondrial toxins including tobacco; excessive alcohol (ethanol and methanol); extreme dehydration; carbon monoxide; cyanide; malnutrition; cocaine; ethambutol; and certain medications known to be mitochondrial toxins including erythromycin, chloramphenicol, linezolid, and

azidothymidine (AZT, a nucleoside analogue reverse transcriptase inhibitor used for HIV, also called zidovudine) [9–22].

Other mitochondrial genotypes may include an LHON-like optic neuropathy including Friedreich ataxia associated with mitochondrial *FXN* gene [23]. Mitochondrial optic neuropathies may present atypically, for example, with bilateral poor vision at birth or in early childhood presenting with nystagmus and/or strabismus, often seen with Leigh Syndrome (which may be nuclear or mitochondrial) [24, 25], or simultaneous vision loss rather than sequential vision loss [26].

LHON may have effects outside of the vision system, typically referred to as LHON-Plus. The most frequent nonvisual manifestation is a cardiac conduction defect, occurring in approximately one-fourth of cases of LHON on screening EKG performed at a mean age of 30 years [27]. Patients also may have dilated cardiomyopathy [28] and coronary artery disease [29]. Given this high frequency, a baseline EKG is recommended at diagnosis. Demyelinating events indistinguishable from multiple sclerosis, including optic neuritis, have been reported [30–32]. Other neurologic complications include seizures and nonepileptic myoclonus, complicated migraine, dystonia, peripheral neuropathy, tremor, and posterior reversible encephalopathy [33–38].

Nuclear optic neuropathies can be inherited in dominant, recessive, or x-linked patterns. Dominant optic atrophy (DOA) is the most common presentation of hereditary optic neuropathy, of which 59% were found to be due to mutations in *OPA1* in a French study [1], similar to 58% found in the UK [39]. Prevalence of *OPA1* in Chinese families with clinical dominant optic atrophy has been reported from 40% to 100% [40, 41]. In the UK, the prevalence of DOA is estimated at 1 in 35,000 [39]. The OPA1 protein is important for maintaining the stability of the mitochondrial inner membrane, and defects can lead to cytochrome c diffusion into the cytoplasm, triggering apoptosis [42]. Additionally, *OPA1* can be associated with syndromic disease often referred to as DOA-Plus. Two separate studies have reported multiple families with *OPA1* mutations with mitochondrial deletions and otherwise normal sequencing in mitochondrial maintenance genes, suggesting that *OPA1* is important for mitochondrial DNA stability, as well [42, 43]. Syndromic manifestations can include ataxia, muscle hypotonia or spasticity, deafness, progressive external ophthalmoplegia, neuropathy, and, in severe cases, multiorgan failure [42–44], and can mimic Leigh syndrome. *OPA1* mutations also have been reported in 3–7% of sporadic optic atrophy cases [40, 41, 44], likely from either incomplete penetrance or de novo mutations.

Syndromic presentations are more common in recessive disease [1] owing to the high rate of *WFS1*-associated Wolfram syndrome [aka diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy, and deafness (DIDMOAD)], although *WFS1* can cause isolated optic neuropathy with both dominant and recessive inheritance, as well as isolated DM and isolated deafness [45, 46]. Recessive optic neuropathies are much less common [1], and the prevalence of Wolfram syndrome is estimated at 1 per 770,000 in the UK [45]. However, prevalence may be higher in specific populations; for instance, one missense variant allele has been reported with a frequency of 1.4% among individuals of Ashkenazi Jewish heritage [47]. Interestingly,

Wolfram Syndrome can have variable presentation, which is more common among dominant disease than recessive disease. A series of 45 Italian patients with *WFS1*-associated type 1 Wolfram syndrome showed only 47% had the complete syndrome, and while 100% of patients had DM and optic atrophy, only 60% had DI, and 58% hearing loss. Additionally, 44% had neuropsychiatric symptoms, 24% neurogenic bladder, 7% endocrinologic defects, and 4% congenital heart defects [48]. A separate series of 40 Wolfram syndrome type 1 patients in the USA showed DM in 88%, DI in 63%, hearing loss in 75%, and optic atrophy in 93% [49]. A third series of 50 patients from Spain with both DM and optic atrophy showed 77% DI, 67% hearing loss, 78% neurogenic bladder, and 62% neuropsychiatric symptoms [50]. The disease severity appears to correlate with allelic severity, [46] and the missense allele among Ashkenazi descendants only showed optic atrophy in 12.5% [47].

Some nuclear genes are directly involved in the respiratory electron transport chain (combined oxidative phosphorylation) related to complexes 1–4 and can cause either an LHON-like picture or a more severe Leigh syndrome-like picture. Other nuclear genes are integral to mitochondrial genome maintenance, and pathologic variants can lead to large mitochondrial deletions causing a chronic progressive external ophthalmoplegia (CPEO)-like picture. Interestingly, sometimes these deletions will involve genes in the electron transport chain causing CPEO plus a slowly progressive optic atrophy.

Diagnosing hereditary optic neuropathies can be a significant challenge given the complexities of polygenic syndromes, multiple genes causing isolated optic neuropathy, recent identification that syndromic genes can cause a spectrum of disease ranging from nonsyndromic optic atrophy to multiorgan failure, and genes causing both autosomal recessive and dominant conditions. Table 9.1 characterizes genes that have been reported to be associated with hereditary optic neuropathy as of June 2020. Clinical clues suggesting a hereditary optic neuropathy include onset before age 50, symmetric disease with slowly progressive vision loss (or rapidly sequential vision loss), and central or cecocentral scotomata (Fig. 9.1). While some patients may have isolated optic neuropathy (nonsyndromic disease), common systemic manifestations include hearing loss, cardiac conduction defects, seizures or other neurologic defects, and failure to thrive. Due to these complexities, it is not practical to make a molecular diagnosis testing one gene at a time. Most commercial labs have developed targeted gene panels using next generation sequencing (NGS), and use of these gene panels can decrease costs of testing compared with whole-exome sequencing. However, there is no one panel that covers all possible genes, and mitochondrial and nuclear genome evaluations require separate lab techniques. In a typical LHON presentation, with a positive family history, the rate of a molecular confirmation with evaluation of the primary three LHON mutations can be expected to be 85–95%. However, in less typical situations, or if the initial panel is unremarkable, then a broad panel should be considered. Additionally, some laboratories have an option for reflex testing, in which an additional panel can be run on an existing specimen if and only if the initial panel is negative, and use of this option may avoid repeat blood draws and insurance authorization. Despite having large gene panels

Table 9.1 Genes involved in hereditary optic neuropathy by inheritance pattern

AD	AR	AR continued	X-linked	Mito
ANTXR1 *ATP1A3* *ATXN7* (SCA7) *C19orf12* *DNA2* (Mito del/CPEO) *DNMT1* *GDAP1* (CMT2K) *GJC2* *GLS* *KIF1A* *MFN2* (CMT2A) *NR2F1* (BBSOAS) ***OPA1* (DOA, DOA+)** ***OPA3* (DOA, DOA+)** *OPA4* *DNM1L* (OPA5) *OPA8* *POLG* (Mito del/CPEO) *POLG2* (Mito del/CPEO)	*ACO2* (OPA9) *ACOX1* *ALG3* (CDG1D) *ANTXR1* *AOPT1* (Leigh, MC4D) *AP3B2* *ATP5MD* (MC5D, Leigh) *AUH* (3MGA-1) *BCS1L* (MC3D, Leigh, GRACILE, Bjornstad) *C12orf65* (SPG55, COXPD, Leigh) *CISD2* (WFS2) *COX: 4I1*, *6A2*, *6B1*, *8A*, *10*, *14*, *15*, *20* (Leigh, MC4D) *C19orf12* (SPG43) *COQ2* (CoQ10D, Leigh) *CRLS1* (*GCD10*, *C20orf155*, MC1D, Leigh) *CYP7B1* (SPG5A) *DDHD2* (SPG54) *DGUOK* (Mito del/CPEO) *DLD* (Leigh) *DNAJC19* (3-MGA-5) *ECHS1* (Leigh) *EIF2B4* *ERCC6* *ERCC8*	*NDUF: A2, A6, A9, A10, A12, A13, AF2–6, AF8, B8, S1, S3, S4, S7, S8, V1* (MC1D, Leigh), *V2* (MC1D, Leigh) *NRDC* *OPA6* *PC* (Leigh) *PDHX* (Leigh) *PDP1* (Leigh) *PDSS: 1, 2* (CoQ10D, Leigh) *PDXK* *PET100* (Leigh, MC4D) *PLA2G6* *PNPT1* *POLG* (Alpers, MNGIE, SANDO, SCAE, CPEO, Mito del) *POLG2* (Mito del/CPEO) *POMGNT1* *PMPCB* (MMDS6, Leigh) *QRSL1* (COXPD, Leigh) *RAB3CAP1* *RNASEH1* (Mito del/CPEO) *RRM2B* (Mito del/CPEO) *RTN4IP1* (OPA10) *SCO: 1, 2* (Leigh, MC4D)	*AIFM1* *ALG3* (XLD) (COXPD, Mito del/CPEO) *CASK* (XLD) *G6PD* *GUST* *GYG2* *NDUFA1* (MC1D, Leigh) *OPA2* *PDHA1* (Leigh-XLD) *PLP1* (SPG2) *PRPS1* (Arts, CMTX5) *RAB40AL* *TIMM8A* (Mohr-Tranebjaerg)	*mt-ATP6* (MC5D, Leigh, LHON) *mt-CO: 1,3* (LHON) *mt-CYB* (LHON) ***mt-ND: 1* (LHON, Leigh, MELAS), *2* (LHON), *3* (LHON), *4* (LHON), *4 L* (LHON), *5* (Leigh, LHON, KSS, MELAS), *6* (LHON, Leigh)** *mt-RNR2* (Leigh) *mt-TC* (MELAS, Leigh) *mt-TH* (MELAS, Leigh) *mt-TK* (MELAS, Leigh)) *mt-TL1* (MELAS, Leigh) *mt-TL2* (KSS)

(continued)

Table 9.1 (continued)

AD	AR	AR continued	X-linked	Mito
POLR1A	*FARS2* (COXPD, Leigh)	*SDHA* (MC2D, Leigh)		*mt-TQ* (MELAS, Leigh)
RANBP2 (Leigh)	*FOXRED1* (MC1D, Leigh)	*SDHAF1* (MC2D, Leigh)		*mt-TS1* (MELAS, Leigh)
RRM2B (Mito del/CPEO)	*FDX2*	*SDHD* (MC2D, Leigh)		*mt-TS2* (MELAS, Leigh)
SDHC	*FDXR*	*SEC31A*		*mt-TV* (Leigh)
SPG7	*FXN* (Friedreich ataxia)	*SERAC1* (3MGA-6, Leigh)		*mt-TW* (Leigh)
SLC25A4 (Mito Del/CPEO)	*GDAP1* (CMT4A)	*SLC19A3* (TRMA)		
TFG	*GFM: 1, 2* (COXPD, Leigh)	*SLC25A4* (Mito del/CPEO)		
TWNK (Mito del/CPEO)	*GJC2*	*SLC25A46* (Leigh)		
WFS1	*GLS*	*SLC44A1*		
	GTPBP3 (COXPD, Leigh)	*SLC52A2*		
	GYG1 (Leigh)	*SPG7*		
	HIBCH (Leigh)	*STT3B*		
	IARS (Leigh)	*SUCLA2* (Leigh)		
	ISCA2 (MMDS4)	*SUCLG1* (Mito del, Leigh)		
	KIF1A	*SURF1* (Leigh, CMT4K)		
	KLC2 (SPG)	*TACO1* (Leigh, MC4D)		
	LARGE1	*TBCE*		
	LIPT1 (Leigh)	*TFAM* (Mito del, KSS)		
	LRPPRC (Leigh)	*TFG* (SP57)		
	MECR	*TIMMDC1* (MC1D, Leigh)		
	MGME1 (Mito del/CPEO)	*TK2* (Mito del/CPEO)		
	MFF (EMPF2, Leigh)	*TOP3A* (Mito del/CPEO)		
	MRPS34 (COXPD, Leigh)	*TMEM126A* (OPA7)		
	MRM2 (Mito del, MELAS)	*TSFM* (COXPD, Leigh)		
	mt-FMT (MC1D, COXPD, Leigh)	*TTC19* (MC3D, Leigh)		
	mt-PAP	*TUFM* (COXPD, Leigh)		
	mt-FMT (COXPD, Leigh)	*TXN2* (COXPD)		
	NADK2	*TYMP* (Mito del/CPEO, MNGIE)		
	NARS2 (COXPD, Leigh)	*UCHL1* (SPG79)		
	NBAS	*VPS53*		
	NUP62 (Leigh)	*WDR73* (Galloway-Mowat)		
	***OPA1* (Behr)**	***WFS1***		
	***OPA3* (MGCA3)**	*WWOX* (SCA12)		
		YME1L1 (OPA11)		

AD Autosomal dominant, *AR* Autosomal recessive, *CMT* Charcot Marie Tooth, *BBSOAS* Bosch-Boonstra-Schaaf optic atrophy syndrome, *DOA* dominant optic atrophy, *CPEO* chronic progressive external ophthalmoplegia, *GRACILE* Growth Retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis, and Early death, *MC*D* mitochondrial chain complex deficiency, *SPG* spastic paraplegia, *COXPD* combined oxidative phosphorylation deficiency, *MELAS* Mitochondrial Encephalopathy Lactic Acidosis Stroke-like episodes, *MMDS* multiple mitochondrial dysfunction syndrome, *MNGIE* mitochondrial neurogastrointestinal encephalomyopathy, *TRMA* thiamine-responsive megaloblastic anemia, *OPA* optic atrophy, *WFS* Wolfram syndrome, *XLD* X-linked dominant, *Mt* mitochondrial, *EMPF* encephalopathy due to mitochondrial and peroxisomal fission, *SANDO* sensory ataxia neuropathy dysarthria and ophthalmoparesis, *SCAE* spinocerebellar ataxia with epilepsy, *MGCA* methylglutaconic aciduria, *CDG1D* congenital disorder glycoprotein syndrome, *KSS* Kearns Sayre syndrome, *LHON* Lebers Hereditary Optic Neuropathy, *SCA* spinocerebellar ataxia, *Mito del* mitochondrial deletion, *XLD* X-linked dominant

[a]**Bolded** are the most commonly involved genes clinically

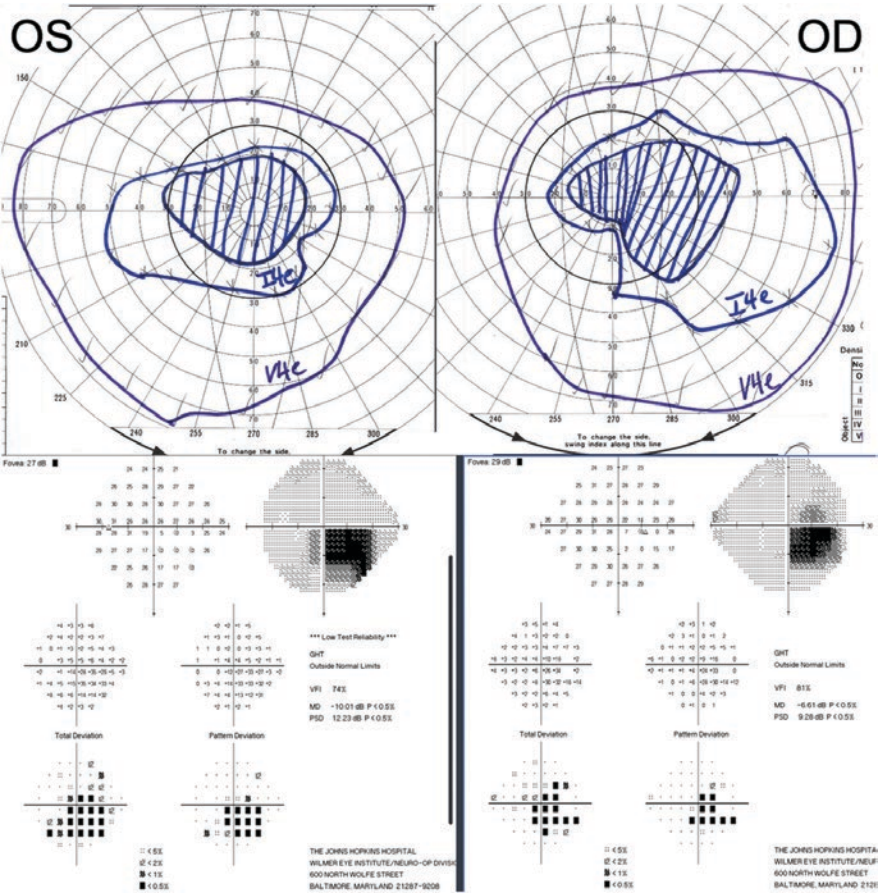

Fig. 9.1 Classic visual fields in hereditary optic neuropathy. (Top) Goldmann visual perimetry with cecocentral scotomata. (Bottom) Automated visual field with cecocentral scotomata

available, a detailed clinical and family history is helpful for interpreting genetic testing results, and sending parental or sibling samples can also be helpful to determine if a mutation segregates in the family or has occurred de novo. Involvement of a genetic counselor, who has specialized training and experience in patient and family counseling, test selection, and the logistics of ordering genetic testing, often is helpful and is an excellent option for any provider who suspects hereditary optic neuropathy but is unsure of the best approach for confirmatory genetic testing.

As of June 2020, there are no FDA-approved treatments for any hereditary optic neuropathies. A randomized controlled trial in 2011 evaluated the use of idebenone, a synthetic analogue of coenzyme Q10, for molecularly confirmed LHON with a primary mutation and failed to meet its primary outcome of visual acuity recovery, although a post hoc analysis showed significant improvements in patients with

discordant vision loss (interocular difference of logMAR >0.2). These results suggest a possible benefit for patients who initiate idebenone treatment early in the disease process, specifically when only one eye has lost vision [51]. However, a retrospective study looking at patients starting idebenone more than 5 years after onset of vision loss found a significant improvement in visual acuity but only a trend toward improvement in visual field [52]. Idebenone has been approved for use in patients with LHON in Europe, and an international consensus statement published in 2017 recommends treatment with idebenone for patients identified within the first year after onset of vision loss in the second eye, with treatment for at least 1 year or until a plateau in improvement is reached [53]. Preliminary results from Phase 3 randomized controlled trials for gene therapy to transfer wild-type mitochondrial *ND4* in patients with molecularly confirmed 11778 LHON failed to meet primary end points due to a surprising improvement in sham injected fellow eyes of patients receiving gene therapy in the primary eye, with some data suggesting the gene therapy may have had an effect in both eyes.[54] Even without proven treatments, benefits of confirming a molecular diagnosis in patients with hereditary optic neuropathy include psychological benefits of confirming the condition; better sense of prognosis; focused evaluation and monitoring for known associated syndromic manifestations, some of which have treatment such as hearing loss (cochlear implants), DM (insulin), and seizure (antiepileptics); family planning; and potential enrollment in future clinical trials. Low vision evaluation is recommended for a safety and mobility evaluation as well as for visual aids and accommodations to allow full participation in school and work.

With advances in technologies for both genetic testing and treatment, management of hereditary optic neuropathies may change rapidly in the near future.

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Compressive Optic Neuropathy

10

Alberto G. Distefano

Case 1

A 26-year-old woman presents with visual distortion in the right eye for 6 months. Visual acuity is 20/20 in the right and left eyes. There is a right relative afferent pupillary defect (rAPD). Color vision is full in both eyes. Extraocular motility is full, and alignment is orthophoric. Hertel exophthalmometry measures 23 mm on the right and 18.5 mm on the left with a base of 92 mm. Anterior segment examination is unremarkable. Dilated fundus examination (DFE) is significant for right optic disc elevation and choroidal striae extending from the optic nerve to the macula, distorting the foveal light reflex. Left fundus appears normal. Humphrey visual field (HVF) shows a few central missed spots in the right eye, but with normal foveal threshold, and is full in the left eye. MRI brain and orbits with and without contrast is ordered due to concern for orbital mass, and it demonstrates an avidly enhancing perineural lesion on the right (Fig. 10.1).

What is the best treatment option for this patient?

(a) Surgical resection
(b) Intravenous (IV) steroid therapy
(c) Radiation therapy
(d) Oral steroid therapy
(e) Chemotherapy

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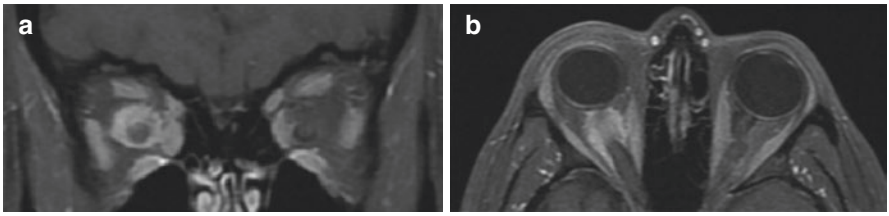

Fig. 10.1 T1-weighted MRI orbits with fat saturation and gadolinium. (**a**) Coronal view with enhancement and thickening surrounding the optic nerve (doughnut sign). (**b**) Axial view with enhancement and thickening along both sides of the right intraorbital optic nerve (tram-track sign).

Management

History of progressive visual change or loss along with imaging showing an enhancing perineural lesion is enough in most cases to make a clinical diagnosis of optic nerve sheath meningioma (ONSM). ONSM is usually a benign tumor originating from the meninges primarily surrounding the intraorbital or intracanalicular optic nerve or secondarily from intracranial meninges [1]. ONSMs spread in subdural and subarachnoid planes, between the optic nerve axons and their extradural blood supply [2]. They are the second-most common primary optic nerve tumor, with the first being optic nerve glioma [1]. Other considerations include leukemic or metastatic infiltration and inflammatory disorders such as sarcoidosis, perineuritis, or myelin oligodendrocyte glycoprotein-associated optic neuritis. Middle-aged women are more frequently affected by ONSM. Younger patients do not show a gender predilection, are more likely to have neurofibromatosis type 2, and tend to have more aggressive tumors [2]. Patients generally present with variable combinations of vision loss, optic nerve edema or atrophy, proptosis, strabismus, and optociliary shunt vessels on the optic disc [1]. The triad of visual loss, optic disc pallor, and optociliary shunt vessels is pathognomonic, yet uncommon and a late finding [2, 3]. T1-weighted MRI of the orbits with fat suppression and gadolinium enhancement is necessary for diagnosis, although CT scan and ultrasonography can also show ONSM with limited soft tissue definition. CT may show calcifications, considered to be due to slow growth [2]. ONSM can be differentiated from optic nerve glioma on imaging with the former showing diffuse, tubular enhancing lesions on MRI, referred to as “tram-track” sign on axial images (originally designated for the same finding on CT scan) and “doughnut” sign on coronal images, while the latter shows a fusiform enlargement of the optic nerve (Fig. 10.1) [2, 4]. Biopsy is not typically indicated unless diagnosis is unclear, such as with atypical imaging findings or aggressive disease course [1]. Observation can be considered for patients with normal vision; however, once vision changes occur, further vision loss is expected [1, 3]. Surgical options also usually lead to vision loss [3]. Attempts have been made at surgical resection, compromising the shared pial vascular supply of the optic nerve and meninges, and with optic nerve decompression, leading to orbital seeding [1].

Complete sacrifice of the optic nerve in eyes with no useful vision and posterior growth of the tumor should be the only surgical method considered [1]. Systemic medical therapy, such as hormone therapy or hydroxyurea, and chemotherapy have not been shown to stabilize or improve ONSM [1, 2]. *Radiation therapy (c)* is the current treatment of choice for ONSM, stabilizing or improving vision and demonstrating a lower complication rate compared with surgical intervention [3]. When using fractionated external beam radiation, a dose between 50 and 55 gray (Gy) and a fractional dose of less than 2.0 Gy is recommended, showing long-term tumor control with minimal ophthalmic complications [3, 5, 6]. Retinopathy may be noted with doses over 50 Gy, with underlying diabetes mellitus reducing the threshold to 45 Gy for both the retina and optic nerve [2]. Earlier treatment with stereotactic fractionated radiotherapy may lead to improved preservation of vision. Deciding when observation, radiation, or rarely surgical therapy is needed requires a multidisciplinary approach guided by complete neuro-ophthalmic evaluation and imaging.

Case 1 Resolution

The patient underwent fractionated stereotactic radiotherapy for treatment of the ONSM, for a total of 50.4 Gy in 28 fractions (1.8 Gy each). Visual function and MRI appearance have remained largely stable over 7 years of follow-up.

Case 2

A 54-year-old man presents with severe, painless decreased vision in the left eye that began 5 weeks ago. His past medical history includes hypertension and type 2 diabetes mellitus. Review of records from the referring provider shows that the patient had an ophthalmic artery occlusion in the right eye 4 years prior. MRI at that time was negative. He is status-post recent cataract extraction in the left eye, best corrected visual acuity after surgery was 20/70, and continued to decline afterwards. On exam, visual acuity is no light perception in the right eye and counting fingers at 1 foot in the left eye. The right pupil is amaurotic. The left pupil sluggishly reacts to light. Intraocular pressures are within normal limits, and extraocular motilities are full. DFE shows right retinal vascular attenuation, scattered dot-blot hemorrhages, and mild pigmentary changes. Retinal vessels in the left eye are thin with scattered dot-blot hemorrhages. The optic nerves have severe diffuse pallor in the right eye and mild pallor in the left eye. HVF of the left eye shows a dense central defect. MRI shows a suprasellar mass with an associated meningeal tail, compressing the chiasm and intracranial optic nerves on the right more than the left (Fig. 10.2).

What is the next appropriate step for this patient?

(a) Radiation therapy
(b) Craniotomy for biopsy
(c) IV corticosteroids

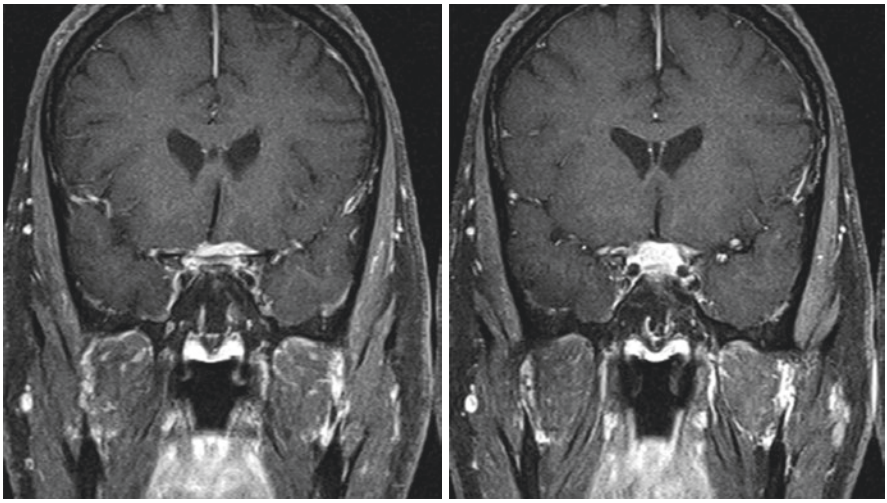

Fig. 10.2 Coronal T1-weighted MRI with fat saturation and gadolinium shows enhancing dural mass compressing the chiasm and intracranial optic nerves on the right more than the left. Meningeal tail was also present posteriorly (not shown). (© AG Distefano 2020. All Rights Reserved)

(d) Oral methotrexate
(e) No further intervention due to severe vision loss

Management

This patient presents with progressively declining vision in the left eye over a short period of time. The case is further complicated by a prior ophthalmic artery occlusion in the right eye; however, the sluggish pupil in the left eye along with optic nerve pallor is consistent with an optic nerve process that could be inflammatory, infectious, secondary to malnutrition, or compressive (from an inflammatory or neoplastic mass). Imaging reveals a mass compressing the intracranial optic nerves and chiasm, radiologically consistent with a planum sphenoidale meningioma. However, due to the rapid progression of vision loss, *(b) craniotomy for biopsy* was recommended to determine a diagnosis and initiate a proper treatment. Minimally invasive approaches, such as the endoscopic transsphenoidal route, also can be pursued in the cases of some sellar or suprasellar masses, for biopsy and decompression of the optic chiasm and nerves [7]. Surgical approach is dependent on mass location, pathology if previously biopsied, relationship with surrounding structures, prior surgical history, and surgeon's experience. The ideal approach takes into account the shortest path to the lesion, while allowing optimal exposure of the lesion and important structures [8]. Pathology in this case was consistent with a low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). While presumed meningiomas may be treated with radiation without biopsy in

some cases (as in Case 1), a pathologic diagnosis is ideal in atypical cases to ensure correct diagnosis and treatment. Lymphoma can be mistaken as meningioma if a biopsy is not performed [9]. Both meningioma and primary dural lymphoma (PDL) have a higher incidence in women with a similar age of onset. Both also have similar MRI characteristics: they are iso- or hypointense on T1-weighted MRI, diffusely enhance with gadolinium, frequently have a dural tail, and can have extra-axial lesions. Underlying vasogenic edema is more common in PDL [9]. PDL is a rare form of primary intracranial lymphoma with an unknown incidence and no association with immunosuppression, as opposed to primary CNS lymphoma [10]. Its pathogenesis is poorly understood as there is no lymphoid tissue in the dura. It is thought that a benign inflammatory condition of the dura may attract polyclonal lymphocytes from which monoclonal PDL can arise [10]. MALT lymphoma is frequently found in the stomach and associated with chronic inflammation from *Helicobacter pylori* in 72–98% of cases [11]. Chronic immune stimulation, such as in Sjögren syndrome and Hashimoto thyroiditis, is also suspected in the pathogenesis at other sites [10]. Further evaluation with neurological staging using contrast-enhanced imaging of the brain and spine, and lumbar puncture for cytological evaluation of the cerebral spinal fluid, is required, along with systemic evaluation including CT chest, abdomen, and pelvis, and bone marrow biopsy [10]. Treatment requires a combination of surgical and medical therapies. Complete resection is often difficult, with most cases requiring adjuvant treatment with radio- or chemotherapy. Prognosis is good with 5-year survival of 86% in the marginal zone subtype [9, 10]. Future systemic monitoring is required as recurrences can take place several years after the initial diagnosis of PDL.

Case 2 Resolution

Our patient underwent surgical resection during the initial craniotomy, with radiation therapy for the remainder of the unresectable tumor and intrathecal chemotherapy. There was no systemic involvement, and vision in the left eye improved to 20/250 with a remaining paracentral inferotemporal visual field defect.

Case 3

A 19-year-old woman without significant medical history presents to her ophthalmologist with decreased vision in the right eye for 2 months. She also complains of intermittent head pressure and pain. Best corrected visual acuity is 20/60 in the right eye and 20/20 in the left eye. There is a trace right rAPD. DFE appears normal in both eyes. HVF shows a bitemporal hemianopia, which respects the vertical midline (Fig. 10.3). MRI of the orbits with and without gadolinium shows a 10 mm sellar mass abutting the optic chiasm (Fig. 10.4).

What it the next best step in management?

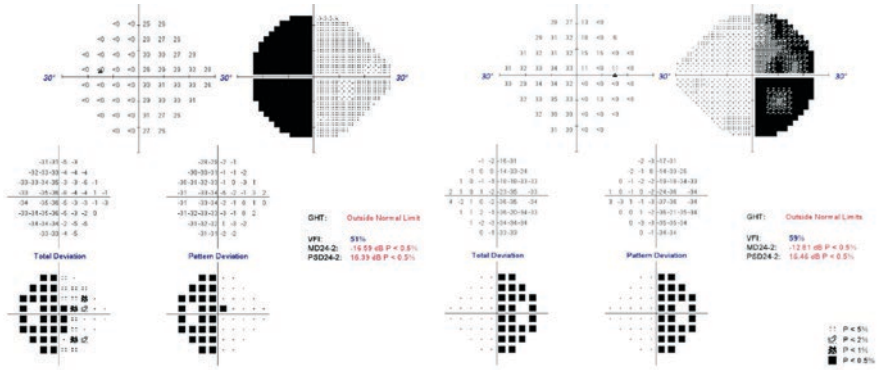

Fig. 10.3 Humphrey visual field 24–2 demonstrating bitemporal hemianopia. (© AG Distefano 2020. All Rights Reserved)

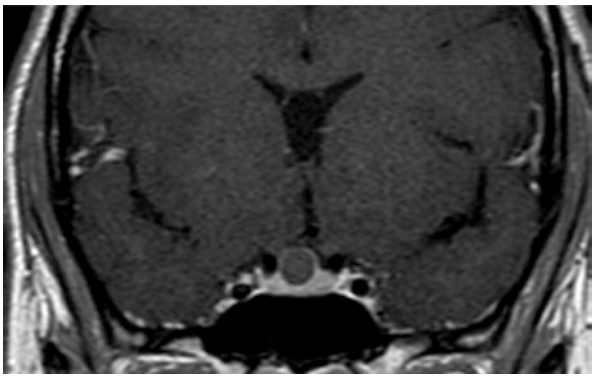

Fig. 10.4 MRI pituitary with gadolinium showing a 10 mm lesion abutting the right optic nerve and chiasm. (© AG Distefano 2020. All Rights Reserved)

(a) CTA or MRA to rule out vascular compromise
(b) Endoscopic transphenoidal surgical resection
(c) Craniotomy for tumor resection
(d) Hormone serology
(e) Radiation therapy

Management

Presentation with headaches and bitemporal visual field defects is consistent with a sellar lesion compressing the optic chiasm. While most of these tumors are presumed to be pituitary adenomas, other lesions such as Rathke cleft cysts and metastatic tumors may present similarly. Pituitary adenomas are relatively frequent tumors, found in about 10% of autopsies without known history of pituitary disease

and in about 10% of MRIs of normal patients [12]. Most patients remain asymptomatic as the tumors stay small and secrete little hormone. Pituitary tumors are classified based on size: microadenomas are below 10 mm, macroadenomas between 10 and 39 mm, and giant adenomas larger than 40 mm [12]. As tumors smaller than 10 mm in diameter are not expected to affect the visual pathways, we focus our discussion on the management of the larger adenomas.

Evaluation should include formal neuro-ophthalmic examination and HVF testing for tumors contacting the optic chiasm. Bitemporal hemianopia results from compression of the chiasmal crossing of nasal fibers corresponding to the temporal half of the visual field [13]. Optical coherence tomography measuring the peripapillary retinal nerve fiber layer (RNFL) can be used as a prognostic factor for visual recovery after surgical resection, with RNFL closer to normal having the best chance for full visual recovery [13]. Endoscopic transphenoidal tumor resection is typically the treatment of choice when intervention is indicated, except in the case of prolactinomas, which can be treated medically and may not require surgery [12]. Therefore, in the presented case, *(d) hormone serology* is the necessary next step in evaluation.

Management of pituitary macroadenomas requires complete systemic evaluation with proper imaging and serologies, as guided by a multidisciplinary team with neuro-ophthalmology, endocrinology, neurosurgery, and otolaryngology. Observation may be appropriate in cases of pituitary macroadenoma, even with apparent chiasmal mass effect, if visual function is unaffected and there are no endocrinologic abnormalities that necessitate intervention. Observation should include HVF every 6–12 months for lesions encroaching on the visual pathways, if surgery is not performed. Serial MRI also may be considered. Endocrinologic evaluation is indicated in the setting of a sellar lesion to evaluate for hypopituitarism as well as hormonal secretion by the tumor, both of which affect optimal management of these lesions. Any patients with hormonal abnormalities in the setting of a pituitary adenoma should be managed by an endocrinologist. Notably, patients with nonsecreting tumors are more likely to present with larger tumors and, thus, with symptoms from mass effect, such as headaches, visual field defects, extraocular motility deficits, and hypopituitarism.

Unlike other pituitary macroadenomas, macroadenomas that are prolactin secreting primarily require medical (rather than surgical) treatment. Hyperprolactinemia can lead to decreased libido, infertility, osteoporosis, oligomenorrhea, amenorrhea, galactorrhea, and erectile dysfunction. While mild elevations of prolactin (i.e., <200 ng/mL) can occur in the setting of pituitary stalk compression from a nonsecreting tumor, significant hyperprolactinemia indicates the presence of a prolactinoma. The usual treatment for prolactinoma, even in the setting of chiasmal compression causing vision loss, is dopamine agonist therapy, either with cabergoline or bromocriptine. Cabergoline is better tolerated than bromocriptine and, thus, usually is the treatment of choice. Significant reduction (over 25%) in tumor size has been shown to occur in over 65% of macroprolactinomas treated with cabergoline, usually leading to decreased chiasmal mass effect and improvement in visual field defects [14]. Reductions in prolactin levels and tumor size are often quite rapid

after the initiation of cabergoline therapy, and improvement in visual fields may be apparent within days. If visual deficits, associated with continued evidence of mass effect on MRI, persist for months despite dopamine agonist treatment, then surgical intervention must be considered [12]. Additionally, inadequate control of the prolactin level and/or persistent symptoms of hyperprolactinemia, as determined by the endocrinologist, also may be surgical indications.

Growth hormone secreting tumors can lead to gigantism in children, as well as acromegaly, diabetes mellitus, hypertension, arthritis, carpal tunnel syndrome, and sleep apnea. Colonoscopy and thyroid ultrasound are indicated due to an increased risk of colon and thyroid neoplasia, respectively. Echocardiogram to rule out valvular disease and sleep studies also can be considered if clinically appropriate. Again, comanagement of these patients with an endocrinologist is prudent. Transsphenoidal resection is considered primary therapy for these lesions, and repeat surgery may be required. Further mild elevations of IGF-1 levels can be controlled with cabergoline in 33% and somatostatin analogues in 67% [12, 15].

Transsphenoidal pituitary resection is performed for tumors that are enlarging or causing symptoms from mass effect. Unless a macroadenoma is determined to be secreting prolactin, then surgical resection to relieve chiasmal compression is indicated to treat visual compromise. It has been recommended that postoperative MRI be performed at 3 months and then yearly for 5 years, and then at 7, 10, and 15 years post resection [16]. Radiation therapy is an option for patients who continue to have elevated hormone levels despite resection, and in those patients in whom total resection is not feasible, to prevent further tumor enlargement. In this setting, hypopituitarism occurs frequently following radiation treatment of any type in up to 80% of patients by 10 years, so they should be counseled regarding this side effect [12].

Case 3 Resolution

Serologic evaluation demonstrated no significant hormonal abnormalities, and, specifically, the prolactin level was within normal limits. The patient underwent transsphenoidal resection of the tumor, and visual field defects resolved.

Conclusion

In summary, compressive optic neuropathy typically presents with slowly progressive decline in visual function. The differential diagnosis of compressive optic neuropathy is broad and includes any disease process causing a mass effect along the optic nerve, not all of which could be covered in detail in this chapter. Graves ophthalmopathy is discussed in Chap. 25. Other inflammatory or autoimmune causes include idiopathic orbital inflammation/IgG4-related orbital disease (discussed in Chap. 15), sarcoidosis (discussed in Chap. 26), and granulomatosis with polyangiitis [17]. A multitude of tumors can compress the optic nerve or chiasm, including benign tumors such as cavernous/capillary hemangiomas, schwannoma, dermoid

cyst, teratoma, bone tumors (osteoma, osteopetrosis, fibrous dysplasia, Paget disease), pituitary adenoma, craniopharyngioma, and meningioma, and malignant tumors such as sarcoma, mesenchymal tumor (fibrous histiocytoma), lymphoma, and metastatic disease. Vascular lesions that may cause optic nerve compression include aneurysms, lymphangioma, orbital varix, arteriovenous malformation, and orbital hemorrhage. Other abnormalities around the orbit that can affect the optic nerve include mucocele, encephalocele, arachnoid cysts of the optic nerve sheath, and hypertrophic or granulomatous cranial meningitis [18]. With such a broad differential, workup depends upon the patient history and physical. A strong clinical suspicion is needed as some presentations of compressive optic neuropathy can be confused with other causes of vision loss, such as glaucoma, due to optic disc cupping. Neuroimaging is necessary regardless of the cause once the clinician suspects compressive optic neuropathy [19]. MRI with gadolinium enhancement is the preferred imaging modality given its excellent visualization of soft tissues and specifically of the orbital apex and optic canal. Fat saturation is a necessary technique in evaluation of the orbits. Treatment depends on the lesion identified on imaging and may include surgery, radiation, and/or medical management.

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Part III

Ocular Motility Disorders

Transient Diplopia

11

Sean M. Gratton

Case 1

A 55-year-old man presents for evaluation of an episode of diplopia. On the morning of evaluation, he was seated at his desk at work when he suddenly developed binocular vertical diplopia. He felt mildly dizzy during the event, but there were no other associated symptoms. The episode lasted for approximately 30 minutes, during which his coworker told him that his eyes were "bouncing." His past medical history is significant for ischemic stroke, diabetes mellitus, hypertension, and osteoarthritis. He reports that his prior stroke occurred 2 years ago and involved right-sided weakness and sensory loss that resolved over several months. He takes aspirin, atorvastatin, and lisinopril. His neurological examination and ophthalmological examination are normal.

What is the most appropriate next step for this patient?

(a) No further workup
(b) Old photograph review for head tilt
(c) Transient cerebral ischemia (TIA) workup
(d) Single-fiber electromyogram
(e) Thyroid-stimulating immunoglobulin

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Management

The most appropriate next step is to perform a *(c) transient cerebral ischemia workup*. His risk for cerebrovascular events is high due to his vascular risk factors including diabetes mellitus, hypertension, and prior stroke. Additionally, the "bouncing" of his eyes was most likely nystagmus, which indicates a central nervous system cause of diplopia.

Diplopia is a common clinical complaint that can herald a serious underlying disease process. There are over 850,000 medical visits for diplopia annually in the United States [1]. Of the roughly 50,000 annual Emergency Department visits for diplopia in the United States, 16% are due to potentially life-threatening causes [1]. It falls on the clinician to determine the appropriate workup to accurately and promptly identify serious causes of diplopia.

Decision-making in diplopia is supported by a thorough history and neurological and ophthalmological examinations. When a patient presents with constant diplopia, the clinical examination includes measuring ocular motility and alignment. These measures provide important localizing information to help guide the workup and establish the level of urgency required. Transient diplopia presents a special challenge, as the ocular motor disturbance has resolved and cannot be measured during a clinic visit. In cases of transient diplopia, the clinician must use historical clues to determine the most appropriate evaluation and management.

For the purposes of this chapter, transient diplopia will be defined as diplopia that has resolved at the time of clinical presentation. This definition encompasses diplopia of many different durations (seconds to days) as well as episodic or recurrent diplopia. While this is a heterogeneous group, these different presentations share the feature that they are not present at the time of the clinical evaluation, and, therefore, the clinician cannot glean any localizing information from the examination. This definition allows for an exploration of the unique challenges of caring for such patients.

It is essential to establish whether the complaint of diplopia is monocular or binocular [2]. This determination marks a major initial decision-making branchpoint in the evaluation of patients with diplopia. When it can be confidently ascertained that the diplopia is monocular, then concern about potentially life-threatening causes dissipates. The diplopia discussed in this chapter can be assumed to be binocular.

The general approach to transient diplopia begins with a careful history with the aim of determining the risk of dangerous underlying pathology, followed by an investigation for less serious, but more common causes. The provider should attempt to understand the characteristics of the diplopia. Is it binocular? How are the objects displaced? Is there subjective incomitance? Is there diurnal variation? Was there a triggering event? Associated symptoms must be carefully explored as they can be important indicators of pathology. Common associated symptoms such as eye pain, headache, ptosis, anisocoria, and other neurological symptoms should be asked about in all diplopia encounters, and additional symptoms should be explored depending on the circumstances (e.g., jaw claudication, proptosis, and eye redness). The patient's

Table 11.1 Historical clues in transient diplopia

History (transient diplopia +)	Suggested localization/diagnosis
Brainstem/cerebellar symptoms (dysarthria, dysphagia, ataxia, hemiparesis, hemihypesthesia, gait impairment)	TIA, vertebrobasilar insufficiency
Vestibular symptoms	TIA
Oscillopsia	TIA, superior oblique myokymia (if monocular oscillopsia)
Witnessed nystagmus	TIA
Transient visual loss	TIA, GCA
Headache, jaw claudication, myalgias/arthralgias, scalp tenderness, excessive fatigue, unexplained weight loss	GCA
Binocular horizontal diplopia that is worse at distance and in lateral gaze in one direction	Sixth nerve palsy
Ptosis	Third nerve palsy, MG
Anisocoria	Third nerve palsy
Occurrence with fatigue/improvement with rest, proximal weakness, dysphagia, dyspnea	MG
Proptosis, eyelid retraction, other orbital signs	Thyroid orbitopathy, orbital tumor
Diplopia at near only	Convergence insufficiency
Diplopia at distance only	Divergence insufficiency
Documented head tilt	Fourth nerve palsy, skew deviation/ocular tilt reaction
History of cranial irradiation	Ocular neuromyotonia
Thunderclap headache/worst headache of life	Aneurysm
Recent facial trauma	Extraocular muscle entrapment

Abbreviations: *GCA* giant cell arteritis, *MG* myasthenia gravis, *TIA* transient ischemic attack

risk factors and demographics also should be taken into account. The presence of vascular risk factors increases the concern for stroke or TIA. Elderly patients are at a higher risk of stroke, giant cell arteritis (GCA), cancer, and other diseases. A detailed medication history can identify diplopia due to medication side effects.

A comprehensive history may allow the provider to accurately localize the lesion to a specific ocular motor structure. If a specific localization cannot be achieved by history alone, then the provider should consider whether the lesion is likely to be central or peripheral. Transient diplopia of central origin raises concern for cerebrovascular disease, which ought to be addressed promptly. Historical factors that should raise concern for a central process include other brainstem symptoms (e.g., ataxia, hemiparesis, hemisensory loss, dysarthria, dysphagia, and oscillopsia), report of nystagmus, older age, transient visual loss, and history of or risk factors for cerebrovascular disease. Historical clues for other localizations and diagnoses are summarized in Table 11.1.

Transient Ischemic Attack

TIA is one of the most worrisome causes of transient diplopia because it establishes that a patient is at imminent risk of stroke [3]. Transient neurological symptoms, including isolated diplopia, have been shown to occur in the days prior to completed

vertebrobasilar strokes [4]. When patients with TIAs are followed over time, those who presented with transient diplopia are just as likely to have a major vascular event in the next year as are patients who present with more traditional TIA symptoms such as motor deficits [5]. Prompt diagnosis of a TIA causing transient diplopia can, therefore, provide an opportunity to intervene to prevent future stroke. Several clinical prediction tools exist to help clinicians stratify the risk of future stroke [6]. The ABCD2 score is a widely used example of one of these tools, which is used to calculate two, seven, and 90-day risk of stroke after TIA using age, blood pressure, clinical features, diabetes mellitus, and duration [7].

The management of TIA is similar to the management of ischemic stroke. The American Heart Association/American Stroke Association provides a class I, level of evidence A recommendation that patients with cerebral ischemic symptoms that have resolved should undergo neuroimaging evaluation within 24 hours of symptom onset or as soon as possible in patients with delayed presentations [8]. This neuroimaging should include noninvasive imaging of the cervical and intracranial vessels [8]. A complete review of the management of TIA is beyond the scope of this chapter, but the main tenets of managing TIA are to perform diagnostic maneuvers to assess TIA mechanism (including vessel imaging, echocardiogram, and heart rhythm monitoring), to institute appropriate antithrombotic agents, and to manage vascular risk factors appropriately.

Case 1 Resolution

The clinical scenario in Case 1 was concerning for a TIA. Despite resolution of the patient's symptoms, his brain MRI showed a small area of diffusion restriction consistent with ischemic stroke in the right dorsal pontomedullary region. His blood pressure was 185/90. Echocardiogram, cervical and cerebral vessel imaging, fasting lipid panel, and heart rhythm monitoring were normal. His aspirin was switched to clopidogrel, and his blood pressure management was optimized. He had no further cerebrovascular events.

Case 2

An 81-year-old woman with a history of osteoarthritis, polymyalgia rheumatica, and hypertension presents for evaluation of three episodes of diplopia. Each episode was binocular and horizontal. The first episode occurred 1 week ago, and the second and third episodes occurred yesterday. The patient cannot identify any triggers. Specifically, she denies a diurnal pattern or precipitation by fatigue. She complains of new right temporal headache in the last 4 weeks but denies other associated symptoms. On examination, she has moderate tenderness in the right temple and 2+ temporal artery pulses. The rest of her neurological and ophthalmological examinations is normal.

What is the most appropriate next step for this patient?

(a) No further workup
(b) Carotid Doppler
(c) Check erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelets
(d) Check ESR only
(e) Single fiber electromyogram

The most appropriate next step is to *(c) check ESR, CRP, and platelets*. The patient's age, history of polymyalgia rheumatica, new onset headaches, and temporal tenderness are concerning for giant cell arteritis (GCA). ESR, CRP, and platelet values can help the provider to determine whether treatment and further diagnostic testing for GCA should be undertaken.

Giant Cell Arteritis

Diplopia, including transient diplopia, can be the initial manifestation of GCA due to ischemia of the ocular motor cranial nerves, extraocular muscles, or vertebrobasilar circulation [9–13]. It is important to recognize the possibility of GCA promptly in order to initiate appropriate workup and treatment to prevent further ischemic sequelae, such as arteritic anterior ischemic optic neuropathy. A multicenter retrospective study demonstrated that compared with diplopia from other causes, patients with diplopia from GCA are more likely to have systemic GCA symptoms (e.g., headache, jaw claudication, scalp tenderness) and elevated inflammatory markers [9]. When older individuals present with transient diplopia, it is prudent to perform a thorough review of systems for systemic GCA symptoms as well as to consider checking the ESR and CRP. If the clinical suspicion is high enough based on these factors, then corticosteroid therapy should be initiated and appropriate diagnostic procedures should be performed. GCA will be covered in more detail later in Chap. 23.

Case 2 Resolution

The patient in Case 2's ESR was 98 mm/h (upper limit of normal corrected for age 45.5 mm/h), and her CRP was 25 mg/L (laboratory defined upper limit of normal 10 mg/L). She was immediately started on prednisone 1 mg/kg, and a temporal artery biopsy showed granulomatous inflammation of the vessel wall with disruption of the internal elastic lamina, consistent with GCA. She had no further episodes of diplopia, and her headaches resolved. She was slowly tapered off prednisone over 18 months.

Conclusion

Beyond TIA and GCA, there are a wide variety of pathologies of the ocular motor system that can cause transient diplopia. Some of these, such as ocular neuromyotonia and cyclic oculomotor palsy, are very rare, while others, such as medication side effects and myasthenia gravis (MG), are more common. A detailed history of transient diplopia should include a review of medications to search for a possible medication side effect. Several medications have been associated with diplopia, including anti-seizure medications (lacosamide, zonisamide, pregabalin, gabapentin, levetiracetam, topiramate, and lamotrigine), neurotoxins (botulinum toxin), antihypertensive agents (amlodipine), and cholesterol-lowering agents (pravastatin), among others [14]. MG is another relatively common cause of transient diplopia. Classically, MG causes diplopia that worsens with fatigue or toward the end of the day. When concerned about MG, the provider should ask about other neuromuscular symptoms including ptosis, dysarthria, dysphagia, and neck and extremity weakness, and perform diagnostic testing such as ice testing, serology for acetylcholine receptor antibodies, and single fiber electromyogram. The management of MG will be covered in detail in Chap. 24. Clinicians should be aware that diplopia from a long-standing decompensated misalignment can also occur when patients are fatigued [2].

Creating a truly exhaustive summary of the causes of specifically transient diplopia is challenging, as one can argue that if an individual's fusional capacity varies, then anything that causes diplopia could cause transient diplopia. Table 11.2 summarizes the causes of diplopia that are likely or somewhat likely to present transiently. Many of these conditions will be covered in more detail in other chapters of this book.

Table 11.2 Causes of transient diplopia by localization and mechanism

Localization	Mechanism	Diagnosis
Brain parenchymal (internuclear, nuclear, fascicular)	Vascular	**TIA** [15, 16] **Vertebrobasilar insufficiency** Vascular malformations Arteriovenous fistulae [18]
	Demyelinating	Multiple sclerosis
	Metabolic	Wernicke encephalopathy
	Other	Convergence spasm Convergence insufficiency Divergence insufficiency
Cranial nerve	Vascular	Microvascular cranial nerve palsy **GCA** Aneurysmal compression
	Trauma	3rd, 4th, or 6th nerve palsy
	Compressive	Meningioma, other tumors
	Other	Cyclic oculomotor palsy Ocular neuromyotonia [17] **Superior oblique myokymia**

Table 11.2 (continued)

Localization	Mechanism	Diagnosis
Neuromuscular junction	Autoimmune	**MG** **Lambert-Eaton myasthenic syndrome**
	Pharmacologic	Botulinum toxin
Extraocular muscle	Autoimmune	Thyroid orbitopathy
	Trauma	Muscle entrapment
Other	Medication side effects	
	Procedure complications	**Local or spinal anesthesia** [19, 20] Ocular or periocular surgery [21]

Abbreviations: *GCA* giant cell arteritis, *MG* myasthenia gravis, *TIA* transient ischemic attack
Bolded diagnoses are likely to present with a normal examination, whereas nonbolded diagnoses are likely to have some abnormal findings on a careful ocular motor examination

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Third Nerve Palsy

12

Thomas M. Bosley

Case

An 81-year-old hypertensive, diabetic, hyperlipidemic gentleman came to the emergency room with the report of right periorbital pain beginning 1 week before in association with diplopia that gradually worsened, then disappeared abruptly, simultaneous with the appearance of complete ptosis on that side. His pain gradually improved after onset, and he denied periorbital edema, visual change, or other neurologic problems. On neuro-ophthalmologic examination, his visual acuity was 20/25 in both eyes with excellent color vision and no relative afferent pupillary defect. His pupils were equal in size and briskly reactive to light. His optic disks, maculae, and retinal peripheries appeared normal except for background diabetic retinopathy. He had no inflammatory cells in the anterior chamber or vitreous on either side. He had complete right ptosis and a normal left palpebral fissure. He had no proptosis and no pain or increased resistance on orbital retropulsion. There was no right eye movement in adduction, elevation, or depression, but ocular motility of the left eye was full. He had a moderate exotropia and left hypertropia in primary gaze with the right eye located down and out compared with the left, his fixating eye. The remainder of his neurologic exam was non-focal.

Questions

- Is the eye movement abnormality an isolated oculomotor nerve (OMN) palsy?
- What additional observations can help with the differential diagnosis of this OMN palsy?
- What additional testing can help with the differential diagnosis?
- What caused this patient's OMN palsy?

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Introduction

Clinical management of OMN palsies is a somewhat complicated topic. The OMN controls four of the six muscles of ocular motility in addition to innervating muscles that, in part, move the lid and the pupil. The OMN follows a complex anatomic course from the midbrain to the subarachnoid space, to the cavernous sinus, and eventually to the orbit. Damage to the OMN in any of these locations may result from some pathologic processes that are benign (and may resolve spontaneously) and other processes implying medical emergencies with potentially lethal implications. These features have, not surprisingly, made the OMN of particular interest to neurologists, ophthalmologists, and neuro-ophthalmologists, an interest reflected in a number of excellent review articles over the last decade or two [1–4]. The differential diagnosis of an OMN palsy is broad, and the clinician must make the correct diagnosis before deciding on the correct treatment.

Evaluation of OMN palsies has a unique place in clinical neuro-ophthalmology because the anatomy of the nerve is unusually complex, because the clinical diagnosis of strabismus and ptosis involves consideration of pathologic processes other than OMN palsies, and because the potential etiologies of OMN palsies include several particularly dangerous diagnoses. The clinician's task is to decide whether a patient's ocular motility problem is due to an isolated OMN palsy, to an OMN palsy plus some other focal neurologic defect, or to some disorder that mimics an OMN palsy. Therefore, the process of diagnosing an OMN palsy always involves answering a few additional clinical questions.

Is This Problem Really an OMN Palsy?

The OMN is responsible for adduction (by innervating the medial rectus), elevation (by innervating the superior rectus), depression (by innervating the inferior rectus), and excyclotorsion (by innervating the inferior oblique) of the ipsilateral globe, and an OMN palsy will affect some or all of these movements. In addition, the ipsilateral lid and pupil are innervated in part by the OMN so that damage to the nerve may result in partial or complete ptosis of the ipsilateral lid and/or mydriasis of the ipsilateral pupil.

It is not uncommon for a clinician to be referred a patient with what is thought to be an isolated adduction problem caused by an internuclear ophthalmoplegia in a vasculopathic patient who may have evidence of an elevation or depression limitation and/or mild ptosis that were previously unrecognized, raising the possibility that the motility abnormality is due to an OMN palsy. Alternatively, such a patient might have ocular myasthenia gravis, particularly if there is binocular involvement or an abduction defect that cannot be due to an OMN palsy, or the patient might have this ocular motility pattern due to thyroid eye disease or orbital inflammatory disease. Mild proptosis and/or conjunctival and periorbital edema may provide clinical clues about orbital involvement, and the patient may have ptosis (possibly due to OMN involvement or myasthenia) or lid retraction (possibly due to thyroid eye disease).

Is the Injury in the Midbrain?

The OMNs begin in the midbrain in third nerve nuclei paired near the midline. Each nucleus is made up of a number of subnuclei responsible for innervating the four muscles of ocular motility controlled by the OMN together with a subnucleus that spans the midline and is responsible for the function of the levator muscles. Subnuclei on each side innervate muscles in the ipsilateral orbit except that fibers from the superior rectus subnuclei are crossed, with the right subnucleus innervating the left superior rectus and vice versa, resulting in the observation that nuclear OMN palsies commonly cause a contralateral upgaze paresis [5]. Such a lesion may also cause ipsilateral mydriasis (due to involvement of the Edinger-Westphal nucleus) or bilateral ptosis (due to involvement of the caudal central nucleus) [1]. These syndromes are most commonly caused by vascular injuries (infarction or hemorrhage), mass lesions, or inflammation.

Fibers from the subnuclei join to form the fascicular portion of the OMN on each side that runs forward through the cerebral peduncles before exiting anteriorly into the CSF space. Fascicular injury can cause dysfunction of the superior division (causing ptosis and limited upgaze) [6] or inferior division (causing limitation of adduction and downgaze) of the OMN or of the entire nerve, making it difficult to distinguish this injury from fascicular injuries involving other locations along the course of the nerve [7–9]. An isolated OMN palsy may also be caused by a rare mass in the cerebral peduncle such as a glioependymal cyst in a child [10].

Injury to the fascicular OMN within the midbrain is often accompanied by clinical evidence of additional brainstem damage that aids in localization. A brainstem mass may cause an OMN palsy and ipsilateral cerebellar ataxia (resulting from involvement of the brachium conjunctivum, called Nothnagel syndrome); or contralateral ataxia (called Claude syndrome); or a contralateral tremor (from a lesion in the region of the red nucleus, called Benedikt syndrome); or a contralateral hemiparesis (from a lesion of the ipsilateral cerebral peduncle, called Weber syndrome) [11, 12]. These lesions are most commonly caused by vascular injuries (stroke or hemorrhage from a vascular malformation), neoplasms (including metastases), or inflammation (including demyelination).

Is the Injury in the Subarachnoid Space?

The right and left OMNs then traverse the subarachnoid space, moving forward between the superior cerebellar artery and the posterior cerebral artery on either side. The nerve in this portion of its course lies free within the cerebrospinal fluid but is nevertheless vulnerable to expansion or hemorrhage of aneurysms of nearby vessels (internal carotid artery, posterior cerebral artery, posterior communicating artery), hemispheric masses causing uncal herniation [13, 14], intrinsic tumors (e.g., schwannomas) [15, 16], or inflammation or infiltration caused by processes involving the meninges and/or cerebrospinal fluid (e.g., bacterial or fungal meningitis or involvement by a subarachnoid malignancy). These processes may cause headache,

cognitive changes, or a contralateral hemiparesis in addition to an ocular motility abnormality. In this area the OMN may also be vulnerable to changes in CSF dynamics including both high and low intracranial pressure [17].

Two specific pathologic processes causing isolated OMN damage within the subarachnoid space are worth highlighting. The OMN is unique among the nerves of ocular motility in that it is exposed to the subarachnoid space while lying superior to the posterior portion of the cavernous sinuses [18], in the area where a posterior communicating artery aneurysm may occur [14]. Pupil enlargement in the setting of an OMN palsy (often with a severe headache) raises the possibility that the OMN may be compressed (particularly superolaterally, where the pupillary fibers run) by an expansion or hemorrhage of a posterior communicating artery aneurysm that compresses the OMN in an area where other cranial nerves of ocular motility are protected within the cavernous sinus.

The most common cause of a partial or complete, isolated, pupil-sparing OMN palsy is microvascular damage caused by small vessel atherosclerotic disease affecting the nerve in or near its course through the subarachnoid space or cavernous sinus [19]. In this setting, typically the pupil is not significantly involved even if the OMN palsy is otherwise complete. The syndrome appears most commonly in individuals greater than 50 years old who have a number of vascular risk factors. Poorly controlled diabetes may be the most important of these risk factors, and individuals younger than 50 with long-standing diabetes may be at risk for microvascular injury as well. Some diabetic patients may even develop an OMN palsy after improved diabetic control [20]. With this type of injury, ipsilateral periorbital pain may begin several days prior to diplopia or ptosis, but the pain commonly lasts only for a week or two before remitting. The ocular motility abnormality resolves spontaneously over a period that averages 3–5 months but may be as long as a year, and this gradual resolution without treatment helps confirm the diagnosis [21]. Individuals who develop this problem are also at risk of developing additional microvascular cranial nerve injuries involving nerves of ocular motility either simultaneously or sequentially. This problem may be more common in parts of the world where atherosclerotic risk factors are currently more poorly controlled [21, 22]. Microvascular OMN palsy is a diagnosis of exclusion and other causes [23, 24] or associations [25] are possible, including an unexpected mass [26].

Is the Injury in the Cavernous Sinus?

The OMNs then dive through the roof of the cavernous sinus and travel through the superior portion of the anterior cavernous sinus together with other nerves of ocular motility, the oculosympathetic nerves, and the first and second branches of the trigeminal nerve to reach the posterior orbit via the superior orbital fissure. In the cavernous sinus, the OMN is potentially contiguous with masses or pathologic processes that may occur in the sella or suprasellar region or in the cavernous sinus itself. These processes may cause OMN palsies by expanding abruptly (e.g., pituitary apoplexy), very quickly (e.g., infection, cavernous sinus thrombosis, carotid cavernous fistula,

inflammation), or gradually (e.g., progressive mass lesions). Permanent or transient OMN palsies may result either from changes in one of these processes or from surgery [27]. Oculosympathetic injury may result in a small or mid-size pupil (Horner syndrome), and involvement of V1 and/or V2 will cause facial pain, numbness, and/or paresthesias. Injury to one or more of the ipsilateral nerves accompanying the OMN by a tumor, inflammatory process, or pituitary apoplexy helps to localize OMN damage to the cavernous sinus. In addition, the cavernous sinus is the vein that drains blood from the orbit, and a large cavernous sinus mass or thrombosis may obstruct venous outflow from the orbit and cause proptosis and periorbital edema in addition to injuring nerves of ocular motility. These processes are generally more common in adults, but on occasion they may occur in children [28].

Is the Injury in the Orbit?

The OMN transits from the cavernous sinus into the orbit through the superior orbital fissure, where it very quickly splits into superior and inferior divisions and then smaller branches. Therefore, a mass or inflammatory process in the posterior orbit may cause injury to the superior or inferior division of the OMN (relatively uncommon outside of the orbit), a superior orbital fissure syndrome (involving more than one of the nerves of ocular motility, and possibly including V1) [29], or an orbital apex syndrome (involving one or more of the nerves of ocular motility together with the optic nerve) [30]. A mass effect within the orbit caused by a process that also injures the OMN may result in proptosis, periorbital edema, and/or conjunctival edema that help to localize the injury to the orbit. Of course, it is also possible for one or more extraocular muscles to be damaged (possibly by infarction or inflammation) within the orbit in a fashion that may look like a partial OMN palsy [31].

Some OMN palsies resist an anatomic localization despite thorough clinical evaluation. A microvascular OMN palsy in a vasculopathic adult falls into this category since pathology is limited because patients rarely die of this disorder [19]. In addition, a young person (average age at onset of 8 years) may rarely experience recurrent, remitting, unilateral OMN palsies over a period of years. This was initially considered to be a migraine variant [32] or ophthalmoplegic migraine [33]. In 2013 the International Headache Society revised their classification, renaming the disorder as recurrent painful ophthalmoplegic neuropathy (RPON) because of concern regarding the pathology of the process [34], and a question regarding whether migraine is involved at all [35]. This uncertainty, and uncertainty regarding the localization of the injury, persist [36].

What Was the Time Course?

A critical component of the clinical evaluation of patients who have an OMN palsy is the time course of the onset, progression, and resolution of the problem. Microvascular OMN palsies, for example, may (or may not) begin with pain

followed within a day or two by diplopia. The ocular motility disturbance may progress over a period rarely longer than 2 weeks and then gradually recovers over 3–5 months [21]. Another important clinical scenario to recognize is the apoplectic onset of a pupil-involving OMN palsy commonly associated with a severe headache and neck stiffness in the setting of an expanding or ruptured posterior communicating artery aneurysm [37, 38]. This constellation of signs and symptoms should not be ignored, although a clinically similar symptom complex can occur with pituitary apoplexy or a hemorrhage into a highly vascular mass in close proximity to the course of the OMN. The abrupt onset of an OMN palsy with ipsilateral or contralateral upper motor neuron or basal ganglion signs may point to an injury involving the nuclear or fascicular portion of the nerve together with nearby brainstem parenchyma. Orbital or cavernous sinus processes (inflammation or an expanding benign or malignant mass) may cause increasing signs and symptoms over a period of days to weeks or even longer.

Would Additional Testing Be Helpful?

It is widely accepted that an individual younger than 50 who develops an OMN palsy for unclear reasons should receive neuroimaging [39–41], generally an MRI scan of the brain and orbits, with MR or CT angiography. If an MRI is not available or cannot be employed for technical reasons, a CT and CTA with and without contrast are useful [42]. In patients older than 50, microvascular palsies become by far the most common etiology [39], but neuroimaging to investigate alternative etiologies is suggested for individuals who have any pupil-involving OMN palsy, a pupil-sparing partial OMN palsy, cancer of any type, other localizing signs or symptoms, or a time-course that has not begun to improve within 1 month or has not resolved completely within 3 months [43, 44]. These have proven to be reasonable guidelines, but availability and clinical yield of neuroimaging continues to improve, the cost has decreased, the risk has declined, and neuroimaging case reports continue to appear showing unanticipated lesions warranting clinical consideration [15, 34, 45–48]. It may be, therefore, that these criteria should be relaxed and that neuroimaging should be performed more often. Due to the concern for aneurysmal compression producing OMN palsies, which is life threatening due to the impending risk for aneurysm rupture and subarachnoid hemorrhage, urgent noninvasive angiography is indicated in all cases requiring neuroimaging. A posterior communicating artery aneurysm must be at least 3–4 mm in size to cause a compressive OMN palsy [49]. While digital subtraction angiography is the gold standard for vascular imaging, it is an invasive procedure with risk for complications, including embolic stroke in 1–2% [50]. Modern noninvasive angiographic techniques, including both CTA and MRA, have been shown to have excellent sensitivity for detecting aneurysms over 3 mm in size [51, 52]. Therefore, both MRA and CTA are technically adequate for evaluating for and excluding aneurysmal compression in the setting of third nerve palsy. However, it is strongly advised that the noninvasive angiogram be reviewed by a fellowship-trained neuroradiologist with accurate clinical information

regarding the diagnosis of OMN palsy and the clinical concern for aneurysm to prevent false-negative interpretations of these scans [49].

It is also widely accepted that systemic inflammatory diseases such as giant cell arteritis (GCA) can injure the OMN. Therefore, it is wise to obtain a panel of blood tests on patients older than 50 that includes a CBC with platelets, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) to evaluate the possibility of GCA [53–56]. Antinuclear antibodies (ANA) are a reasonable consideration given that systemic lupus erythematosus [57–59] and other system inflammatory diseases are possible pathologic mechanisms. In addition, syphilis [60, 61] and Lyme disease [62, 63] can damage the OMN, and testing for these infections is a reasonable choice.

Case Resolution

The gentleman described at the beginning of this chapter had an isolated pupil-sparing right OMN palsy that began abruptly with pain lasting approximately 1 week but without other localizing features. The patient had no history of malignancy, no signs of infection, and no symptoms of systemic disease. For these reasons, it seemed obvious that additional testing would be helpful. MRI of the brain and orbits with and without contrast showed microvascular changes and some diffuse cortical atrophy appropriate for his age and vasculopathic history with no evidence of a mass. CBC, CRP, VDRL, and ANA were normal. Electrolytes were normal except for a mild elevation of BUN, a modest elevation of glucose, and a creatinine of 2.1, likely all compatible with uremia due to poorly controlled diabetes. ESR measured 79, so GCA became a consideration [53, 55, 64–66] even though he was of Middle Eastern ethnicity [21], had modest diabetic nephropathy, and had no systemic symptoms. He was admitted, placed on prednisone 80 mg daily, and scheduled for a temporal artery biopsy (TAB) 2 days later. During the intervening day prior to TAB, he began to complain of abdominal pain that by the next day was quite bothersome. He developed a fever on the day that his TAB was reported positive for granulomatous arteritis, and he was transferred to a general medical unit, where the diagnosis of bowel infarction due to GCA was made despite prednisone treatment from the time of admission. Unfortunately, he died several days later.

This gentleman had a complete, pupil-sparing right OMN palsy with pain at onset in the range of what might be expected in the setting of a microvascular cranial mononeuropathy [21]. Risk factors for a microvascular palsy also included age, poorly controlled diabetes, and hypertension. However, pupil-sparing OMN palsies occur in GCA and, in fact, are more common than pupil-involving OMN palsies [56]. Therefore, the decision was made to perform a TAB. Bowel infarction is one of the more severe systemic manifestations that may occur in the setting of GCA [67–70] and, unfortunately, caused the death of this older gentleman. This case illustrates the breadth of pathologic processes that can injure the OMN and is presented here to emphasize the importance of both clinical assessment and laboratory testing in thinking through the unusually broad differential diagnosis in OMN palsies.

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Sixth Nerve Palsy

13

Praveen Jeyaseelan and Amanda D. Henderson

Case 1

A 64-year-old man with a history of adenocarcinoma of the lung, diabetes, hypertension, and hyperlipidemia presents with 10 days of horizontal binocular diplopia. His afferent function and anterior segment and funduscopic examinations are unremarkable. Extraocular motility evaluation shows limitation of abduction of both eyes with a 30-prism-diopter (Δ) esotropia in primary gaze, which increases in lateral gazes. Neurologic assessment is otherwise unremarkable.

What is the best next step in management in this case?

(a) Observation with reassessment within 3 months
(b) MRI brain with and without contrast with high-resolution skull base images
(c) Strabismus surgery
(d) Prism glasses
(e) CT head and orbits with contrast

Case 2

A 52-year-old woman with no significant past medical history presents with 2 weeks of binocular diplopia. One week prior to the onset of her symptoms, she was kicked in the face by her 8-month-old granddaughter. She had a CT head without contrast that was read as normal 2 days after the onset of her symptoms. She has limitation of abduction of her left eye with a 6Δ esotropia in primary gaze

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worsening to 18Δ in left gaze. Ophthalmologic and neurologic examinations are otherwise unremarkable.

What is the best next step in management in this case?

(a) Observation with reassessment within 3 months
(b) MRI brain with and without contrast with high-resolution skull base images
(c) Lumbar puncture
(d) Prism glasses
(e) CT head and orbits with contrast

Case 3

A 68-year-old man with history of diabetes, hypertension, hyperlipidemia, and congestive heart failure presents with sudden onset of horizontal binocular diplopia associated with dull pain in the right eye. He has no prior history of cancer. His afferent examination is unremarkable. Extraocular movements show right eye abduction deficit, with a 30Δ esotropia in primary gaze, increasing in right gaze. Dilated fundus exam reveals moderate nonproliferative diabetic retinopathy in both eyes and is otherwise unremarkable.

What is the best next step in management in this case?

(a) Reassurance of patient, no further follow-up recommended
(b) Observation with reassessment within 3 months
(c) Urgent MRI brain with and without contrast with high-resolution skull base images
(d) Lumbar puncture
(e) Strabismus surgery

Management

For Case 1, the patient needs evaluation with (b) *MRI brain with and without contrast with high-resolution skull base images*. The patient is 64 years old and has vasculopathic risk factors, which indicate that he is at risk for a self-limiting microvascular cranial nerve palsy; however, his history of lung cancer mandates neuroimaging to evaluate for metastases to the brain, skull base, or leptomeninges. Additionally, the presence of *bilateral* sixth nerve palsies is highly suggestive of an underlying structural lesion or increased intracranial pressure and is another absolute indication for neuroimaging.

For Case 2, the best next step also is option (b) *MRI brain with and without contrast with high-resolution skull base images*. The patient is 52 years old, has no known vascular risk factors, and had only a minor head trauma preceding the onset of symptoms by a week. It is unlikely that a trivial head trauma would cause a cranial nerve palsy, and even less likely that the onset would be delayed; therefore, it is

likely that the trauma is a red herring in this case. Although the patient had undergone a CT scan, CT is not sufficient for identifying structural lesions in the setting of a cranial nerve palsy. MRI allows for better visualization of soft tissue structures than CT, and the use of a gadolinium-based contrast agent improves visualization of lesions that cause breakdown of the blood-brain barrier, particularly inflammatory and neoplastic lesions. The acquisition of high-resolution skull base images further improves visualization of the cranial nerves.

For Case 3, choice (b) *observation with reassessment within 3 months* is an appropriate option. Elderly patients with vasculopathic risk factors, presenting with acute, isolated sixth nerve palsy, can be monitored for a presumed microvascular palsy, as long as there are no other features that necessitate neuroimaging. If, however, during the period of monitoring, new neurologic signs or symptoms occur, or if the palsy does not improve within 3 months, then neuroimaging with gadolinium-enhanced MRI is indicated. If, based on patient or physician preference, MRI is pursued initially, then it can be obtained on a non-urgent basis.

The sixth nerve nucleus is located in the caudal dorsal pons. From there, the fibers leave the nucleus as the sixth nerve fascicle, then exit the brainstem at the pontomedullary junction to travel within the subarachnoid space. The nerve fibers pass over the clivus and the petrous apex, then exit the dura mater to enter the cavernous sinus. Within the cavernous sinus, the sixth nerve travels lateral to the internal carotid artery, unprotected by dura, then enters the orbit via the superior orbital fissure within the annulus of Zinn and innervates the lateral rectus. Sixth nerve palsy is the most frequent isolated ocular motor nerve palsy, accounting for 50–59% of all isolated ocular motor nerve palsies [1–4].

Causes of sixth nerve palsy are shown in Table 13.1. In a large, population-based study, microvascular disease, in the setting of diabetes and/or hypertension, was reported to account for 49% of new, non-traumatic, isolated sixth nerve palsies; multiple sclerosis for 8%; and neoplasm for 2% [5]. Interestingly, all cases of neoplasm associated with isolated sixth nerve palsy in this study already carried the diagnosis prior to palsy onset. Due to sixth nerve anatomy, it is particularly prone to compression by tumors, and, of patients with an underlying structural lesion identified, neoplasm has been reported as the causative lesion for isolated sixth nerve palsy in 19–67% of cases [1–3, 6–9]. Because these studies predominately come from tertiary referral centers, and because the time course of included cases of sixth nerve palsy varies among studies, findings regarding overall incidence of neoplasm in these cases likely is not generalizable to all patients presenting with acute, isolated sixth nerve palsy.

When presented with a patient with acute, isolated sixth nerve palsy, the first question in management often is whether or not neuroimaging is required and, if so, what neuroimaging studies to order. Whether all such patients require neuroimaging is controversial. Some authors recommend imaging all acute, isolated sixth nerve palsies [6, 7], whereas others argue that non-traumatic, isolated sixth nerve palsy without any "red flags" may be amenable to a more limited workup and close monitoring [4, 5, 8, 10].

Table 13.1 Causes of sixth nerve palsy by location [1, 19, 29–33]

Brainstem
Ischemic
Demyelinating
Neoplastic
Subarachnoid space
Inflammatory
Infectious
Aneurysm
Increased intracranial pressure (false localizing sign)
Ischemic (microvascular)
Ophthalmoplegic migraine
Clivus/petrous apex
Inflammatory
Neoplastic
Traumatic
Cavernous sinus
Cavernous sinus thrombosis
Carotid-cavernous fistula
Neoplastic
Aneurysm
Inflammatory
Orbit
Neoplastic
Infectious
Inflammatory
Traumatic

Population-based data support the watchful waiting approach for patients presenting with acute, isolated sixth nerve palsy, when careful history and neurologic evaluation do not increase suspicion for an underlying structural lesion [5]. Miller et al. developed a practice pathway recommendation for acute sixth nerve palsy based on a retrospective chart review, in which they advised deferment of neuroimaging in cases of isolated, sixth nerve palsy in patients over age 55 with vasculopathic risk factors. In their study, 158 such cases were identified, 23 of which had undergone CT scan, and 81 of which had obtained MRI. In none of these cases was an underlying lesion identified, and none of these patients went on to develop further neurologic issues over a mean follow-up period of 6.5 years [10]. The authors showed that this approach would decrease the cost of evaluation. Additionally, reducing unnecessary neuroimaging could decrease patient inconvenience and discomfort. Several authors who support non-universal neuroimaging have suggested characteristics that should prompt neuroimaging, even in older patients with vascular risk factors, including trauma, history of cancer, progression or lack of improvement over a 3- to 4-month period, or development of other neurological signs or symptoms [8, 10].

Despite the data supporting a watchful waiting approach in some cases of acute, isolated sixth nerve palsy, other reports suggest that this approach could result in delayed diagnosis of underlying neurologic disease. One study, in which all patients with acute, isolated sixth nerve palsy underwent high-resolution MRI, found that 63% had a structural lesion [6]. The authors noted that 15% of those with an

underlying lesion, including two with metastases, one with meningioma, and one with cavernous carotid aneurysm, had a history consistent with vasculopathy. It was unclear whether those with metastases, a diagnosis that clearly would change acute management, had a prior history of cancer. Notably, those with a demonstrable lesion on MRI were younger and had lower frequency of vascular risk factors [6]. In another study, Chou et al. identified three cases, among a total of 23 acute, isolated sixth nerve palsies in patients age 50 and older, in which urgent MRI identified a causative lesion that the authors claimed would change acute management—one each of pituitary apoplexy, demyelinating disease, and brainstem infarct. It was not clear whether these individual patients had microvascular risk factors [7]. Similarly, Tamhankar et al. found that in a cohort of patients 50 years of age or older, with vasculopathic risk factors and no other significant past medical history, with acute, isolated sixth nerve palsy, two patients with structural lesions were identified—one each with B-cell lymphoma infiltrating the cavernous sinus and with petroclival meningioma [11]. These studies suggest that basing the decision for deferment of neuroimaging an acute, isolated sixth nerve palsy on a vasculopathic history alone is not adequate, and they raise the question of whether all such cases should undergo MRI.

While microvascular palsies are common in older patients [5], sixth nerve palsies in patients younger than 50 are more concerning for underlying pathology, and these younger patients should undergo expeditious MRI [9]. Any patient with a history of cancer, no matter how remote, may be at risk for metastatic disease, and this finding would change immediate management. Therefore, every patient presenting with a cranial nerve palsy should be questioned specifically about any history of cancer. In the setting of a cancer history, MRI is indicated as part of the initial workup for an isolated sixth nerve palsy.

Any patient with a known pituitary adenoma could be at risk for apoplexy, and apoplexy has been reported to cause acute, initially isolated sixth nerve palsy [7, 12]. Therefore, any patient with a history of pituitary adenoma and a new cranial nerve palsy should receive expedited neuroimaging. Of course, the presence of altered mental status or other focal neurologic deficits also would be independent indications for emergent, same-day imaging.

In the case of significant head trauma, neuroimaging should be pursued to evaluate for temporal bone fracture, skull base fracture, or skull base epidural hematoma, which could cause damage to the sixth nerve. Minor trauma is less likely to cause a sixth nerve palsy, and it should not be assumed that such a palsy is related to trauma without excluding other causes on MRI [13, 14]. In cases in which fracture is suspected based on history, CT should be obtained, as it is superior to MRI for evaluating for bony abnormalities.

While studies have demonstrated that delayed neuroimaging does present the potential for missing some structural lesions in patients with acute, isolated sixth nerve palsies, the use of a careful history for selection of patients who require more urgent neuroimaging markedly decreases the risk of missing dangerous pathology that would affect immediate management decisions. We recommend neuroimaging for any cases of acute, isolated sixth nerve palsy in patients:

- Younger than 50 years of age
- Without known microvascular risk factors
- With any history of cancer, whether active or remote
- With a history of pituitary adenoma
- With a recent history of trauma
- With a prior history of cranial nerve palsy

We also recommend neuroimaging in any case of non-isolated sixth nerve palsy, as well as any case that does not resolve within 3 months after onset.

The presence of other focal neurologic findings, specifically, the presence of bilateral sixth nerve palsies, multiple cranial nerve palsies, papilledema, or meningeal signs, should prompt MRI, as the coexistence of multiple focal neurologic findings makes microvascular palsy quite unlikely. Specific combinations of focal neurologic signs may assist with localization of an underlying structural lesion, and this topic will be covered in detail in Chap. 15. It is worth mentioning specifically that, although multiple cranial nerve palsies typically are expected in the setting of a cavernous sinus lesion, the central location of the sixth nerve adjacent to the internal carotid artery within the cavernous sinus places it at higher risk of injury than the other cranial nerves that are protected by the dura in the lateral wall of the sinus. Therefore, a cavernous sinus lesion may affect the sixth nerve first and only involve other cranial nerves and/or the sympathetic fibers later in the course.

Increased intracranial pressure can present with sixth nerve palsy as a false localizing sign [15]. Therefore, space-occupying lesions (even when not directly affecting the sixth nerve), pseudotumor cerebri, and cerebral venous sinus thrombosis all may be associated with sixth nerve palsy. Notably, patients with sixth nerve palsy related to one of these issues would be expected to present with other symptoms and signs of increased intracranial pressure. Bilateral sixth nerve palsies should be treated as a case of multiple cranial neuropathies, with strong suspicion for either a structural lesion or increased intracranial pressure. A study of 69 patients with bilateral sixth nerve palsies showed that trauma, vascular lesions, and tumors accounted for most cases, although only 36% of cases had direct sixth nerve involvement, with the remainder mediated by indirect processes like increased intracranial pressure. There was only one case of bilateral sixth nerve palsy ascribed to a vasculopathic cause, indicating that bilateral sixth nerve palsies rarely are microvascular and emphasizing the importance of neuroimaging in these cases [16].

Even in the setting of an acute, currently isolated sixth nerve palsy, we recommend neuroimaging for patients who have a prior history of cranial nerve palsies that have resolved. While recurrent microvascular palsies have been described in the literature [4, 17, 18] and are encountered not infrequently in clinical practice, recurrent palsies nonetheless warrant further evaluation [19, 20].

Microvascular cranial nerve palsies typically are expected to resolve within 3 to 4 months [10]. A deviation from this expectation, in a case being monitored as a presumed microvascular palsy, should prompt neuroimaging with MRI, as would be recommended in cases of chronic sixth nerve palsy [21].

Monitoring without neuroimaging can be considered in patients age 50 and older with established vascular risk factors—such as diabetes mellitus, hypertension,

hyperlipidemia, coronary artery disease, signs of hypertensive end-organ damage like left ventricular hypertrophy, and smoking [5, 11, 4, 22, 23]—and no other indications for neuroimaging. Microvascular palsy is likely in these cases, and dangerous underlying pathology is unlikely. Progression of ophthalmoplegia within the first few weeks after onset of a microvascular sixth nerve palsy is common and not an indication for further workup [24].

MRI with contrast is the imaging modality of choice for the evaluation of sixth nerve palsy. MRI is superior to CT for visualization of soft tissue detail, specifically, ischemic stroke, tumor, and edema, and the addition of a gadolinium-based contrast agent allows for better visualization of any lesion that produces blood-brain barrier disruption. Focused imaging with special sequences can help in the early identification of structural lesions. Orbital fat produces a bright signal on T1-weighted (and to a lesser degree, T2-weighted) MRI sequences. The use of fat saturation, included in most orbital MRI protocols, suppresses the bright signal typically produced by fat within the orbit, thus allowing for improved visualization of pathology within the orbit [25]. High-resolution three-dimensional (3D) MRI sequences of the skull base allow for visualization of the sixth nerve along most of its course, and thus are able to identify structural lesions in areas not well evaluated by conventional MRI [26]. Specifically, the cisternal portion of the sixth nerve can be identified in 98% of cases using high-resolution 3D MRI versus only 13% using conventional T2-weighted MRI with fat saturation [27]. Similarly, the cavernous portion of the sixth nerve can be visualized in 95% of cases using high-resolution, contrast-enhanced 3D MRI versus only 65% with conventional contrast-enhanced MRI [28].

In the right clinical scenario, additional medical investigations may be considered in the workup of an acute, isolated sixth nerve palsy, and this testing should be guided by the history. As giant cell arteritis can cause an isolated cranial neuropathy, a thorough history, asking about headache, scalp tenderness, jaw claudication, fever, weight loss, and polymyalgia rheumatica, should be completed in any patient over age 50. If giant cell arteritis is suspected, then serum laboratory tests, including complete blood count, erythrocyte sedimentation rate, and C-reactive protein, are indicated. Based on clinical suspicion and laboratory results, urgent steroid treatment and temporal artery biopsy should be considered.

If there is concern for an infectious or inflammatory etiology based on young age, lack of vascular risk factors, or other historical data, then MRI is indicated, along with appropriate serologic testing. Social history may identify risk factors for syphilis or Lyme disease that may prompt additional serologic workup. Further inflammatory workup, including serologic testing, lumbar puncture with cerebrospinal fluid analysis, and chest CT, may be pursued if MRI evidence suggests an underlying inflammatory condition.

When diagnosing sixth nerve palsy, mimickers, including myasthenia gravis and medial rectus restriction from Graves ophthalmopathy or myositis, also may be considered. Symptom variability or fatigability would be suggestive of myasthenia, as would associated ptosis, dysphagia, dyspnea, and proximal weakness. A history of thyroid disease, as well as presence of lid retraction, lid lag, proptosis, or restriction, would indicate further workup for Graves ophthalmopathy.

Case Resolution

In Case 1, MRI of the brain with and without contrast with high-resolution skull base sequences showed heterogeneous enhancement of the clivus, consistent with bony metastasis causing his bilateral sixth nerve palsies. Lumbar puncture had normal opening pressure with no evidence of malignancy. He underwent external beam radiation to the skull base and continued systemic chemotherapy. Subsequent follow up showed mild improvement of abduction in both eyes with significant residual esotropia. After stable alignment was demonstrated, he underwent strabismus surgery with an excellent result.

In Case 2, MRI brain with contrast with high-resolution skull base sequences showed an enhancing mass of the left cavernous sinus with a dural tail, consistent with a meningioma. Radiation therapy was offered, but the patient elected monitoring with serial MRI.

In Case 3, the motility deficit and misalignment completely resolved by 3 months after symptom onset, consistent with a microvascular palsy. No additional workup was pursued.

Conclusion

In conclusion, careful clinical evaluation, with a thorough history and examination, allows identification of patients with sixth nerve palsy who require expedited neuroimaging and those who may benefit from a watchful waiting approach. Specifically, any patient younger than 50 years old, or with a history of cancer or pituitary adenoma, recent trauma, prior cranial nerve palsy, or associated neurologic signs or symptoms requires imaging with gadolinium-enhanced MRI. Patients with sixth nerve palsy, none of the aforementioned risk factors, and known microvascular risk factors may be observed for presumed microvascular palsy. Microvascular palsies typically are expected to improve within 3 months, and absence of improvement should prompt neuroimaging at that point. Additionally, the appearance of additional neurologic signs or symptoms at any point is an indication to proceed with MRI.

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Fourth Nerve Palsy

14

Philip Kim and Amanda D. Henderson

Case 1

A 22-year-old man presents with binocular vertical diplopia when looking downwards for 3 months. He reports no diplopia in primary gaze. His past medical history is significant for a large quadrigeminal cistern cyst that was previously compressing the tectum and superior cerebellar surface, resulting in obstructive hydrocephalus. He underwent a suboccipital craniotomy for cyst fenestration, and, upon awakening from the surgery, he noted onset of diplopia. Examination demonstrates visual acuity of 20/20 in the right and left eyes. There is no relative afferent pupillary defect. Confrontation fields are full to finger counting in each eye. Extraocular motility testing demonstrates limitation of depression of both eyes in adduction. Results of cover test examination are shown in Fig. 14.1. Double Maddox rod testing reveals an excyclotorsion of 15 degrees. Anterior and posterior segment evaluations are unremarkable.

What is the most appropriate management for this patient?

(a) Observation +/− monocular occlusion
(b) Prismatic therapy
(c) Orthoptic exercises
(d) Strabismus surgery

This patient has postsurgical bilateral fourth nerve palsies. His symptoms of diplopia when looking downwards correlate with the cover test findings. His extraocular motility testing is consistent with bilateral superior oblique weakness, and he has a large excyclotorsion (greater than 10 degrees) with double Maddox rod testing,

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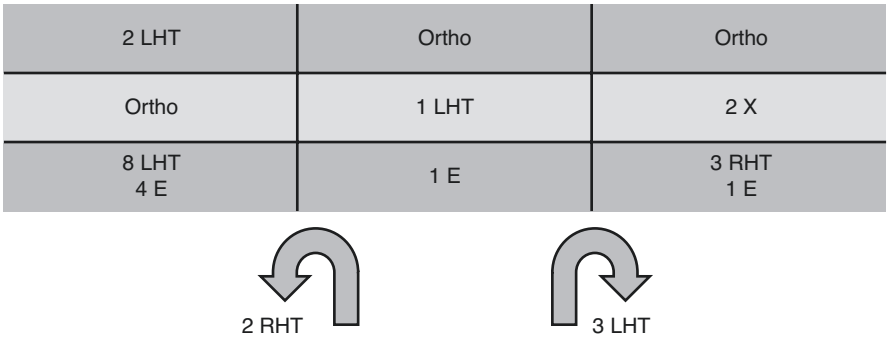

Fig. 14.1 Alternate cover testing shows a right hypertropia in down and left gaze and in right head tilt, and a left hypertropia in down and right gaze and in left head tilt

which strongly suggests *bilateral* fourth nerve palsies. Since he is not symptomatic for diplopia in primary gaze, prismatic therapy is not appropriate. Orthoptic exercises are not beneficial in the setting of cranial nerve palsy. While strabismus surgery could be considered when/if stability of his alignment has been demonstrated, the time course in this case makes the decision for strabismus surgery at this time to be premature (as the condition could improve without intervention). Therefore, (a) *observation*, with monocular occlusion for symptomatic control as needed, is the best option for this patient.

Case 2

A 75-year-old man presents with worsening longstanding vertical diplopia. He is currently wearing prismatic spectacles to alleviate his vertical diplopia at distance. He has a pertinent history of non-insulin-dependent type 2 diabetes. During his initial visit, his visual acuity is 20/20 in the right and left eyes. Confrontation fields are full to finger counting in each eye, and there is no relative afferent pupillary defect. Extraocular motility testing demonstrates overaction of the left inferior oblique. His cover test is shown in Fig. 14.2. The patient also displays large vertical fusional amplitudes of seven prism diopters and a longstanding head tilt, present in previous photographs. His anterior and posterior segment evaluations are unremarkable.

What is the likely etiology of this patient's condition?

(a) Microvascular
(b) Compressive
(c) Congenital
(d) Traumatic

The likely diagnosis of this patient is a (c) *congenital* left fourth nerve palsy. The presentation of a longstanding diplopia with ipsilateral inferior oblique overaction,

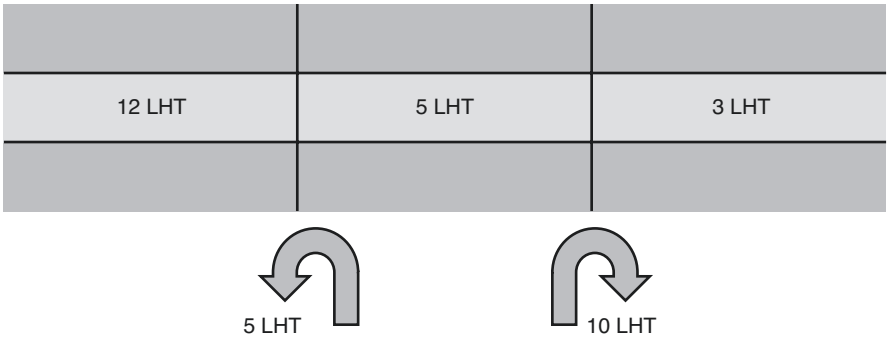

Fig. 14.2 Alternate cover testing shows a left hypertropia, worse in right gaze and left head tilt

large compensatory fusional vergence ranges, and contralateral head tilt supports a congenital etiology.

Anatomy

The trochlear nerve, also known as the fourth cranial nerve, is responsible for innervating the superior oblique muscle. It has the longest course of all cranial nerves and, thus, is easily susceptible to trauma. The fourth nerve nucleus originates at the level of the inferior colliculus of the midbrain, beneath the Sylvian aqueduct. From there, the fasciculi of the bilateral fourth nerves decussate. Then, each nerve emerges dorsally and curves forward around the brain stem, running beneath the free edge of the tentorium and passing between the posterior cerebral artery and the superior cerebellar artery to pierce the dura and enter the cavernous sinus, where the nerve runs laterally and inferiorly to the oculomotor nerve, above the first division of the trigeminal nerve. The fourth nerve then passes through the superior orbital fissure outside the annulus of Zinn to innervate the superior oblique muscle.

The superior oblique muscle originates from the body of the sphenoid bone and passes into the trochlea (a fibrous pulley that redirects the action of the superior oblique) by traversing along the medial border of the roof of the orbit. After looping through the trochlea, the superior oblique attaches to the sclera at the posterior temporal aspect of the globe. This pathway leads to three major functions of the superior oblique muscle: (1) the primary action of globe intorsion, (2) the secondary action of globe depression, and (3) the tertiary action of globe abduction.

Etiology

Traumatic injury is the most common cause of a trochlear nerve palsy [1–3]. The trochlear nerve is most susceptible to injury due to being the longest and thinnest of all the cranial nerves and is especially vulnerable to shear and crush injuries at the

area where its course passes the free edge of tentorium through the prepontine cistern [4]. Bilateral fourth nerve palsies are often due to injury at the anterior medullary vellum where the nerves decussate and can arise from minor head injuries without loss of consciousness or skull fractures [5].

Decompensation of a congenital fourth nerve palsy is another common etiology of symptomatic vertical diplopia associated with a trochlear palsy. Mostly presenting in adulthood, patients with a congenital fourth nerve palsy often have a longstanding compensatory head tilt that is contralateral to the side of fourth nerve involvement and can be affirmed through examination of past photographs. When this condition presents in a child, the primary complaint usually is torticollis rather than diplopia, as there is often central suppression in one eye [6]. In addition, other characteristics of congenital fourth nerve palsy include large hypertropia (often greater than 10 prism diopters), relatively mild and often intermittent symptoms of diplopia, inferior oblique overaction, and large compensatory vertical fusional amplitude (greater than three prism diopters).

Microvascular ischemia may cause an acquired fourth nerve palsy, particularly in patients over age 50 with vascular risk factors including hypertension, diabetes, and high cholesterol. As with other microvascular cranial nerve palsies, these fourth nerve palsies generally resolve spontaneously over the course of several months. Neuroimaging becomes a necessity if an acquired, presumed microvascular palsy does not improve within about 3 months of the onset of the diplopia, or when other neurological symptoms or signs are present.

Other causes of fourth nerve palsy may be due to infectious, inflammatory, or neoplastic etiologies. These conditions can also affect multiple cranial nerves, and neuroimaging is essential when multiple cranial nerves are affected. The management of multiple cranial neuropathies is discussed in detail in Chap. 15.

Examination

Extraocular motility and measurement of ocular alignment are the major tools to evaluate a patient presenting with diplopia. Motility testing can grossly discern a problematic extraocular muscle, isolate for one or multiple superior oblique muscle underactions, and evaluate for an associated overaction of the ipsilateral inferior oblique (suggesting a likely congenital etiology).

The cover (cover-uncover and/or alternate cover) tests or the Maddox rod test can be used to quantify diplopia in various gaze positions and, typically, will show a specific pattern in the setting of superior oblique weakness. Most often the alignment pattern of a fourth nerve palsy will reflect the expected outcomes of the Parks-Bielschowsky test in that the affected eye will have a hypertropia, with worsening of deviation in contralateral gaze and ipsilateral head tilt. The Parks-Bielschowsky three-step test historically has been the gold standard for diagnosing superior oblique palsy, but recent studies suggest that 30% of cases of superior oblique atrophy can be left undetected using this method [7]. This level of sensitivity may reflect longstanding palsies that have undergone spread of comitance, in which, over time,

alignment measurements may appear more uniform in the various gaze positions (i.e., more comitant), without the characteristic alignment pattern of hypertropia worsening in contralateral gaze and ipsilateral head tilt [8]. In our experience, there may be residual incomitance in head tilt in many of these cases, which may be suggestive of the underlying diagnosis.

Vertical deviations that do not map out to a fourth nerve palsy on alignment testing should be investigated for alternative causes including skew deviation, thyroid eye disease and other orbital processes, myasthenia gravis, and partial third nerve palsies. Furthermore, bilateral fourth nerve palsies will not match the characteristic alignment pattern in the traditional sense, as typically the ocular misalignment will have increasing deviation toward both sides of the lateral inferior gazes with a change in the hypertropia correlated with the problematic superior oblique.

In addition to extraocular motility and cover test examinations, double Maddox rod testing is often useful to quantify the degree of cyclotorsion in a patient's ocular misalignment. Due to the superior oblique's primary role of intorsion, weakness in the superior oblique will lead to relative excyclotorsion of the involved eye. A value of greater than 5 degrees is a positive yield, and a result of 10 or more degrees is suggestive of bilateral fourth nerve palsies. This test is also useful in clinically discriminating a fourth nerve palsy from a skew deviation, as the latter typically results in a relative intorsion as opposed to excyclotorsion.

Management

Compared with third and sixth nerve palsies, fourth nerve palsies are less likely to be caused by structural lesions like aneurysms and tumors [9–11], and this finding is explained by the anatomic characteristics of the nerves, as discussed further in Chaps. 12 and 13. Therefore, fourth nerve palsies are less likely to require neuroimaging than their third and fourth nerve counterparts. Imaging may not be necessary in chronic, stable fourth nerve palsies, particularly if there is evidence of congenital origin. However, we do recommend imaging with MRI with gadolinium enhancement in cases of fourth nerve palsy that show progressive worsening; acute onset in young patients or in patients without vascular risk factors; or association with other neurologic or systemic signs or symptoms.

The standard options for treatment of symptomatic diplopia from a fourth nerve palsy include prisms, occlusion therapy, and strabismus surgery. Trochlear palsies that are expected to resolve or change in severity or pattern within a few months may be treated with monocular occlusion versus prismatic therapy, with Fresnel prism placed over one spectacle lens. Fresnel prisms provide some notable advantages compared with ground-in prisms, including access to larger magnitudes of prismatic correction (up to 40 prism diopters), lighter weight, and a larger diameter of correction. However, Fresnel prism will induce blur in the eye over which the prism is placed, resulting in decreased patient satisfaction in some cases. While they provide improved cosmesis over monocular occlusion, Fresnel prisms are faintly

visible when placed on a spectacle lens and, therefore, are cosmetically unacceptable to some patients.

In patients with diplopia and stable ocular alignment who tolerate prismatic correction well, incorporating prism into the spectacle lenses may be the best choice. In these cases, unlike when using Fresnel prism, the prismatic correction should be split between the two lenses, thus reducing distortion in each individual lens and maintaining similar weight and thickness of the two lenses. In a recent study by Tamhankar, et al., ground-in prims resulted in high levels of satisfaction among patients with transient and stable diplopia [12]. These prisms are most beneficial for modest deviations of less than 10 vertical prism diopters, but reports from this study also shared some success in patients beyond this set standard. The overall advantages of ground-in prisms (compared with Fresnels) are better cosmesis, improved visual clarity and contrast, increased availability in optical dispensaries, and, in our experience, more success when addressing coexistent vertical and horizontal deviation compared with oblique Fresnel placement. In cases in which the vertical hypertropia is expected to be stable, such as in our patient with congenital etiology, ground-in prisms and extraocular muscle surgery are the first-line options for treatment. In these cases, patients require less prismatic strength for their diplopia, as they generally retain large vertical fusional amplitudes to assist in their fusion. Use of prism in these cases most often is restricted by patient tolerance of ground-in prismatic correction (standard upper limit remains approximately 10 prism diopters), and noticeable lens thickness and weight that becomes apparent near the upper limit. Additionally, while currently available prismatic technology can address both vertical and horizontal components of strabismus, it cannot provide any correction of torsion. When the magnitude of the prism is large, recommending a small lens size to minimize lens weight, high index material to reduce lens thickness, and splitting the prisms equally between both lenses for symmetry can improve patient tolerance of and satisfaction with the lenses. Overall, the success rate of prism therapy is reported to be as high as 92.8% in patients with congenital fourth nerve palsy and 86% in patients with acquired fourth nerve palsy [12].

Strabismus surgery is indicated for individuals with large angle strabismus that falls outside the capabilities of prisms, for those patients with a significant torsional component to their ocular misalignment (which cannot be addressed with prism), and for patients who do not tolerate prism glasses. Strabismus surgery should not be performed until stable ocular misalignment has been demonstrated for at least 4 to 6 months [1]. The goals of surgical intervention are to minimize vertical strabismus and to reduce anomalous head posture. Many surgical approaches are available with selection based on multiple factors including the magnitude of deviation and the presence of other extraocular muscle involvement. However, presently there is no general consensus regarding the best surgical approach for this disorder [4].

Case Resolution

The first patient was given the recommendation to set reading material at primary gaze (to decrease the functional limitation from his diplopia in down gaze) and was advised to return in 1 month. His diplopia improved with time, and he presently remains asymptomatic at distance in primary gaze.

The second patient received updated glasses with ground-in prism and has continued to do well with prismatic correction.

Summary

As discussed above, superior oblique palsy can manifest in several different presentations in the clinical setting. Patients most commonly display the hallmark features of the Parks-Bielschowsky three-step test. However, due to the heterogeneity of this condition, it is important to consider the disorder's many classifications and various mimickers; thus, performing additional testing may be necessary to attain the correct diagnosis. Neuro- and orbital imaging may be indicated when the vertical strabismus displays an atypical or nonspecific alignment pattern, and these imaging results can either support or refute the initial diagnosis of a superior oblique palsy. Multiple treatment options are available for fourth nerve palsy, and prismatic correction can lead to a high level of satisfaction but also can, at times, be limited due to its inability to correct for large deviations and torsion. Therefore, some cases require strabismus surgery to address these issues (after stability over the course of about 6 months has been demonstrated).

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Multiple Cranial Neuropathies

15

Anna M. Gruener

Case

A 57-year-old woman reports her eyes "not working properly together" for some time. Furthermore, she complains of tearing and discomfort in her right eye, alongside occasional self-limiting headaches. She has a visual acuity of 20/20 and 20/16 in the right and left eye, respectively. Pupil examination is normal. Ocular motility testing reveals a mild deficit in adduction and reduced range of vertical movements, all on the right side. Anterior segment examination of the right eye shows mild conjunctival injection and punctate epithelial erosions, with somewhat reduced corneal sensation. Dilated fundus examination is unremarkable. The Hess screen test shows features of a right third and fourth nerve palsy.

What is the patient's most likely diagnosis?

(a) Myasthenia gravis
(b) Mucormycosis
(c) IgG4-related disease
(d) Tolosa-Hunt syndrome
(e) Graves ophthalmopathy
(f) Cavernous sinus meningioma

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Management

Although the patient's history is somewhat vague (as is often the case), her presentation suggests a rather indolent disease process involving the third (III), fourth (IV), and ophthalmic division of the fifth (V_1) cranial nerve (CN), all on the right side, most consistent with (f) *cavernous sinus meningioma*.

The first step in managing a patient with multiple cranial neuropathies is to localize the lesion, which, in turn, requires some anatomical knowledge of the skull base and related structures. In neuro-ophthalmology, we are particularly concerned with the course taken by CNs II-VI.

Brainstem disease (e.g., due to stroke and multiple sclerosis) is generally accompanied by neighborhood signs (e.g., corticospinal tract dysfunction, nystagmus, gaze palsies, and internuclear ophthalmoplegia), and confirmed with MR imaging [1].

Traversing the subarachnoid space, cranial nerves may be subject to many disease processes affecting the CSF, meninges, brain parenchyma, and vasculature. These include infections (bacterial, viral, and fungal) and neoplasms (e.g., lymphoma and leukemia), as well as inflammatory (e.g., neurosarcoidosis), vasculitic (e.g., giant cell arteritis and granulomatosis with polyangiitis), and paraneoplastic disorders [2–6]. Making the correct diagnosis can be challenging and may involve repeat lumbar puncture and CSF analysis. Careful history taking (including travel, sexual practices, exposure to animals, tick bites, and immune status) is key, as is a full neurological examination that, in the context of multiple cranial neuropathies, is likely to reveal other signs.

On entering the cavernous sinus, CNs III, IV, V_1, and V_2 travel in its lateral wall, while CN VI lies in the substance of the cavernous sinus inferior and lateral to the internal carotid artery (Fig. 15.1). Sympathetic fibers are carried by the intracavernous internal carotid artery before briefly joining CN VI and then V_1. From the cavernous sinus, all ocular motor CNs (III, IV, and VI) enter the orbit through the superior orbital fissure, which is divided by the annulus of Zinn (Fig. 15.2). While the superior and inferior divisions of CN III and CN VI enter the orbit through inside the annulus, CN IV enters the orbit outside of the annulus. As for sensory nerves, terminal branches of V_1 (lacrimal, frontal and nasociliary) pass through the superior orbital fissure, while terminal branches of V_2 (infraorbital and zygomatic) take a more meandering course before entering the orbit through the inferior orbital fissure. Amid this crowded space lies the optic nerve (CN II), which passes through the orbital apex via the optic canal. Although CN II does not traverse the cavernous sinus, it lies in close proximity (Fig. 15.1).

As the orbital apex, superior orbital fissure, and cavernous sinus are neighboring anatomical structures, their syndromes and disorders manifest with similar symptoms and signs. Combinations of ocular motor nerve palsies present with many varieties of ophthalmoplegia that may be accompanied by partial or complete ptosis, anisocoria, and proptosis. Both mild ptosis and anisocoria should prompt consideration of autonomic nervous system involvement, and may help with lesion localization.

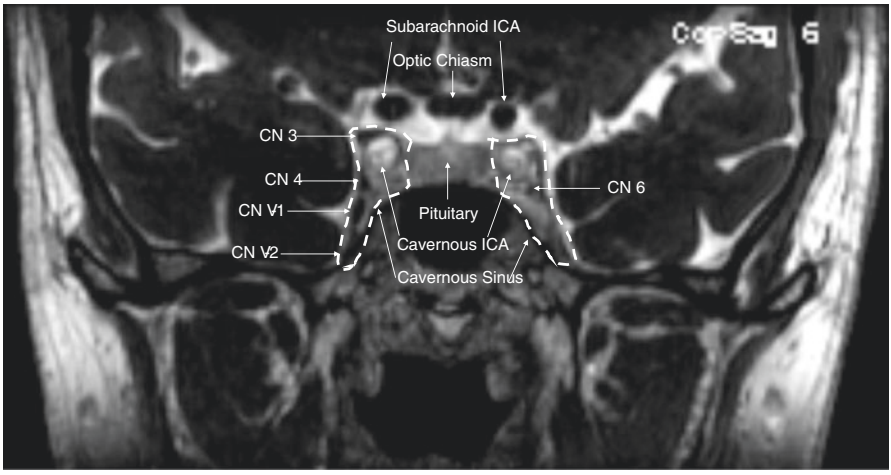

Fig. 15.1 Cavernous sinus. Coronal CISS MRI shows the structures of the cavernous sinuses (outlined by the dotted lines). CNs III, IV, V1, and V2 are protected within the dural wall of the cavernous sinus, whereas CN VI is located more medially within the cavernous sinus. (© AR Carey 2020. All Rights Reserved)

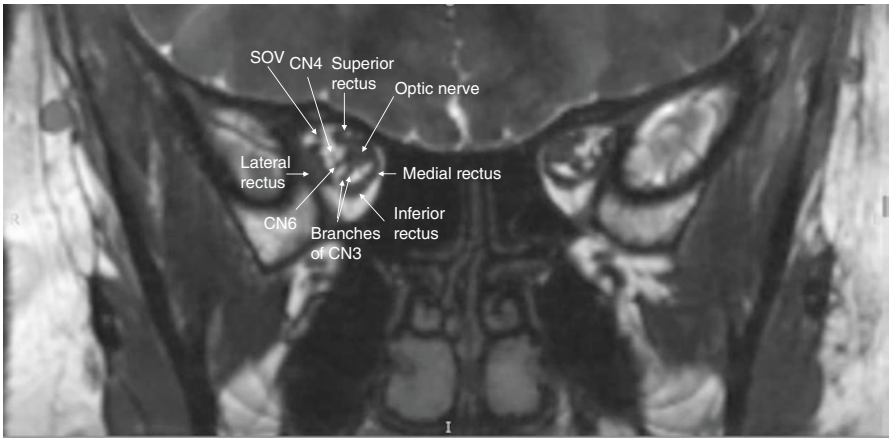

Fig. 15.2 Orbital apex. Coronal CISS MRI shows the structures of the orbital apex. CNs III, IV, V1, and VI enter the orbit through the superior orbital fissure (CNs III, nasociliary branch of V1 and VI within the annulus of Zinn, and CN IV and lacrimal and frontal branches of V1 outside the bounds of the annulus). (© AR Carey 2020. All Rights Reserved)

Overall, superior orbital fissure syndrome is rare, more often than not linked to trauma, and not accompanied by optic nerve involvement [7]. In contrast, multiple cranial neuropathies associated with signs of an optic neuropathy, with either a normal-appearing or pale optic disc, generally point toward an orbital apex syndrome, or, much less commonly, a cavernous sinus syndrome that has spread to involve the chiasm [8]. Optic disc swelling is very rare and more specific to an orbital apex

syndrome due to venous congestion. In addition, a postganglionic Horner syndrome, alongside a CN VI palsy, strongly suggests a lesion in the cavernous sinus (e.g., tumor or cavernous sinus fistula), as does involvement of V_2. Dysfunction of V_2 manifests as sensory disturbance of the midface, and, unless associated with trauma or surgery, indicates cancer (e.g., perineural spread from squamous cell carcinoma of the head and neck), infection (e.g., mucormycosis), or IgG4-related perineural disease [9, 10]. Enlargement of the infraorbital nerve may be detected clinically and on imaging, and biopsy may be indicated [11]. In the context of sudden-onset severe headache, marked visual loss (due to compression of the optic chiasm) and ophthalmoplegia (often bilateral due to cavernous sinus involvement) should lead to consideration of pituitary (tumor) apoplexy, which constitutes a neuro-ophthalmic emergency [12].

Infectious processes (e.g., mucormycosis) tend to present rather acutely and are generally accompanied by pain and systemic upset (e.g., fever and malaise). Cavernous sinus thrombosis, usually due to contiguous spread of infection (e.g., from paranasal sinusitis, a mid-facial infection or orbital cellulitis), is another neuro-ophthalmic emergency characterized by worsening pain, proptosis, orbital congestion, and ophthalmoplegia that may eventually involve both eyes [13, 14]. Pain in inflammatory disorders can range from severe (e.g., Tolosa-Hunt syndrome) to relatively mild (e.g., IgG4-related orbital disease or sarcoidosis with infiltration of the extraocular muscles). However, marked pain may also indicate metastatic cancer. Patients with carotid-cavernous fistulas (CCF) occasionally report severe pain, but more commonly experience a lesser degree of discomfort. Clinical signs depend in part upon whether there is high or low flow, and include proptosis, arterialization of conjunctival and episcleral vessels, chemosis, an ocular bruit (subjective +/− objective), raised intraocular pressure, and ophthalmoplegia [15]. The latter may be due to either orbital congestion or ocular motor nerve dysfunction or both. More specific to high-flow fistulas are proptosis (that may be pulsatile), chemosis, and a bruit. Given the exposed location of CN VI adjacent to the cavernous portion of the ICA, isolated CN VI involvement in CCF is most common, but multiple cranial neuropathies, even in the absence of other signs, have been reported [1, 16]. Recurrent painful ophthalmoplegic neuropathy (formerly named ophthalmoplegic migraine) typically occurs in younger patients, and almost exclusively affects CN III, but may present with multiple ocular motor neuropathies [17–19].

When evaluating a patient who appears to have multiple cranial neuropathies, mimickers should also be considered in the right clinical context. Although classical myasthenia gravis (discussed further in Chap. 24) can mimic almost any type of ophthalmoplegia, it never involves the pupil (except in very rare circumstances in which the antibody affects the muscarinic cholinergic receptor) or sensory nerves including CN V [20]. Other mimickers of multiple cranial neuropathies include Graves ophthalmopathy (discussed further in Chap. 25), orbital floor fracture, and chronic progressive external ophthalmoplegia. The Miller Fisher variant of Guillain-Barré syndrome is a rare, self-limiting autoimmune-mediated peripheral neuropathy that is also characterized by ophthalmoplegia [21].

From a diagnostic standpoint, multiple cranial neuropathies localizing to the orbital apex, superior orbital fissure or cavernous sinus, require timely

neuroimaging in the first instance. Gadolinium-enhanced MR imaging will detect the majority of lesions in this region. However, CT imaging may be complementary or preferable when bony structures in the paranasal sinuses need to be visualized (e.g., mucormycosis and sino-orbital aspergillosis). Additional ultrasound and digital subtraction angiography (DSA) may be needed when a CCF is suspected [15].

Mucormycosis is most commonly associated with diabetes, followed by hematological malignancy and solid organ transplantation [22]. Furthermore, increased serum level of unbound iron predisposes the host to mucormycosis [23]. The site of infection is usually rhino-orbital, but may be complicated by intracranial extension (rhino-orbital-cerebral mucormycosis). *Rhizopus spp*, and less commonly *Mucor spp*, are the most frequently implied pathogens and can be identified on histopathology and culture. Although mucormycosis can occur at any age, it is rare in children and tends to affect adults in their fifth and sixth decades [22]. Patients usually present with gradually progressive proptosis and orbital apex syndrome. Naso- and oropharyngeal examination may reveal areas of necrosis, and facial numbness indicates more invasive disease. An important mimicker of mucormycosis, which may be indolent or rapidly progressive, is aspergillosis [24, 25]. In immunocompetent patients with invasive sino-orbital fungal infections, aspergillosis is a more likely diagnosis than mucormycosis [26, 27]. Management of mucormycosis is not straightforward and often influenced by individual clinician experience. Even with timely diagnosis, it is associated with high morbidity and mortality that exceeds 90% in disseminated disease [28]. In general terms, treatment involves: (i) reversal of any underlying predisposition (i.e., correction of hyperglycemia and withdrawal/interruption of immunotherapy), (ii) removal of infected tissue, and (iii) high-dose systemic antifungals. Management of invasive fungal infections is discussed in more detail in Chap. 8.

IgG4-related orbital disease (IgG4-ROD) is an underrecognized disease entity, the etiology of which remains unknown. It affects both men and women with a median age of 59 years (range 30–86 years) [29]. Clinical signs frequently include chronic lid swelling and proptosis. Unlike nonspecific orbital inflammation that typically has an acute onset, IgG4-ROD develops more insidiously. Although orbital disease most commonly targets the lacrimal glands, infiltration may also be found in the optic nerve sheath, the infraorbital nerve, and the cavernous sinus [29]. Pachymeningitis presents with gradually worsening headache and may be complicated by optic nerve involvement and visual loss [30]. Extraocular muscle infiltration favors the lateral rectus, is usually bilateral, and typically spares the tendons. Ophthalmoplegia does not necessarily ensue, but if it does, tends to be relatively painless [31]. There are a multitude of differential diagnoses that include lymphoma, sarcoidosis, ANCA-mediated systemic vasculitis, reactive lymphoid hyperplasia, as well as Erdheim-Chester and Rosai-Dorfman disease. The gold standard for diagnosis remains histopathological confirmation of hallmark features [32]. Glucocorticoids (GC) are an effective initial therapy for IgG4-related disease (IgG4-RD) in general, but relapses are common [33]. Conventional steroid-sparing agents (azathioprine, mycophenolate mofetil, methotrexate, etc.) are sometimes used, but there are no studies comparing their efficacy. Whether or not rituximab may be superior to GC in terms of long-term efficacy and safety remains to be seen. Rituximab certainly appears to be effective in IgG4-RD, even without concomitant

GC therapy, as a prospective open-label trial that involved 30 patients showed complete remission at 6 and 12 months in 47% and 40% of patients, respectively [34]. Major drawbacks of rituximab therapy are the risk of serious infection, as well as hypogammaglobulinemia [35].

Tolosa-Hunt syndrome (THS) is a rare, granulomatous disorder of unknown origin that occurs in both children and adults [36–38]. Primarily affecting the cavernous sinus, it may also involve the superior orbital fissure and rarely orbital apex. Ophthalmoplegia may involve all three ocular motor nerves in varying combinations, and is accompanied or preceded by considerable pain. The pain of THS is known to dramatically respond to GC within 72 hours, but there is no widely accepted guidance with regards to dosage or duration [39]. Without treatment, THS runs a self-limiting course that may last several weeks, but THS may develop as a relapsing disorder over time. As various other causes of cavernous sinus syndrome (e.g., lymphoma, metastatic cancer, sarcoidosis, and IgG4-ROD) may show a similar therapeutic response to steroids, both clinically and neuroradiologically, THS remains a diagnosis of exclusion. The utility of the syndrome dates back to a time when limited imaging techniques often did not reveal a lesion in such cases [40]. In the current era, the syndrome remains useful only because of the difficulty in obtaining biopsy confirmation of inflammatory lesions in the cavernous sinus and superior orbital fissure, where a small volume of inflammatory tissue causes a major syndrome of pain and double vision.

While it is helpful to have an awareness of the conditions highlighted above, it is important to remember that the most common cause of multiple cranial neuropathies is neoplasm of the cavernous sinus [1]. Especially when there is a prior history of cancer, metastatic disease must be considered [41–43]. However, the majority of primary cavernous sinus lesions are meningiomas [44]. Cavernous sinus meningiomas are generally slow growing, and rarely life threatening. However, ophthalmoplegia and associated double vision may eventually ensue and involve any combination of ocular motor nerves. CN III involvement may be accompanied by anisocoria, but pupil sparing with slowly growing cavernous sinus lesions is not uncommon [44]. CN VI involvement may be accompanied by Horner syndrome. The neurosurgical literature pays relatively little attention to the importance of trigeminal dysfunction, yet it is crucial to remember that it may cause significant discomfort and even lead to neurotrophic keratitis and loss of vision. Headache and facial pain may also be accompanying features, but are much less common, and more often than not suggest an alternative pathology. Although cavernous sinus surgery is technically possible, it may be complicated by CSF leak, infection, and stroke [45, 46]. In addition, surgery may cause both transient worsening of preexisting and even new cranial neuropathies [47]. Iatrogenic damage to CN III is almost expected, and often complicated by aberrant regeneration that may produce persistent diplopia [44, 48]. As total surgical removal of a cavernous sinus meningioma is rarely possible, regrowth is highly likely. Radiosurgery (RS) has been used both alongside and instead of surgery since the 1990s [49, 50]. A meta-analysis from 2010 examined factors affecting outcome following treatments of patients with cavernous sinus meningiomas and concluded that RS improved rates of tumor control

compared with surgery alone, independent of the extent of resection [51]. A systematic review and meta-analysis from 2018 suggested increased tumor volume regression with RS when compared with fractionated radiotherapy (RT) [52]. Both methods appeared to achieve similar clinical posttherapeutic outcomes for CNs III and V. Radiation optic neuropathy (discussed further in Chap. 3) may be a long-term complication of either. The overall aim of cavernous sinus meningioma management should be the avoidance of neurological deficits. To this end, following an initial period of expectant management, a combination of limited surgical resection of any extracavernous tumor extension, which aids in confirming diagnosis, combined with some form of radiation may be the best option for most patients [53]. Up to 51% of motor cranial nerve palsies from meningiomas resolve with radiation, and an additional 11% have some improvement [54], with higher rates of improvement in patients with partial versus complete palsies [55]. Time to improvement ranges from 1 to 30 months with a median of 6 months [56]. In patients with residual motility deficits, strabismus surgery can be considered; however, there are limited data on timing of surgery due to variable time to recovery.

Case Resolution

MRI demonstrated a right-sided, enhancing lesion of the cavernous sinus, consistent with meningioma. Interestingly, our patient had purchased a Groupon voucher for an MRI scan due to headaches, and the meningioma was identified incidentally, as is commonly the case. As she became increasingly troubled by her ophthalmoplegia, she eventually opted for fractionated RT. Our hope is that the RT will prevent or at least delay the onset of double vision in the primary position due to involvement of CN VI, and protect her cornea from worsening dysfunction of CN V_1.

Conclusion

In summary, the presence of multiple cranial neuropathies alerts the physician to the possibility of a mass lesion or, in some cases, a more diffuse infectious or inflammatory process. The combination of CNs involved, as well as associated neurologic signs, is helpful for lesion localization and to direct neuroimaging.

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Nystagmus and Superior Oblique Myokymia

16

Kemar E. Green and Daniel R. Gold

Introduction

Nystagmus is an involuntary, rhythmic ocular movement that is initiated by a slow drift and comes in two varieties (Fig. 16.1): (1) jerk nystagmus (alternating slow and fast phases) and (2) pendular nystagmus (back-to-back slow phases). Both jerk and pendular nystagmus can have horizontal, vertical, or torsional components in isolation or combination. Some nystagmus manifests very early in life (infantile), while acquired nystagmus can be associated with a variety of pathologic conditions. Acquired nystagmus becomes symptomatic when the pathologic slow phase moves the eyes away from fixation, often causing oscillopsia, or an illusory movement of a stationary object. Therapies proposed for nystagmus include pharmacologic, chemodenervation (e.g., botulinum toxin), surgical, and optical among others. The goal of treatment is to improve vision by stabilizing retinal images. While large-scale randomized controlled trials are generally lacking for the treatment of nystagmus, we will discuss those therapies for which at least some evidence exists.

Case 1

A 30-year-old man presented with a known diagnosis of spinocerebellar ataxia type 8 with complaints of diplopia at distance and "bouncing" of his vision. His neurologic examination demonstrated severe limb and gait ataxia. Ocular motor examination was significant for impaired smooth pursuit and vestibulo-ocular reflex suppression (VORS, i.e., a saccadic appearance with combined eye-head movements), saccadic hypermetria, and gaze-evoked nystagmus (e.g., right-beating nystagmus [RBN] in right gaze and left-beating nystagmus [LBN] in left gaze) with

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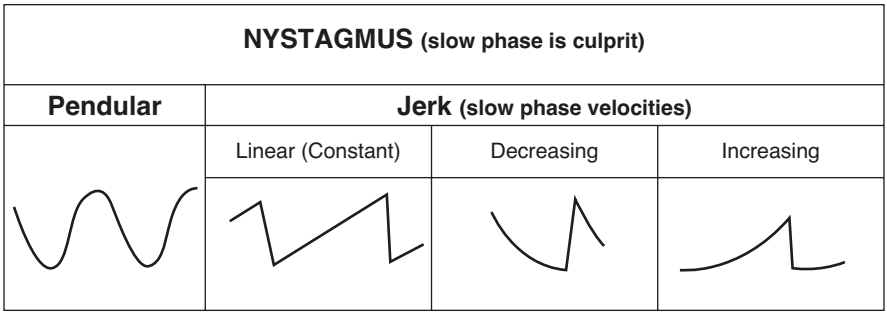

Fig. 16.1 Waveforms of jerk and pendular nystagmus. In pendular nystagmus, back-to-back slow phases (having equal velocities) cause a pendular appearance. Jerk nystagmus can have constant, increasing, or decreasing slow-phase velocity, which can have localizing value or help distinguish etiologies (e.g., increasing velocity waveform is common in infantile nystagmus). With jerk nystagmus, the slow (pathologic) phase is followed by the fast (position reset or named) phase. (From Neuro-Ophthalmology Virtual Education Library: NOVEL (online) Available at: https://collections.lib.utah.edu/ark:/87278/s6hx56nc)

rebound nystagmus (e.g., RBN in right and LBN when looking back to center; LBN in left and RBN when looking back to center). He experienced binocular horizontal diplopia at distance but not at near, and while there were no abduction deficits, there was an esotropia at distance consistent with divergence insufficiency (common in patients with cerebellar ataxia). His vertical "bouncing," or oscillopsia, was explained by downbeat nystagmus (DBN), which increased in lateral and downgaze (see video example – https://collections.lib.utah.edu/ark:/87278/s6dj8q9h). Afferent function was normal without evidence of optic nerve or retinal disease, although visual acuities were 20/50 OU, attributed to his significant DBN.

Which of the following treatment options should be tried first?

(a) 4-Aminopyridine
(b) Alprazolam
(c) Topiramate
(d) Botox
(e) Surgery

Management

This patient with a known cerebellar degeneration experienced ataxia and a variety of ocular motor abnormalities, although most visually symptomatic was his DBN. While the combination of impaired (saccadic) pursuit and VORS, gaze-evoked and rebound nystagmus, and DBN localize well to the cerebellar flocculus/paraflocculus, occasionally DBN can result from involvement of the cerebellar nodulus/uvula or even the brainstem paramedian tracts (rare). Bilaterally hypermetric saccades suggest involvement of the cerebellar fastigial nucleus (unilateral or

bilateral). Of these medications, *(a) 4-aminopyridine (4-AP)* has the most evidence for its use. There are three main theories for DBN which include: overactive anterior semicircular canal pathways due to loss of Purkinje cell inhibition cause a slow-phase drift upward; Purkinje cells of the vestibulocerebellum preferentially fire for downward ocular movements, and so injury may cause an upward drift; or an otolithic vertical tone imbalance may be responsible [1–3].

The most commonly used medications for DBN include 4-AP, chlorzoxazone, clonazepam, and baclofen. Of these options, 4-AP has been the most rigorously tested and reported on (at least in recent years), and this medication acts on potassium channels. Potassium channel antagonism is thought to restore the cerebellum's innate inhibitory effects on the vestibular nuclei by prolonging the Purkinje cell action potentials [4]. In the United States, 4-AP is marketed as dalfampridine (Ampyra), which is not FDA approved to treat DBN. Unfortunately, insurance companies rarely cover dalfampridine for this indication, and without coverage its price is exorbitant. For this reason, compounded 4-AP is commonly prescribed in the United States, although the patient should be counseled that the FDA does not verify the safety or the effectiveness of the compounded formulation. There are a few randomized trials showing the efficacy 4-AP and associated compounds (e.g., 3,4-diaminopyridine) on downbeat nystagmus [5]. When compared with placebo, the 3,4-diaminopyridine has been shown to decrease the slow-phase velocity of the DBN, as well as the degree of oscillopsia and postural instability [6]. At similar doses (10 mg), 4-AP was shown in a small ($n = 8$) double-blinded prospective crossover study to be more effective than 3,4-diaminopyridine in decreasing the slow-phase velocity of the nystagmus [7]. Interestingly, in one study, a 5 mg dose of 4-AP administered four times daily showed greater reduction in slow-phase velocity and improvement in visual acuity and gait as compared to 10 mg four times daily [8]. Even if the clinician does not have access to eye movement recording equipment, visual acuities can be a useful objective measure to follow. Overall, 4-AP is well tolerated with only rare seizures and paresthesia reported as the main side effects. Therefore, it is contraindicated in patients with comorbid seizures [9].

There is class IV evidence from a small pilot study that chlorzoxazone 500 mg three times daily can improve visual acuity and reduce DBN [10]. Support for using other medical treatments is largely limited to case reports and small case series. In patients refractory to medication, there is some evidence from prospective case series for moving the upgaze eccentric null point in downbeat through a combination of bilateral superior rectus recessions and inferior oblique myomectomies [11]. However, surgical and medical therapies for DBN have not been directly compared.

Case 2

A 25-year-old woman developed vision loss due to bilateral optic neuritis, and months later experienced oscillopsia and binocular horizontal diplopia which led to the diagnosis of multiple sclerosis (MS). She presented to clinic several months later with the following afferent examination: visual acuities of 20/60 OD and

20/125 OS with a mild relative afferent pupillary defect OS. Ishihara color plates were 15/16 OD and 13/16 OS, and there was mild temporal pallor OU. On efferent examination, adduction deficits were noted bilaterally in addition to abducting nystagmus OU in lateral gaze. In primary gaze, there was spontaneous upbeat nystagmus (UBN), and there was gaze-evoked nystagmus vertically (UBN in upgaze and downbeat in downgaze). Smooth pursuit appeared to be normal. While she had evidence of bilateral optic neuropathies, her dyschromatopsia was somewhat better than expected if her poor acuities were based on optic nerve disease alone. Therefore, it was felt that the UBN was contributing to her poor visual function (see video example – https://collections.lib.utah.edu/ark:/87278/s64517rm).

Which of the following treatment options should be tried first?

(a) Alcohol
(b) Clonazepam
(c) Memantine
(d) Botox
(e) Surgery

In this patient, bilateral internuclear ophthalmoplegia (INO) was due to bilateral medial longitudinal fasciculus injury (common in MS). Upbeat nystagmus is typically the result of midline medullary and pontomesencephalic lesions. UBN may be due to disruption of the anterior (upward or antigravity) semicircular canal pathways, which ascend via three projections: medial longitudinal fasciculus (MLF), ventral tegmental tract, and superior cerebellar peduncle/brachium conjunctivum [12]. Usually, with asymmetric damage to the anterior semicircular pathways, the nystagmus is UB and torsional as opposed to pure UBN. Another common cause of (pure) UBN is injury to the dorsal caudal medulla (including the nucleus of Roller and nucleus intercalatus), which was demonstrated on MRI in this patient. In this case, the most appropriate treatment is *(c) memantine*.

Evidence for the treatment of UBN is limited to case reports and small observational studies. Unlike DBN, UBN is usually a transient phenomenon, lasting only a few weeks, and in some cases can convert to DBN (e.g., Wernicke's encephalopathy) [13], making it difficult to conduct randomized treatment trials. Memantine 10 mg four times daily has been shown to suppress UBN in a small ($n = 10$) double-masked, crossover study [14]. 4-AP (5–10 mg three times daily) is also beneficial in decreasing the slow-phase velocity in UBN [15]. Finally, gamma-aminobutyric acid $(GABA)_B$-ergic augmentation through baclofen (5 mg three time daily) reduced the slow-phase velocity and oscillopsia imposed by symptomatic UBN in a small ($n = 2$) uncontrolled trial – proving that like DBN, augmenting inhibition between the cerebellar flocculus/parafloccculus and the brainstem vestibular nuclei may mitigate UBN [16]. The low prevalence of symptomatic UBN may limit the conduction of large randomized trials.

Case 3

A 30-year-old man with a 15-year history of multiple sclerosis (MS) presented with horizontal "shakiness" of his vision for 12 months. Afferent exam demonstrated visual acuities of 20/100 OU with 0/10 Hardy Rand and Rittler plates OU and significant bilateral optic atrophy on fundus exam. Efferent exam demonstrated gaze-evoked nystagmus, saccadic smooth pursuit, and hypermetric saccades, each of which could be explained based on a significant number of MRI demyelinating plaques in the posterior fossa. Additionally, there was horizontal pendular nystagmus, which suppressed transiently following the termination of saccades and after blinks (typical features of acquired pendular nystagmus in MS, see video example of this patient – https://collections.lib.utah.edu/ark:/87278/s6nc9v0z).

Which of the following treatment options should be tried first?

(a) Gabapentin
(b) Trihexyphenidyl
(c) Botox
(d) Surgery
(e) Prisms

The horizontal oscillopsia in this patient is secondary to acquired pendular nystagmus (APN) secondary to MS. Neural integrator instability secondary to disrupted brainstem/cerebellar dysfunction is the likely mechanism in MS and other demyelinating diseases [17], although the nystagmus is typically more intense in the eye with poorer vision. The two most common causes of APN are MS and oculopalatal tremor (OPT), with the latter caused by a lesion within the Guillain-Mollaret triangle, often due to pontine hemorrhage damaging the descending central tegmental tract (see video example – https://collections.lib.utah.edu/ark:/87278/s6mh1mnm). APN due to MS is commonly horizontal or elliptical, but may have vertical, torsional, or convergent-divergent components. APN due to OPT is commonly vertical and/or torsional, although horizontal and convergent-divergent components are also possible. The nystagmus in either disorder may be disjunctive, or slightly different in each eye. The answer is *(a) gabapentin*, although memantine is also commonly used as well.

Both gabapentin and memantine have been shown over the years to be effective in the treatment of APN [9, 14]. Improved visual acuity and decreased nystagmus velocity were observed with the use of gabapentin (up to 900 mg/ day) in one double-masked controlled study [18]. A prospective single-masked, crossover study comparing the efficacy of memantine (40 or 60 mg/day) and gabapentin (1200 mg/ day) in a cohort of MS patients with APN showed 50% or greater reduction in the nystagmus in both treatment arms [19]. More recently, evidence from a single-center controlled crossover trial studying the effects of gabapentin (300 mg four

times daily) and memantine (10 mg four times daily) on visual outcome in APN showed that both options are fairly well tolerated, with each improving near monocular visual acuity as well as the amplitude, velocity, and intensity of the nystagmus [20]. In the same study, memantine was found to be more effective at decreasing oscillopsia at distance.

Case 4

A 70-year-old woman presented to the emergency department with the acute onset of the acute vestibular syndrome (AVS, vertigo, imbalance, spontaneous nystagmus, nausea and vomiting, and head motion intolerance), and the HINTS (Head Impulse, Nystagmus, Test of Skew) examination demonstrated (1) a normal head impulse test (HIT), (2) direction-changing/gaze-evoked nystagmus (e.g., right beating in right gaze and left beating in left gaze), and (3) normal vertical ocular alignment (i.e., a normal test of skew). Taken together, the gaze-evoked nystagmus and normal HIT were highly suggestive of a central (vascular) etiology of the AVS, and MR diffusion-weighted imaging (DWI) demonstrated a right posterior inferior cerebellar artery (PICA) territory infarction with a right PICA high-grade stenosis. She experienced oscillopsia due to the spontaneous nystagmus, which improved mildly over a few days. When examined as an outpatient for persistent oscillopsia weeks later, there was mild spontaneous RBN. The nystagmus was observed for 2 minutes, and gradually the RBN slowed and then stopped (i.e., null period), at which time LBN became apparent and increased in intensity. After another 90–120 seconds, the LBN transitioned back to RBN, then LBN, etc. She was diagnosed with periodic alternating nystagmus (PAN), and upon review of the initial MRI, there was in fact involvement of the cerebellar nodulus on the right side, which is supplied by the right PICA. Oscillopsia due to PAN was significant enough to affect the clarity of her vision and her ability to read (see video example of this patient – https://collections.lib.utah.edu/ark:/87278/s6pc708r; see more profound example of PAN in a cerebellar degeneration – https://collections.lib.utah.edu/ark:/87278/s62k013r).

Which of the following treatment options should be tried first?

(a) Gabapentin
(b) Baclofen
(c) Memantine
(d) 4-Aminopyridine
(e) Surgery

PAN is a condition that can easily be overlooked if the examiner assesses the nystagmus only once during the evaluation. Preferably, any patient with spontaneous horizontal nystagmus should be observed for at least 2 minutes to evaluate for PAN. There may also be an associated compensatory head turn that a patient uses to mitigate oscillopsia – for example, while the nystagmus is RBN, the RBN will be maximal in right gaze (i.e., in the direction of the fast phase in accordance with

Alexander's law) and minimal in left gaze; therefore, during the RBN, the patient's head may be turned to the right so that the gaze is directed toward the left. If the patient has an underlying DBN or saccadic intrusions such as square wave jerks, these may be apparent during the null phase when the PAN transiently disappears.

It is important for the clinician to recognize PAN because it localizes well to the cerebellar nodulus/ventral uvula, and *(b) baclofen* can be a highly effective medication. If the onset is abrupt and accompanied by other neurologic symptoms (e.g., acute onset of vertigo in this patient), the etiology should be assumed to be vascular until proven otherwise. Also consider encephalitis and medication toxicity (e.g., lithium and antiseizure medications) with acute to subacute onset of symptoms. If the oscillopsia due to PAN is more chronic, in young patients consider a Chiari malformation (especially with occipital headaches) or MS, and in an older patient, consider a cerebellar degeneration. Infantile PAN should be considered in a patient who lacks visual symptoms or oscillopsia, and albinism is one common association. Instead of the typical transition after 90–120 seconds in acquired PAN, patients with infantile PAN can have much shorter and more random cycles. Ocular etiologies such as vitreous hemorrhage and cataract have been associated with PAN as well, with resolution of the nystagmus once vision is restored [21].

The nodulus and ventral uvula have extensive connections with the vestibular nucleus and play a major role in velocity storage. Given the mechanical constraints of the semicircular canal (i.e., endolymph, cupula, etc.), a "velocity storage" mechanism is necessary to perseverate vestibular afferents during prolonged head rotations. The nodulus/uvula normally inhibits velocity storage via GABA, and this is the rationale for why the $GABA_B$ agonist baclofen seems to be so effective in PAN [22, 23]. Memantine may be effective for some patients as well [24].

Case 5

A 45-year-old man presented with complaints of a transient "shimmering" of his vision lasting for seconds at a time, with associated vertical diplopia. This occurred many times each day and resolved when closing both eyes or just the right eye. Ocular alignment between attacks was normal; however, during an attack, there was a measurable two to three prism diopter left hypertropia (explaining vertical diplopia) in addition to rapid and repetitive incycloduction movements in the right eye (explaining oscillopsia OD). The diagnosis of right superior oblique myokymia (SOM) was made, and MRI brain was normal without obvious neurovascular compression involving the right fourth nerve see example of this patient – https://collections.lib.utah.edu/ark:/87278/s69w3q5b; see more subtle examples recorded with video oculography – https://collections.lib.utah.edu/ark:/87278/s6993k7q).

Which of the following treatment options should be tried first?

(a) Carbamazepine
(b) Gabapentin

(c) Oxcarbazepine
(d) Topical timolol
(e) Any of the above

This patient has superior oblique myokymia (SOM) which is thought to arise from ephaptic transmission of the trochlear nerve resulting from segmental demyelination [25]. SOM may be due to neurovascular compression of the fourth nerve, due to trauma [26], or related to other compressive lesions [25, 27]. In this case A-D would be reasonable to try first in this patient so the answer is *(e) any of the above*. The decision of which medication to try first should be made based on the side effect profiles as well as the presence of comorbid conditions – for example, topical timolol in a patient with mild symptoms who does not tolerate oral medications well; carbamazepine, oxcarbazepine, or gabapentin in a patient with more significant SOM symptoms who also suffers from neuropathic pain.

The evidence for medical therapy for SOM is limited to case series and observational studies given the low prevalence of the condition, as well as its unpredictable natural history. The goal of medical therapy is to reduce trochlear nerve excitability. In one retrospective review (n = 20), carbamazepine (200 mg three to four times daily) was tolerated and provided symptomatic improvement in over 80% of cases [28]. In the same study, phenytoin and propranolol provided mixed results. Case reports provide some evidence for gabapentin [29–31], topical beta-blockers (e.g., timolol) [32, 33], and memantine [34]. The evidence for surgical options is even weaker, and surgery is reserved for medication refractory cases. A superior oblique tenotomy followed by a recession or myomectomy of the ipsilateral inferior oblique muscle is another proposed treatment for refractory cases but can be complicated by diplopia (especially in downgaze) [35]. In cases of confirmed brainstem root entry zone compression of the trochlear nerve, evidence from case reports shows that microvascular decompression surgery may be effective in symptom control [36–39].

Conclusions

The evidence for the treatment of nystagmus (e.g., DBN, UBN, PAN, and APN) and nystagmoid movements (e.g., SOM) is limited. This is primarily due to the relatively low prevalence of these disorders, as well as the fact that the exact pathophysiology may not be well understood or may vary from patient to patient with the same condition (e.g., DBN due to asymmetric vertical otolithic tone in one patient and DBN due to asymmetric vertical semicircular canal pathways in another). Available evidence is summarized in Table 16.1. Recognition of PAN or SOM can result in selection of a medication that leads to significant symptomatic relief, and in the authors' experience, some patients with DBN, UBN, or APN may also experience a dramatic response to certain medications. Unfortunately, most of the medications discussed above have the potential for significant side effects including dizziness or sedation, which in many patients may outweigh the benefits. Starting at low doses (or half of the lowest dose) and escalating slowly while having the patient

Table 16.1 Evidence for pharmacological therapy of nystagmus and superior oblique myokymia

Drug	Evidence	Standard dosage	Contraindications	Adverse effects
Downbeat nystagmus				
4-Aminopyridine	RCT [6–8]	5 mg (BID to QID)	Kidney disease and seizure history	Seizures and paresthesia
Chlorzoxazone	Small pilot study [10]	500 mg (TID to QID)	Liver disease	Drowsiness, dizziness, GI bleeds, and fatal hepatotoxicity
Clonazepam	Case series [40]	1–2 mg (BID to TID)	Liver disease and narrow-angle glaucoma	Drowsiness, ataxia, and respiratory suppression
Baclofen	Case series [16]	5–25 mg (TID)		Drowsiness, insomnia, fatigue, and weakness
Gabapentin	Crossover study [14]	Up to 1200 mg TID	Kidney disease	Dizziness, somnolence, and peripheral edema
Upbeat nystagmus				
Memantine	Crossover study [14]	5–10 mg (BID to TID)		Fatigue, dizziness, confusion, headaches, and transient worsening of neurologic symptoms in MS
4-Aminopyridine	Case report [15]	5–10 mg TID	See above	See above
Baclofen	Case series [16]	5–25 mg (TID)		See above
Acquired pendular nystagmus				
Memantine	RCT [17, 18] & crossover study [14]	40–60 mg/day		See above
Gabapentin	RCT [18–20] & crossover study [14]	Up to 1200 mg TID	See above	See above
Clonazepam	Case series [41]	1–2 mg (BID to TID)	See above	See above
Periodic alternating nystagmus				
Baclofen	Case series [23]	5–10 mg TID	See above	See above
Memantine	Case report [24]	5–10 mg QID	See above	See above
Superior oblique myokymia				
Carbamazepine	Retrospective review [28]	200 mg (BID-QID)	Blood dyscrasia, liver disease, renal failure, cardiac disease, and pregnancy	Steven-Johnson syndrome, cytopenia, hyponatremia, and dizziness

(continued)

Table 16.1 (continued)

Drug	Evidence	Standard dosage	Contraindications	Adverse effects
Gabapentin	Case reports [29–31]	Up to 1200 mg TID	See above	See above
Memantine	Case report [34]	40–60 mg/day		See above
Topical timolol	Case reports [32, 33]	1–2 drops per day of a 0.5% solution	Complete heart block and asthma	Diplopia, blur, eye pain, and dizziness
Phenytoin	Retrospective review [28]	Up to 100 mg TID	Cardiac disease, myasthenia gravis, kidney disease, and pregnancy	Nausea, dizziness, tremor, gingival hyperplasia, and lymphopenia

MS multiple sclerosis, *RCT* randomized clinical trial, *BID* twice daily, *TID* three times daily, *QID* four times daily

keep a journal to track symptoms can assist in finding the lowest effective dose for a particular patient. Combinations of medications are often needed as well, as in using gabapentin and memantine for APN due to MS or OPT. Partial improvement in oscillopsia is more typical than complete resolution, so the clinician and patient must also discuss goals of therapy to ensure that expectations are aligned prior to the initiation of therapy.

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Part IV

Transient Visual Symptoms

Transient Monocular Vision Loss

17

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Case 1

A 75-year-old Caucasian female with a history of migraines, hypercholesterolemia, asthma, and gastroesophageal reflux disease presented after experiencing five episodes of monocular distorted vision in her left eye (OS) that spanned over 3 months. She described her vision loss as "looking through a Picasso painting or a kaleidoscope." She denied complete opacification, or loss of vision, and was always able to identify images in her visual field despite the overlying distortion. All episodes lasted 10–30 minutes and resolved spontaneously. She denied any associated headaches, pain, photophobia, nausea, or diplopia. She had no similar episodes in the past or in the contralateral eye. There was no specific inciting factor, and all episodes occurred at rest. Review of systems was otherwise negative. Her visual acuity (VA) was 20/20 in both eyes (OU), intraocular pressure (IOP) was normal, and there was no afferent pupillary defect (APD). Fundus examination revealed healthy perfused optic nerves without pallor or edema, and no vascular attenuation or obstruction. Humphrey visual fields were full and optical coherence tomography (OCT) of the retinal nerve fiber and ganglion cell layers were normal bilaterally. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain, head, and neck revealed no mass, vascular abnormality, or evidence of vasospasm.

What is the best management option for this patient?

(a) Nortriptyline
(b) Verapamil
(c) Sumatriptan
(d) Aspirin

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Management

This patient's diagnosis is likely retinal migraine, which is a diagnosis of exclusion. Calcium channel blockers (CCBs), like (b) verapamil, may decrease the frequency and severity of symptoms. Tricyclic antidepressant therapy is occasionally used as migraine prophylaxis but is not the best option for prophylaxis in patients with retinal migraines. Triptan therapy is contraindicated in retinal migraines.

The patient describes a characteristic presentation consisting of distorted geometric shapes in one eye, not associated with complete vision loss, headache, pain, or focal neurological deficits. Migraines affect approximately 15% of the general population. Within those that have migraines, approximately 1 in 200 patients will experience retinal migraines. [1]. The true prevalence of retinal migraines that includes those not experiencing an associated migraine headache is unknown [2, 3]. The International Headache Society defines a retinal migraine as "repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, [that can be] associated with migraine headache" [4]. This definition can be controversial as patients also have isolated retinal migraines without any associated headaches. The main distinguishing factor between retinal migraine and similar diagnoses of acephalgic migraine and migraine with aura is that the visual changes are monocular in retinal migraines. [5].

As a diagnosis of exclusion, diagnosis of retinal migraines requires a thorough history, including duration of visual symptoms, frequency, onset, location, precipitating factors, presence of focal neurological symptoms, associated symptoms, and history of cardiovascular disease, particularly in patients over 50 years old [6]. Precipitating factors for retinal migraines are similar to those of typical migraines and include stress, smoking, hypertension, oral contraceptives, exercise, dehydration, hypoglycemia, and excessive heat [7–9]. Most commonly, patients with retinal migraine experience negative visual phenomena that resemble black, gray, or white shaded areas appearing suddenly or over the course of minutes [1]. Approximately 65% experience negative visual phenomena, whereas 4% report exclusively positive and 31% describe mixed positive and negative visual phenomena [3]. Studies have shown that approximately half of retinal migraine patients report monocular blindness or blurring of the entire visual field [3, 10]. Patients who experience complete monocular vision loss require urgent neuroimaging and vascular imaging of the head and neck, as well as an echocardiogram to rule out cardioembolic or vascular causes. Although most are shorter, retinal migraine episodes may last up to 1 hour and commonly have gradual onset and resolution [3, 11].

Given the transient nature of visual symptoms, ophthalmologic exam is oftentimes normal in the clinical setting. However, retinal vasospasm and hypoperfusion may be visible on fundoscopic exam, and a relative APD is rarely present [8, 11, 12]. Fluorescein angiogram (FA) during attacks may show delayed filling or occlusion of the central retinal artery and its branches with preserved ciliary circulation [5, 13, 14]. Patients with history of chronic migraines may have thinning of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and choroidal layers compared with healthy controls [15]. Of note, given its well-documented association

with vaso-occlusion, the presence of intrapapillary drusen in patients with vasospasm from retinal migraines may increase susceptibility to retinal infarction [16].

Despite permanent visual scotomas occurring on occasion in patients with retinal migraines, visual prognosis is favorable [3]. Treatment should focus on promoting lifestyle changes to decrease migraine incidence, including limiting outside stressors, controlling blood pressure, avoiding hormonal oral contraceptives, and smoking cessation [5, 17]. While limited data are available on the best treatment options for patients with this diagnosis, there are reports that treatment with CCBs, like (b) verapamil, decreases frequency and severity of symptoms as these medications have been shown to reduce vasospasm, promote vasodilation, and decrease platelet aggregation [5, 18, 19]. Abortive therapy is not indicated as episodes are typically short-lived. Contraindications to CCBs include heart failure with reduced ejection fraction, severe hypotension, and recent ST-elevation myocardial infarction [20]. Tricyclic antidepressants and antiepileptics like valproate, gabapentin, and topiramate can also be used to decrease migraine symptoms. Aspirin monotherapy has previously been used for its antiplatelet properties, yet recent studies have shown greater risk than benefit for primary cardiovascular disease prevention due to increased risk of significant hemorrhagic events. Treatment with low-dose (81 mg) aspirin twice a week may be another reasonable option [3, 21]. Triptans and ergots are avoided in retinal migraines given their vasoconstrictive properties [3]. Reassurance and follow-up may be an acceptable option based on the severity of the patient's symptoms.

Case 2

A 60-year-old female with a chronic history of migraines presented 1 month after a 2-minute episode of complete left-sided monocular vision loss. She described the episode as a "dark blob" that obscured most of her visual field, which gradually filled in starting in the periphery. She also described a second episode of monocular left visual field blurring that lasted for less than a minute after abruptly turning her head. The episodes differed from her typical migraines, described as jagged shapes moving left to right across her visual field for approximately 20 minutes, accompanied by a headache. She denied concurrent dizziness, weakness, pain, or other focal neurological deficits. Past medical history included hyperlipidemia, cervical stenosis, hyperglycemia, vertigo, and mitral valve disease. Family history was significant for multiple early deaths due to myocardial infarctions. Physical exam revealed bilateral VA of 20/20 and normal IOP. Dilated fundus exam was significant only for a chronic posterior vitreous detachment. Echocardiogram was unremarkable, and carotid ultrasonography showed no signs of plaque formation or stenosis. Computed tomography angiography (CTA) of the head and neck revealed moderate luminal irregularity resembling a beading pattern at the distal end of the left internal carotid artery (ICA), suggestive of fibromuscular dysplasia (FMD) (Fig. 17.1). There was no significant intracranial stenosis. The patient was started on aspirin and a statin for stroke prevention.

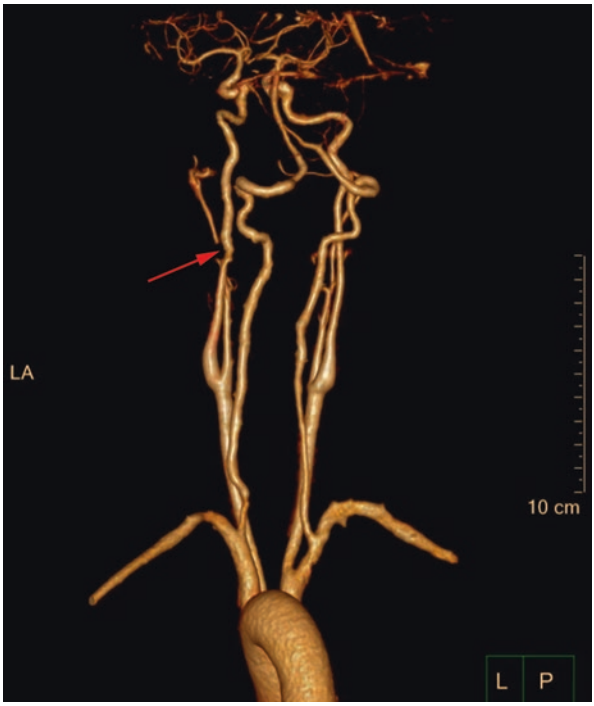

Fig. 17.1 Computed tomography angiography (CTA) of the head and neck demonstrate moderate luminal irregularity resembling a beading pattern at the distal end of the left internal carotid artery (red arrow). (© LS Ediriwickrema 2020. All Rights Reserved)

What other diagnostic testing should be done in this patient with FMD?

(a) Arterial biopsy
(b) Head to pelvis computed tomography (CT)
(c) Formal angiography to evaluate degree of arterial stenosis
(d) No further testing is indicated

Management

FMD is an uncommon cause of TMVL. Given its propensity to affect multiple vascular beds, any patient diagnosed with FMD should undergo (b) a one-time CT scan from head to pelvis.

As a noninflammatory and nonatherosclerotic arterial disease, FMD affects small- and medium-sized vessels, most commonly the renovascular circulation (approximately 75%) and cerebrovascular system (between 25% and 72%) [22, 23]. The vast majority of patients with FMD are female (~ 90%) and Caucasian (~95%) [23, 24]. Overall prevalence in the population is uncertain as many patients are asymptomatic, but one study found a rate of 3.3% among healthy renal transplant donors [25].

Patients with renovascular involvement complicated by hypertension can manifest symptoms of headache and tinnitus. Ocular symptoms are uncommon in FMD. There are, however, reports of patients as young as 12 years old developing TMVL and rarely central retinal artery occlusion (CRAO) [26, 27]. As a result, patients may present with sudden painless, transient unilateral vision loss, reporting episodes of 10–20 seconds of vision loss that recur multiple times throughout the day, or several days of painless blurred vision [27–30]. While these patients can be younger with lower suspicion for CRAO from atherosclerotic emboli, they should undergo testing for evidence of atherosclerotic disease. Fundoscopic exam may be normal, but can reveal arteriolar constriction and tortuous vessels [31]. FA may show filling defects from retinal artery occlusion or beading of retinal arteries [26–28, 32]. Inner retinal atrophy on OCT may help explain the cohort of patients who experience painless and slowly progressive unilateral vision loss due to chronic intermittent retinal ischemia [31].

Noninvasive vascular imaging is widely accepted as the key diagnostic modality, given the risks associated with arterial biopsy or digital subtraction angiography. The classical appearance of multifocal FMD resembles beads on a string, caused by alternate narrowing and dilation of the affected vessels. Since focal FMD only shows one segment of narrowing, it can initially be confused with atherosclerotic disease. However, FMD typically affects the distal extracranial aspect of the ICA, whereas atherosclerosis is generally present within 1 cm of the proximal ICA [22]. Histological analysis is rarely done, but reveals medial fibroplasia in 91% of patients. Intimal fibroplasia (7%) and perimedial fibroplasia (0.7%) can also occur [24].

Management of FMD focuses on blood pressure control, decreasing risk of thromboembolism through antiplatelet agents, and intermittent imaging of involved vascular beds to monitor for complications [33]. Arterial dissection (19.7%), stroke or transient ischemic attack (19.2%), and aneurysm (17%) can occur in FMD patients [24]. Urgent ocular symptoms can, therefore, arise from vascular injury with extension or ischemia affecting the ophthalmic or ciliary arteries [29]. Visual prognosis is variable and depends on the etiology and management of vascular compromise. In a patient with recurrent TMVL without evidence of CRAO or chronic retinal ischemia, acuity may return to baseline, especially with anticoagulation or revascularization [29, 30, 34].

Case 3

A 39-year-old female with no significant past medical history presented with 3 months of transient, alternating, bilateral blurry vision and photophobia. She denied focal visual scotomas, tinnitus, diplopia, pain with eye movements, nausea, and vomiting. Occasionally, she experienced transient monocular visual obscurations lasting seconds in either eye. On examination, her VA was 20/20 in the right eye (OD) and 20/25 OS. IOP was normal. Pupils were equal and reactive to light without an APD. Hardy-Rand-Rittler color testing was 8/10 in each eye. Slit lamp

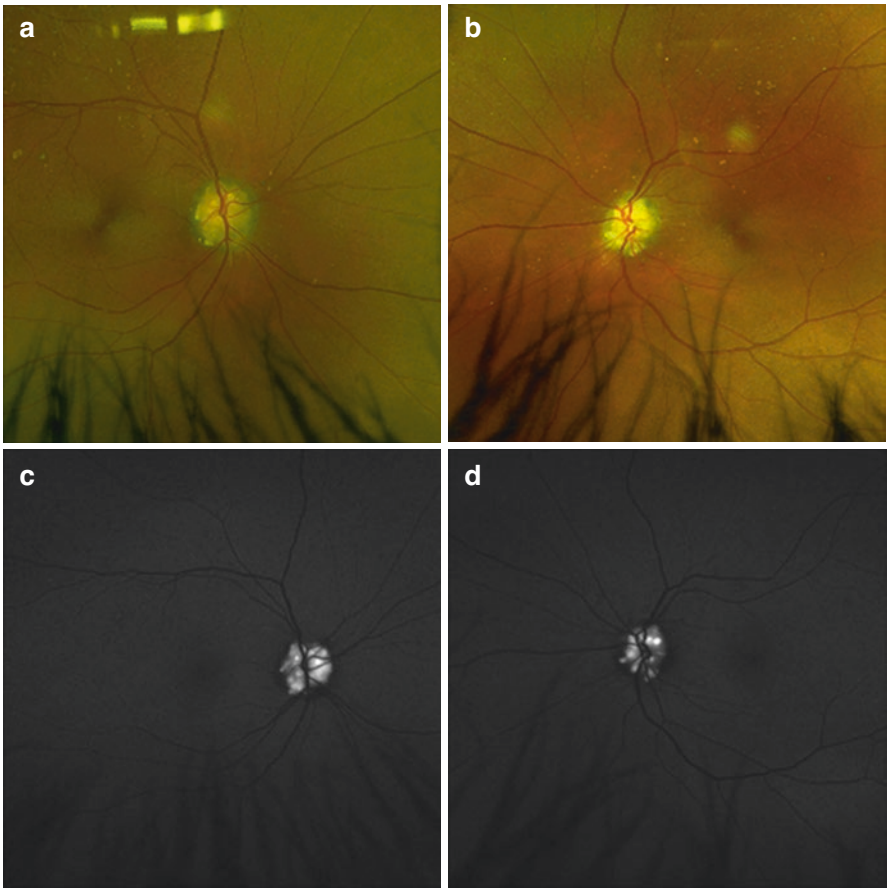

Fig. 17.2 Color fundus photos of the right (**a**) and left (**b**) eyes demonstrating moderate blurring of the disc margins with optic nerve head and macular drusen. Fundus autofluorescence of the right (**c**) and left (**d**) eyes demonstrating hyperautofluorescence of the optic nerve head drusen. (© LS Ediriwickrema 2020. All Rights Reserved)

examination was notable for hyperreflective optic nerve head drusen and preserved peripapillary vessel architecture. Fundus autofluorescence (Fig. 17.2) identified hyperautofluorescent foci along the surface of both optic nerve heads. HVF 24-2 revealed inferior arcuate defects OU coinciding with superotemporal thinning on RNFL OCT.

What is the most appropriate next step in management?

(a) Urgent lumbar puncture with opening pressure
(b) MRI brain and orbits with and without contrast
(c) Pachymetry and gonioscopy
(d) Reassurance with follow-up in 6 months

Management

This patient presented with findings consistent with bilateral optic nerve head drusen (ONHD). Fundoscopic evaluation, fundus autofluorescence, OCT, and/or ultrasonography can confirm the diagnosis and distinguish it from optic nerve head edema. Thus, (d) reassurance and observation is the most appropriate next step in management.

Up to 8.6% of patients with ONHD may experience TMVL, although most patients are asymptomatic [35]. The diagnosis is usually made incidentally. If the ONHD are superficial, fundoscopic exam reveals an elevated and nodular optic disc with blurred margins without obscuration of peripapillary vessels [36]. Patients with buried optic nerve drusen can, however, have fundoscopic findings mimicking papilledema [37]. Formal visual field testing reveals field deficits in up to 87%, most commonly arcuate field defects, enlarged blind spots, nasal steps, and constriction [36, 38, 39].

Confirmation of ONHD is heavily dependent on fundus examination augmented by ocular imaging. B-scan ultrasonography can show hyperechoic calcium deposits with posterior acoustic shadowing, particularly at low to medium gain settings. Compared with orbital CT scan and fundus autofluorescence, B-scan ultrasonography has been shown to detect significantly more cases of ONHD; however, its utility for buried ONHD that are not fully calcified is limited [40]. Additionally, fundus autofluorescence may reveal autofluorescent disc drusen, and FA can demonstrate staining of drusen [41]. FA is useful in differentiating ONHD (which demonstrate late peripapillary staining [75%] or early nodular staining [25%]) from optic nerve head edema (ONHE) (which displays diffuse, early fluorescein leakage) [40, 42]. OCT may detect buried drusen, even when they are not calcified. With the advent of spectral domain (SD-OCT) and enhanced depth imaging (EDI-OCT), the ability to differentiate ONHD from ONHE has improved dramatically. EDI-OCT can evaluate deeper areas of the optic nerve and has a higher detection rate (76%) for buried ONHD than B-scan ultrasonography (59%) [40]. OCT is now the gold standard for detecting drusen, which appear as hyporeflective masses, often with hyperreflective margins (Fig. 17.3) [43].

While the most common complication of ONHD is peripheral visual field defects, choroidal neovascular membranes, nonarteritic anterior ischemic optic neuropathy (NAION), central retinal vein occlusion (CRVO), and CRAO have also been described [35, 44–48]. Studies have shown that patients with ONHD have crowding and compression of optic nerve axons with significantly decreased vascular density and rarefaction in the peripapillary circulation compared with normal controls, which may explain the predisposition to these complications [49, 50].

Overall, ONHD appear as clusters of acellular calcific deposits in and surrounding the optic nerve head. About 73–90% of ONHD are bilateral [44, 51–53]. Pathogenesis remains incompletely elucidated, yet most evidence shows a disruption in axoplasmic transport and axonal degeneration, subsequently leading to mitochondrial efflux with formation of calcific concretions [54]. Prevalence is estimated

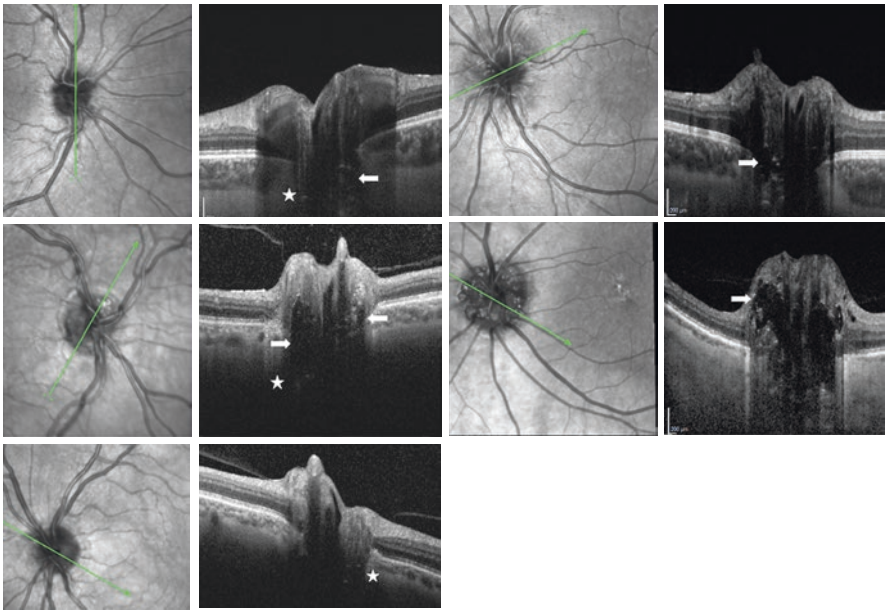

Fig. 17.3 Enhanced depth imaging optical coherence tomography of optic disc drusen of varying depths and sizes. (*Arrows*) Definite drusen with hyperreflective anterior margin and hyporeflective core, sometimes with visible posterior margin. (*Stars*) Hyperreflective dots and lines just anterior to lamina cribosa suggestive of tiny buried disc drusen.

to be 0.4–3.7%, and having an affected family member increases likelihood by a factor of 10 [41]. Factors that may lead to development of ONHD include small inherited optic disc size and vascular dysplasia as a result of mesodermal dysgenesis [37, 55]. ONHD are also found at higher rates in certain ocular and systemic diseases, including retinitis pigmentosa, pseudoxanthoma elasticum, Usher syndrome, Alagille syndrome, phacomatoses, Best disease, and craniosynostosis [51, 56].

Current treatment options are limited. Some use intraocular pressure lowering drops as a potential glaucoma protective strategy, as visual field loss is increased in patients with combined ocular hypertension and ONHD compared with those with ONHD alone. However, there is a lack of evidence-based data to support this approach [57]. Others have speculated about the utility of vasoactive agents such as pentoxifylline to increase optic nerve head perfusion, but no studies have established a protective role for this intervention to date [36, 40]. Despite the lack of effective treatment options, visual outcomes remain favorable overall. Given the rarity of TMVL caused by ONHD, other sources of vision loss should be investigated prior to ascribing the symptoms to ONHD particularly if the history, presentation, fundus examination, and ocular imaging are not supportive of the diagnosis. Observation is the mainstay for these patients.

Case 4

A 59-year-old male with history of hyperlipidemia, hypertension, and heavy smoking presented with intermittent TMVL OS over multiple years. He reported two to three episodes per month, often with his vision going completely black and slowly returning to normal after a few minutes. Occasionally, the vision was blurry, and he also reported intermittent dizziness after the episodes. He denied headaches, scalp tenderness, pain with chewing, and muscle weakness. He denied visual complaints OD. The patient's medication regimen included felodipine and atorvastatin. His VA was 20/25 in OU, IOP was normal, and slit lamp and fundus examinations were normal. HVF 30-2 was full in each eye, and RNFL OCT showed no edema or thinning. Echocardiogram was normal, but CTA revealed a right middle cerebral artery fusiform aneurysm as well as 70% stenosis of the left ICA (Fig. 17.4). Aneurysm repair was urgently scheduled. He, however, developed a spontaneous, diffuse subarachnoid hemorrhage, and emergent aneurysm clipping was performed. On follow-up examination, he reported no additional episodes of TMVL or subsequent visual decline.

What is the best next step in management?

(a) Close observation with blood pressure and cholesterol control
(b) Urgent referral for surgical evaluation of left carotid artery stenosis
(c) Dual antiplatelet therapy
(d) Carotid ultrasonography

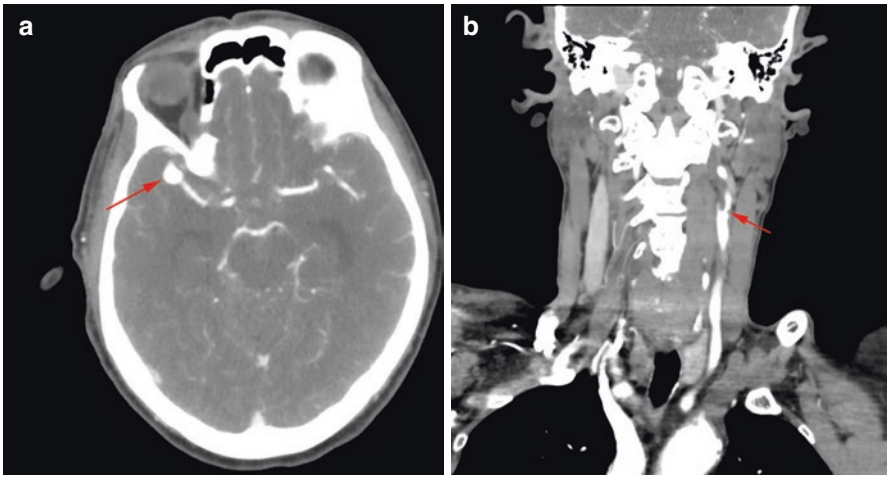

Fig. 17.4 Computed tomography angiography demonstrating (**a**) right middle cerebral artery aneurysm (*arrow*) and (**b**) left internal carotid artery luminal stenosis (*arrow*). ()

Management

This patient is most likely experiencing TMVL from atherosclerotic emboli originating in his stenotic ICA. Current *American Academy of Neurology* guidelines suggest patients with symptomatic carotid stenosis within the past 6 months should be (b) referred urgently to vascular surgery, with a recommended cutoff of 70% stenosis as an indication for carotid endarterectomy [58]. Additional treatment revolves around management of cardiovascular risk factors, statin therapy, and antithrombotic agents.

TMVL secondary to atherosclerotic emboli originating from a severely stenotic ICA presents with sudden, painless loss of vision [59, 60]. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) found the average episode of TMVL was 4 minutes in the setting of carotid atherosclerosis, and others have reported that up to 85% of patients will have visual symptoms lasting less than 15 minutes [61, 62]. While most patients experience partial or complete vision loss, up to one-third of patients will experience positive light phenomena such as scintillations [61]. Further, some evidence suggests that changes in altitude can predispose individuals with carotid disease to thromboembolism [60, 63]. As with other causes of TMVL, ophthalmologic exam is frequently normal.

About 10–15% of patients with transient ischemic attack (TIA) have a stroke within 90 days, half of which occur within 48 hours after the initial event [64–66]. The current definition of TIA is "a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction" in conjunction with the "absence of ischemia on fundoscopic exam and diffusion-weighted imaging MRI" [67]. Based on this definition, one should consider any patient with TMVL as high risk for impending stroke and in need of urgent testing.

Some question remains as to who needs urgent cardiovascular workup after TMVL. In general, patients under age 45 are unlikely to have symptomatic atherosclerosis and carotid stenosis, and a complete workup is not always recommended. Several studies have followed patients under the age of 45 for 3–6 years after an episode of TMVL and found that none of the combined 58 patients surveyed had a single vascular event [68, 69]. In patients 45 and older, however, embolism is the most common cause of ocular hypoperfusion and subsequent retinal TIA (r-TIA), defined as TMVL of ischemic origin lasting less than 24 hours. Up to 25% of patients experiencing either r-TIA or retinal artery occlusion with signs of retinal ischemia subsequently show evidence of a silent acute infarction on diffusion-weighted imaging MRI, prompting a recommendation by the *American Heart Association* to evaluate these patients with neuroimaging within 24 hours of TMVL symptoms [67, 70–72]. Studies have also investigated the risk of stroke in patients with significant carotid stenosis that experience either r-TIA or hemispheric TIA (h-TIA), defined as focal cerebral dysfunction of ischemic origin lasting less than 24 hours. Subgroup analysis of the NASCET trial data comparing risk of stroke between these two groups after medical management alone showed a 2-year stroke

risk of 16.6% and 43.5% in r-TIA and h-TIA patients, respectively [73]. While medical management at the time of the NASCET trial did not include statin therapy and thus likely overestimates stroke risk in this population, the data clearly establish the urgency and necessity of neurovascular evaluation in these patients. Implementation of urgent treatment with a combination of antiplatelet agents, blood pressure and lipid control, anticoagulation if atrial fibrillation is present, and carotid endarterectomy when indicated may decrease stroke risk by up to 80% in patients with any form of TIA [74, 75].

Workup for patients suspected of having r-TIA due to thromboemboli should always include large vessel imaging with either CTA or MRA of the head and neck. Doppler ultrasound of the carotids may also be used. An echocardiogram is required to rule out a cardiac source for thromboembolism. Blood tests including complete blood count, coagulation panel, lipid panel, and hemoglobin A1C are recommended. Finally, smoking cessation, diabetes management, lipid lowering therapies, and blood pressure control must all be addressed. With regard to revascularization surgery, patients with isolated TMVL in the setting of 50% or greater stenosis may actually have increased stroke risk in the 3 years following revascularization. Other high-risk characteristics (age ≥75, male sex, history of h-TIA or stroke, history of intermittent claudication, 80–94% ICA stenosis, absence of collateral circulation on angiography) can help identify patients who will benefit from revascularization. While patients with one or fewer risk factors have an absolute risk reduction (ARR) of −2.2%, patients with 2 or ≥3 have an ARR of 4.9% and 14.3%, respectively [62]. For ophthalmologists, the most vital task is to get these patients to an emergency department affiliated with a stroke center for expedited workup.

Conclusion

TMVL is a frequently encountered complaint that carries a broad differential (Table 17.1). Confirming unilaterality, type and description of vision loss, patient age, the presence or absence of pain, and type of visual field defect are all essential to the initial evaluation. The highlighted cases included TMVL due to retinal migraine, fibromuscular dysplasia, optic nerve head drusen, and atherosclerotic embolism (Table 17.2). When facing a patient with TMVL, one must confidently rule out an atheroembolic source, dissection, or severe fibromuscular dysplasia, as these patients are at a significant risk of impending stroke. Giant cell arteritis and angle closure must also be considered to mitigate the risk of permanent vision loss. Once ruled out, clinicians may turn their focus to other potential causes such as hyperviscosity syndromes, ocular surface abnormalities such as severe dry eye, and gaze evoked amaurosis secondary to compression by an orbital tumor. Patient counseling is also vital to enhance their understanding and improve adherence to recommended evaluation and treatment.

Table 17.1 Differential diagnosis for transient monocular vision loss

Diagnosis	Key clinical characteristics	Clinical exam, lab and imaging findings
Cardiovascular		
Atherosclerotic embolism	Complete loss of vision with potential resolution in minutes to hours	AV[a] nicking, Hollenhorst plaques; carotid ultrasonography or angiogram of head and neck may show stenotic vasculature; risk factors include hypertension, hyperlipidemia, diabetes mellitus
Carotid stenosis		
Fibromuscular dysplasia		
Vasospasm		
Autoimmune		
Giant cell arteritis	Age >50, headache, jaw claudication, proximal muscle aches, scalp tenderness over superficial temporal arteries, severe vision loss (may be preceded by TMVL)	Pale, swollen optic nerve head, flame hemorrhages; elevated ESR[a], CRP[a], and platelets; fluorescein angiogram with delayed choroidal and central retinal artery filling; diagnostic temporal artery biopsy, characteristic ultrasound findings
Other vasculitis subtypes: Lupus, Crohn disease, Takayasu arteritis	Variable presentation, may be asymptomatic or have varying levels of visual field and visual acuity impairment; personal or family history of autoimmune disease	Cotton wool spots, retinal hemorrhages; autoimmune workup may reveal diagnosis; fluorescein angiography key to evaluate retinal ischemia and degree of vasculopathy
Hematologic		
Hypercoagulability	History of hematologic abnormalities, cancers, OCP[a] use; variable presentation	Cotton wool spots, retinal hemorrhages, retinal ischemia; may have abnormal PT/PTT/INR[a], platelet, fibrinogen, protein C, protein S, antithrombin, factor V Leiden, lupus anticoagulant
Neurologic		
Migraine	Visual disturbance lasts minutes to an hour, known history of migraines, preceding classic headache	Normal visual acuity, usually no visual field defect, labs and imaging normal
Intracranial hypertension with papilledema	Bilateral transient visual obscurations that last for seconds, associated with postural headaches and pulsatile tinnitus	Variable visual acuity and visual field defects (e.g., blind spot enlargement, arcuates), optic nerve head edema; lumbar puncture with elevated opening pressure; MRI[a] may demonstrate empty sella, flattening of posterior globes, optic nerve head protrusion, space-occupying lesion; MRV[a] may demonstrate sinus venous stenosis or thrombosis
Ophthalmic		
Intermittent angle closure glaucoma	Variable duration of visual disturbances accompanied by eye pain	May demonstrate arcuate visual field defects, enlarged cup to disc ratio, RNFL[a] thinning on OCT[a]; gonioscopy reveals anatomically narrow angles, +/− cataract

Table 17.1 (continued)

Diagnosis	Key clinical characteristics	Clinical exam, lab and imaging findings
Severe dry eyes	Intermittent blurry vision +/− foreign body sensation or eye pain	Cornea has punctate epithelial erosions with fluorescein staining
Intraorbital tumors	Transient vision loss that can be reproducible with sustained eye movements	Ocular exam variable, but may be normal; CT[a] or MRI of the orbits demonstrates intraorbital mass
Retinal migraine	Often age <40, visual aura without headache, can recur	Normal ocular examination, labs, and imaging
Optic nerve head drusen	Vision loss or visual field constriction for seconds, rarely permanent sequelae	Anomalous optic disc appearance; fundus autofluorescence with hyperautofluorescent foci on optic nerve head; b-scan with hyperechoic opacities with posterior shadowing; OCT with hyporeflective masses often with hyperreflective borders

[a]*AV* arteriovenous, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *OCP* oral contraceptive pill, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalized ratio, *MRI* magnetic resonance imaging, *MRV* magnetic resonance venography, *RNFL* retinal nerve fiber layer, *OCT* optical coherence tomography, *CT* computed tomography

Table 17.2 Case summary of transient monocular vision loss

Etiology	Symptom onset	Length of symptoms	Pattern of vision loss	Significant complications
Retinal migraine	Gradual, over minutes	Up to 1 hour	Complete monocular blindness/blurriness (up to 50%), zig-zags, graying of field, movement throughout field	Permanent visual scotoma
Fibromuscular dysplasia	Sudden, may increase	10–20 seconds, recurring; or constant for several days	Darkening/blurring of entire visual field	Arterial dissection (19.7%), stroke/TIA[a] (19.2%), aneurysm (17%)[b]
Optic nerve head drusen	Sudden	Seconds	Blurred vision, constriction of visual field	Permanent visual field defects (87%), CNVM (24.5%), NAION, CRAO, CRVO[a,b]
Carotid embolism	Sudden	Minutes	Altitudinal onset or resolution (partial or complete), scintillating scotomas	Stroke (16.6%, 2-year risk)[b]

[a]*TIA* transient ischemic attack, *CNVM* choroidal neovascular membrane, *NAION* nonarteritic anterior ischemic optic neuropathy, *CRAO* central retinal artery occlusion, *CRVO* central retinal vein occlusion

[b]Percentages are listed whenever data were available

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Transient Binocular Vision Loss

18

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Case

A 37-year-old woman presents to the ophthalmology clinic for new onset episodes of vision loss and a new type of headache. Her past medical history is significant for obesity, essential hypertension (HTN), type 2 diabetes (T2DM), and migraine headaches with aura. Her family history is notable for myocardial infarction (MI) at a young age in her mother. She reports her vision loss started several weeks ago and further describes a "black out" of the vision in both eyes, lasting a few minutes before returning to normal. These episodes of "black out" in the vision may occur with or without headaches. Upon further questioning, she notes the "black out" only affects the left visual field in both eyes. She has checked this by closing one eye at a time. In regard to her new type of headaches that started 2 months ago, she reports they are different from her chronic migraines, in that they are milder, bitemporal headaches lasting 30 minutes to 1 hour and do not have associated photophobia or nausea. She has tried acetaminophen, caffeine, and sumatriptan for the headaches with minimal relief. Review of systems is positive for chest discomfort and episodes of heart "racing" with associated confusion and shortness of breath. These episodes last for a few minutes and have never been evaluated as the patient has attributed them to anxiety. On exam, the patient has normal visual acuity, equal and reactive pupils with no afferent pupillary defect, normal color vision and normal intraocular pressures. Cranial nerve exam is unremarkable. Anterior segment exam is normal.

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Dilated fundus exam is negative for papilledema. Spontaneous venous pulsations are present bilaterally.

What is the best next step?

A. Reassure patient that vision loss is non-ophthalmic and refer to neurologist for better migraine control.
B. Send patient to emergency department for stroke evaluation.
C. Start artificial tears and have patient return to clinic in 1 week.
D. Refer to primary care physician for evaluation of chest discomfort in the setting of past medical history of HTN, obesity, and T2DM as well as a positive family history for MI.

The correct choice is *(b) send the patient to emergency department for stroke workup*. The patient has transient binocular vision loss in a homonymous pattern as well a change in her typical headaches. In addition, she is a vasculopathic young female with chest discomfort, shortness of breath and past medical history of HTN, obesity, and T2DM as well as a positive family history for MI at a young age.

Discussion

Transient binocular vision loss (TBVL) is defined as episodic vision loss involving both eyes that lasts less than 24 hours and results in complete recovery of vision [1]. The case above demonstrates the variability of symptoms and complicated history of a patient presenting with TBVL. It is important to properly manage these patients since a missed diagnosis could lead to devastating consequences, including permanent blindness, stroke, and death.

The differential diagnosis of TBVL includes ophthalmic, neurologic, and systemic conditions as summarized in Table 18.1. To narrow this differential, it is vital to elucidate the nature of the patient's "vision loss," which may encompass a variety of symptoms from mild blurring of the vision, to positive visual phenomena

Table 18.1 Etiologies of TBVL

Vascular	TIA (carotid or vertebrobasilar distribution), PRES
Cortical	Migraine, epilepsy
Elevated intracranial pressure	Increased CSF production (choroid plexus papilloma), decreased CSF outflow/absorption (obstructive hydrocephalus, meningitis, SAH), decreased venous outflow (venous sinus thrombosis, jugular vein compression), intracranial masses
Systemic	Giant cell arteritis, atherosclerotic disease [light-induced amaurosis], hypercoagulability, thrombotic emboli
Ophthalmic	Dry eyes, cataracts, optic disc drusen, retinal arterial/venous occlusions, angle closure, gaze-evoked amaurosis fugax

Abbreviations: *CSF* cerebrospinal fluid, *PRES* posterior reversible leukoencephalopathy syndrome, *SAH* subarachnoid hemorrhage, *TBVL* transient binocular vision loss, *TIA* transient ischemic attack

covering the vision, to total blackouts or tunneling of the vision. Care must be taken to differentiate homonymous defects affecting one side of the vision in both eyes, from monocular deficits in which the vision loss truly affects only one eye. Patients with a homonymous type of transient vision loss may only report vision loss in one eye (typically, the eye with the temporal field missing). The pattern of vision loss is the first step in determining the etiology of acute vision loss and whether an expedited work up is needed. *Complete* loss of vision transiently affecting both eyes tends to be more consistent with bilateral optic disc edema whereas *hemifield* loss suggests transient ischemic attack (TIA), migraine and/or occipital lobe seizure activity [2].

While the description of the vision loss is important, it is also vital to obtain a detailed medical history including past medical and ocular history, review of systems, family and social history as well as a thorough ophthalmic and neuro-ophthalmic exam with dilation [3]. Red flags in the past medical history may include significant vascular risk factors, such as diabetes, hypertension, hyperlipidemia, heart disease, or other illnesses that increase risk of vasculopathy or intracranial pathology such as cancer. Family history of cancer, autoimmune disease, or cardiac disease, particularly at a young age are also important to note and may suggest that a more urgent workup for transient vision loss be pursued. Below we will review the various causes of TBVL, how to differentiate these causes clinically, and the pertinent diagnostic workup.

Vascular Causes

One of the most concerning etiologies of TBVL is a vascular phenomenon. Abnormalities in vascular perfusion caused by blood pressure dysregulation, vasospasm, or thrombotic emboli may lead to stroke, TIA (in carotid or vertebrobasilar distribution), and posterior reversible leukoencephalopathy syndrome (PRES).

Transient Ischemic Attack (TIA) TIA should be suspected in individuals of all ages who present with TBVL without a clearly discernible ophthalmic cause such as dry eye syndrome, acute diabetic cataracts or episodes of acute angle closure glaucoma [4]. Though history of vascular risk factors should further lower threshold for emergency room evaluation, even patients without a significant vascular history may present with TIA. Thus, if ophthalmic causes can be ruled out, and the history is consistent with TIA, then a stroke evaluation is indicated. The most common manifestation of episodic visual loss secondary to TIA is monocular vision loss; however, binocular presentations include transient homonymous hemianopia, bilateral positive visual phenomenon and, least commonly, complete bilateral loss of vision or blindness [5]. In a retrospective study of 826 patients with transient visual symptoms related to TIA, approximately 20% had a major source of embolism detected, requiring urgent intervention or management, and atrial fibrillation was particularly frequent in patients with transient homonymous hemianopia [5]. About one-quarter of strokes and TIAs occur in the vertebrobasilar distribution.

Since vertebrobasilar strokes present differently from classic hemispheric strokes, a through history may help a physician to rule in TIA. For example, whereas hemispheric/anterior strokes tend to commonly present with asymmetric face droop, arm/leg weakness and speech difficulty, vertebrobasilar insufficiency (VBI) may cause vertigo (most common), ataxia, syncope, dysphagia/dysarthria, nausea/emesis, nystagmus, and altered consciousness/confusion. That being said, some authors suggest that in cases of isolated binocular vision loss without other accompanying neurologic deficit, ischemia of the visual cortex should be suspected, and patients should be sent for urgent evaluation in the same way one would manage patients with suspected vertebrobasilar TIA with other focal neurologic findings [6]. When a recent TIA is suspected, an expedited work up in the emergency room is necessary to evaluate for grave cardiac abnormalities and hemodynamic instability requiring immediate management, as well as to address the fall risk associated with these episodes. The clinician should refer the patient for urgent neuroimaging and stroke evaluation [4]. This workup will likely include magnetic resonance imaging (MRI) of the brain, MR or CT angiogram of the blood vessels of the head and neck, and an echocardiogram; serum testing to include a lipid panel, glycosylated hemoglobin, and thyroid stimulating hormone; and heart rhythm evaluation with telemetry or electrocardiogram. The goal of this work up is to assess for potentially modifiable problems that can be managed to decrease the patient's overall stroke risk.

Posterior Reversible Leukoencephalopathy Syndrome (PRES) PRES should be suspected in patients with a history of HTN, autoimmune or renal disease, or chronic immunosuppression who present with headache, visual symptoms (including TBVL), confusion, and seizures. Vision loss, though bilateral and transient, tends to be longer, lasting hours to sometimes days. The transient vision loss presentation is very similar to stroke and TIA as discussed above, and thus, patients may be misdiagnosed and worked up as a vascular event until they undergo neuroimaging with paucity of ischemic findings. Diagnostic work up includes brain MRI with diffusion-weighted imaging, which characteristically shows vasogenic edema with T1 hypointensity, T2 hyperintensity and increased apparent diffusion coefficient (ADC) at cortical and subcortical levels in watershed regions of the brain [7]. Since PRES is typically related to persistent and significantly elevated blood pressure, management involves blood pressure control and close monitoring, with treatment of seizures if already present. Visual recovery is favorable with many reports of return to normal baseline vision after correction of blood pressure [8, 9].

Intracranial Causes

Epilepsy Epilepsy can cause both positive transient visual phenomena and headaches, and therefore, must be distinguished from migraine. Epileptics commonly experience headache as a post-ictal event, as reported in 40–45% of patients with epilepsy [10]. When trying to determine whether visual auras are secondary to seizure versus migraine, a detailed history should include a description of the visual

phenomena along with the duration. Epileptic visual auras may cause transient bilateral visual phenomena that are usually brightly colored, circular, or spherical images that move rapidly, are stereotyped (almost always on the same side) and occur for a few minutes or less. In contrast, migraine auras tend to be more geometric or linear, commonly switch sides, build over several minutes and last longer, from 15 minutes to an hour [10]. Workup for epileptic etiology of transient bilateral vision disturbance should include MRI of the brain and electroencephalogram (EEG). If the events are occurring a couple times a week, a standard 60-minute EEG study may be normal. In these cases, it may be useful to monitor the patient for a longer duration by ordering an ambulatory EEG study, which is typically done for 48–72 hours, or by admitting the patient to an epilepsy monitoring unit (EMU) for a week long continuous monitoring with EEG in the hospital. If you are an ophthalmologist, your neurology colleagues may be able to help guide you in this endeavor depending on what EEG monitoring studies are available at your hospital. Typically, if suspicion is high for seizure as the cause for TBVL, work up can be done as an outpatient, rather than sending the patient to the emergency room. The exception to this recommendation is if the patient has associated loss of consciousness with the visual ictal events, in which case evaluation should be expedited.

Elevated Intracranial Pressure (ICP) Elevated ICP may be caused by increased CSF production (choroid plexus papilloma), decreased CSF outflow/absorption (obstructive hydrocephalus, meningitis, SAH), or decreased venous outflow (venous sinus thrombosis, jugular vein compression and intracranial masses), all of which can lead to papilledema. Papilledema is classically defined as swelling of the bilateral optic discs secondary to elevated intracranial pressure [11]. About 68–72% of patients with papilledema describe transient visual obscurations (TVOs) [12]. TVOs secondary to papilledema may be binocular or monocular, usually last seconds and are associated with positional changes. Patients may describe a brief "tunneling in" of the vision or episodic "blacking out" of the vision in both eyes. Interestingly, similar TVOs can occur in the setting of optic disc drusen and other anomalies affecting the optic disc [13]. It is believed that TVOs are caused by transient ischemia of the optic nerve head that occurs when an edematous optic nerve head (increased interstitial pressure) compromises perfusion pressure, which is then further compromised in the setting of fluctuations in arterial, venous, and CSF pressure. While TVOs are common in the setting of papilledema, they have not been shown to correlate with visual outcome and do not require specific treatment aside from treating the underlying intracranial hypertension [14]. Management of papilledema is discussed in detail in Chap. 6.

Migraine Headaches The differentiation of benign migraines from the more urgent TIA can be quite challenging. When a migraine patient presents with *new* headaches of a different character and different associated symptoms (i.e., paresthesia, paralysis, vision loss, speech difficulty, and facial weakness), TIA should be high on the clinician's differential. Migraine headaches may present with visual auras described as "lines or waves" that can occur minutes prior to the onset of a headache and may *last up to 60 minutes*. These auras typically affect both eyes in a homonymous, hemifield pattern. Some patients may struggle to describe the

hemifield effect or may not appreciate that one side of the field of both eyes is affected. Clues that may indicate that the patient's bilateral visual complaint is related to migraine rather than TIA include the absence of vascular risk factors, such as HTN, hyperlipidemia, heart disease and diabetes, and the clinical description of a positive visual phenomenon compared with a negative one. Though patients with migraine are more likely to complain of something added to the vision (sparkles, lines, waves, and colors) as opposed to a "black out" or "gray out" of vision, patients with TIA may also rarely present with positive visual phenomenon. We have also seen patients with new occipital strokes complaining of positive visual phenomenon such as "cartoon figures" in the vision, in a homonymous hemi-field pattern. Thus, it may be challenging to clinically distinguish migraine from stroke. Perhaps a more helpful clinical clue is that positive visual phenomenon in migraine may spread or build over the duration of the episode. For example, a small part of the vision may be involved initially, and the area may grow to cover more of the visual field over the duration of the migraine aura (typically up to an hour). This pattern is different from TIA, in which the vision change classically starts suddenly, does not build or expand, and is not necessarily accompanied by headache before, during or after the event. However, due to uncertainty of clinically differentiating TIA versus migraine and the risk of "migrainous stroke," some authors have recommended a low threshold for vascular, neuro-ophthalmic and neuroimaging work up in patients presenting with new onset of migraine with aura [15].

Systemic Causes

Many systemic diseases can lead to transient binocular vision loss, including giant cell arteritis (GCA), cardiac thromboemboli, hypercoagulability, and atherosclerotic disease.

Giant Cell Arteritis Among all causes of TBVL, GCA is a true emergency with significant threat for permanent vision loss in one or both eyes. GCA is a nodular, granulomatous inflammation of medium and large-sized arteries [16]. It classically presents in patients older than 50 years as transient monocular or binocular vision loss associated with jaw claudication, polymyalgia rheumatica, and temporal artery tenderness. The transient vision loss associated with GCA is usually described as amaurosis fugax (or total blackout of vision in one eye), though complete episodic loss of vision in both eyes may less frequently occur. These episodes usually occur days prior to the permanent vision loss and are secondary to transient retinal/choroidal/optic nerve ischemia. In those patients with GCA who suffer permanent vision loss, up to 85% are diagnosed with arteritic ischemic optic neuropathy, while the remaining 15% have permanent vision loss secondary to retinal artery occlusion [17, 18]. In addition to vision loss, patients may also note diplopia or eye pain. If not promptly managed with corticosteroids, GCA can swiftly lead to permanent bilateral vision loss as well as cerebrovascular accidents [19]. If GCA is suspected based on history and/or exam findings of retinal artery occlusion or optic disc edema/pallor, then emergent management is indicated, as discussed in detail in Chap. 23.

Ophthalmic Causes

A thorough ophthalmic history and exam may be useful to rule out anterior segment conditions causing TBVL such as dry eye syndrome (DES), acute angle closure and acute diabetic cataracts.

Dry Eye Syndrome DES commonly presents with intermittent vision changes, which may be described as "blurry, foggy or hazy," and can also include monocular diplopia and eye discomfort. A detailed ocular surface exam will show punctate epithelial erosions with fluorescein staining, decreased tear break up time, tear film debris, Meibomian gland dysfunction, blepharitis, or any combination of the above. An irregular air-tear interface can significantly affect visual acuity causing bilateral or unilateral monocular diplopia or significant blurring of the vision. Management consists of lubrication and addressing the underlying cause of ocular surface dryness (e.g., Meibomian gland dysfunction, blepharitis, thyroid eye disease, neurotrophic cornea, and exposure keratopathy) [20].

Acute Angle Closure Glaucoma If TBVL is associated with eye pain or redness and/or colored haloes around lights, then the presence of elevated intraocular pressure (IOP), a hyperopic refraction, conjunctival injection, corneal edema with glaukomflecken on slit lamp exam, and narrow angles on gonioscopy should raise concern for primary acute angle closure glaucoma. These patients should **not** be pharmacologically dilated until the underlying issue has been addressed and may require iridotomy to prevent future episodes of angle closure [21].

Cataract Diabetic cataracts should be suspected in patients with uncontrolled diabetes and snowflake opacities within the crystalline lens on exam. History may reveal symptoms of hyperglycemic episodes (e.g., polydipsia, polyuria, hunger, and weight loss).

In summary, careful history and exam findings may help distinguish benign causes of TBVL from potentially vision-threatening causes. When there is concern for a vascular cause, urgent neuroimaging and stroke evaluation are indicated. If the patient describes any features concerning for GCA, corticosteroids should be initiated as soon as possible, and the patient should undergo immediate evaluation.

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Visual Aura

19

Kiel M. Woodward and Amrita-Amanda D. Vuppala

Case

A 26-year-old woman is referred for treatment of headaches with associated visual disturbance. The patient reports severe, pulsatile head pain that is located behind both eyes with radiation to her occiput and down her neck. These headaches are associated with photophobia and nausea and last several hours, sometimes up to a day. Occasionally, her headaches are preceded by flashing lights that spread to involve most the left side of her vision in both eyes. This vision disturbance typically lasts about 30 minutes. The patient has been seen in the local emergency room for these symptoms multiple times, with normal brain MRI and CT angiography of her head and neck. She also had an electroencephalogram (EEG) that was unremarkable. The patient is an otherwise healthy woman who denies use of tobacco, and whose only medication is a low-dose combined estrogen–progestin oral contraceptive pill. Her neurologic and ophthalmic examinations are both unremarkable.

1. Which of the following would you consider prescribing for acute migraine treatment in this patient?
   A. Oral triptans
   B. Oral magnesium
   C. Intranasal ketamine
   D. Single-pulse transcranial magnetic stimulation
   E. All of the above

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Answer This patient is most likely suffering from episodic migraine with and without aura. There are an increasing number of treatments available for migraine aura and *(e) all of the above* have shown some efficacy at alleviating aura associated with migraine. There is no evidence that triptans cause intracranial vasoconstriction or increased risk of stroke.

2. The patient has been told in the past that her risk of stroke is higher given her history of migraine with visual aura. What would you advise her based on the most recent available literature regarding migraine with aura and stroke risk?
   A. Do not worry, there is no difference in stroke risk between young women who suffer from migraine with aura and those who do not.
   B. Find another mode of contraception, there is an increased risk of stroke in young women suffering from migraine with aura who use estrogen-containing contraceptive pills.
   C. Do not worry, while there is an increased risk of stroke in women who use high-dose estrogen combined hormonal contraceptive pills, there is not an increased risk of stroke in women who use low-dose estrogen combined hormonal contraceptive pills.
   D. Find another mode of contraception, if you stop using estrogen-containing contraceptive pills your risk of stroke will be normal.

Answer Multiple studies have demonstrated an increased risk of stroke in migraineurs with aura, and this risk is compounded by the use of estrogen-containing combined hormonal contraceptives (CHCs) and smoking. There is rising controversy among neurologists regarding long-standing guidelines of migraine with aura being an absolute contraindication to the use of estrogen-containing CHCs due to the majority of studies being completed in an era where high doses of estrogen (>50 μg) were used in CHCs, whereas the estrogen doses in today's CHCs are much smaller (10–35 μg). Although there is controversy, there are no studies that directly compare doses of estrogen in CHCs with stroke risk. We would advise the patient to *(b) find another mode of contraception, since there is an increased risk of stroke in young women suffering from migraine with aura who use estrogen-containing contraceptive pills.*

Discussion

Visual Aura Classification

Visual auras (aura – Latin origin meaning "breeze") are a combination of positive and negative visual phenomena that can occur in migraine, epilepsy or vascular events such as transient ischemic attack or stroke. Visual aura may present as a monocular (in the case of retinal migraine) or homonymous binocular (in the case

Table 19.1 ICHD-3 criteria for migraine with aura

A.	At least two attacks fulfilling criteria B and C
B.	One or more of the following fully reversible aura symptoms: Visual Sensory Speech and/or language Motor Brainstem Retinal
C.	At least two of the following four characteristics: At least one aura symptom spreads gradually over ≥5 minutes and/or two or more symptoms occur in succession. Each individual aura symptom lasts 5–60 minutes. At least one aura symptom is unilateral. The aura is accompanied, or followed within 60 minutes, by headache.
D.	Not better accounted for by another ICHD-3 diagnosis.

Abbreviations: *ICHD-3* International Classification of Headache Disorders-3

of cortical origin) visual disturbance [1]. Manifestations of visual aura may be experienced as simple hallucinations, such as photopsias or scotomata, or more complex visual hallucinations, such as fortifications, teleopsia, or metamorphopsia [1]. Blurred vision is often reported in patients experiencing migraine and focal seizures, but no consensus exists on whether this represents an aura phenomenon [2].

The criteria for migraine with aura are listed in Table 19.1, as adapted from the most recent International Classification of Headache Disorders (ICHD)-3 criteria published in 2018 [3]. Of the aura subtypes, visual aura is by far the most common, occurring in more than 98% of migraine auras compared with sensory and language disturbances that occur in 36% and 10% of auras, respectively [1, 4]. The reasoning for why visual aura is so much more common than the other types of aura and why visual aura as a symptom is so variable is poorly understood. It should be noted that aura associated with migraine may occur independently of headache or head pain in general. When visual aura is accompanied by headache, there is no fixed temporal relationship, and it can occur before, during, or after the onset of head pain [2].

The pathophysiology of visual aura in migraine is now widely accepted to be due to cortical spreading depression (CSD). This process was first described by Leão using a rabbit model in 1944 and later shown in humans with perfusion weighted and functional MRI studies [5–7]. CSD is a slowly propagating wave of depolarization in cortical neurons and glia, followed by hyperpolarization that moves across the cortex at a rate of 3-5 mm/min and is accompanied by dramatic shifts in ion homeostasis and neurotransmitter release [8]. The body's attempt to restore homeostasis is met with an increased energy demand and subsequent transient increase in cerebral blood flow. Although animal model studies have demonstrated that CSD can be triggered by mechanical probing of the cortex, electrical stimulation, and application of potassium solution and endothelin, the exact trigger for CSD in humans is not known [8].

Differentiating Migraine with Visual Aura from Visual Aura Due to Focal Cerebral Lesions

While the most common cause of visual aura is migraine, visual aura may occur in the setting of epilepsy, stroke, tumors, or other focal cerebral lesions or dysfunction. The occurrence of typical migraine-like visual aura due to a structural lesion without other focal neurologic signs is rare, yet knowing which patients require further investigation with neuroimaging is a common clinical challenge. The characteristics of the aura and the demographics of the patient can help determine the need for further work-up.

A study that compared visual aura in migraine and epilepsy found that the visual aura of migraine is usually longer lasting (5 to 60 minutes in migraine vs. 1–2 minutes for epilepsy), less frequent (one to two times per month in migraine vs. three to four times per month for epilepsy) and typically not stereotyped or lateralized in visual field appearance. In addition, due to centrifugal spreading that occurs with migraine, visual aura in migraine is often followed by the characteristic nausea/vomiting and photophobia or phonophobia [9]. If these classic migraine characteristics are not observed or if there is loss of consciousness with the visual aura episodes, work up with routine EEG to rule out seizure should be pursued.

A case series that analyzed characteristics of visual aura due to structural brain lesions proposed some indicators, or red flags, that may warrant further imaging: visual aura without headache, visual aura lasting less than 5 minutes, age of onset greater than 40, stereotypical visual aura (especially locked-hemifield aura), increasing frequency or changing pattern of long-standing aura, persistent scotoma following a typical aura, and presence of seizures [10]. In patients with any of these red flags, MRI brain with and without contrast to evaluate for ischemic, infectious, space-occupying, or inflammatory structural changes is warranted.

Migraine with Visual Aura and Cardiac Associations

In the last decade, cardiac associations surrounding migraine with visual aura, including the overall increased stroke risk in patients having visual aura with migraine and the role of patent foramen ovale (PFO), have gained significant attention.

Several studies have shown a correlation between young migraineurs with aura and the presence of a PFO, with larger PFO and the presence of a right-to-left shunt showing the highest correlation [11]. Studies comparing PFO closure versus sham have not found a significant decrease in migraine attacks overall, although secondary analysis did show a significant decrease in the frequency of migraine aura [12]. There is also a correlation between migraine with aura and hereditary hemorrhagic telangiectasia, a syndrome in which pulmonary arteriovenous malformations are frequently seen and can cause right-to-left shunts [13]. This correlation between migraine aura and right-to-left shunting has raised the hypotheses that either microemboli or hypoxia may be triggers for cellular injury and resultant CSD.

Evidence for increased risk of stroke in the setting of migraine with aura (compared to migraine without aura) has been described in multiple recent studies [14]. The risk of stroke in migraine with aura is highest in young female patients (<45 years old) and is compounded by smoking and use of CHCs [14]. One study demonstrated that frequency of aura may be directly correlated with stroke risk, as patients with aura ≥13 times per year had a higher risk (OR 10.4) compared with those with aura <13 times per year (OR 3.58) [15]. While there is evidence that migraine with aura is associated with increased risk of stroke, the etiology of this increased risk is not clear. Proposed mechanisms include paradoxical stroke due to the increased incidence of PFO and the concept of "migrainous infarction," in which stroke is presumed to be due to vasoconstriction and hypoperfusion from numerous biochemical shifts occurring after CSD.

Data regarding stroke risk with use of CHCs have led to the current guideline from the World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG) that migraine with aura is an absolute contraindication to the use of all CHCs [16]. Debate about this recommendation has arisen among neurologists due to several confounding factors present in the investigations that implicated estrogen's risk: estrogen dose, aura frequency, definitive stroke diagnosis with MRI imaging, and other stroke risk factors. The original studies that led to these findings took place when the standard dose of estrogen in CHCs was >50 μg (now considered "high-dose" and no longer recommended for routine use), whereas "low-dose" options (10–35 μg) are available today [14]. A recent retrospective study investigating stroke risk in migraineurs and use of CHCs, presumably with "low-dose" CHCs, continued to show an increased risk of stroke in migraine with aura and use of CHCs (OR 6.1) compared with migraine with aura and no use of CHC (OR 2.7), although this study was not able to identify a stratified risk of stroke with the dose of estrogen [17]. No studies exist that investigate the relationship of estrogen dose and risk of stroke in migraineurs with aura. While multiple studies report a higher relative risk of stroke in women with migraine with aura using estrogen-containing oral contraceptives, the absolute risk of stroke is small with a study finding an absolute risk of ischemic stroke of 3.56 per 100,000 reproductive-aged women [18]. Although the current guidelines recommended avoiding use of all CHCs in migraine with aura patients, there is an increasing demand for evidence to support this claim.

Finally, an important part the discussion of stroke risk in patients with migraine and visual aura includes the question of whether this population of patients require hypercoagulability workup and/or initiation of an antithrombotic agent, such as aspirin. Though the data for this are also limited, the most recent recommendation in 2017 from the American Headache Society suggests that if a patient has significant personal or family history of thrombosis, or if the patient has prior MRI evidence of ischemia (microvascular or large vessel), hypercoagulability workup is warranted. For patients with migraine with aura who do not have any significant medical history of hypercoagulable disorder personally or in their family, physicians may consider screening for markers of endothelial activation that have some evidence for a link to migraine with aura, including von Willebrand factor, C-reactive

protein and fibrinogen. Though pertinent risk factors, including hypertension, hyperlipidemia, diabetes and thrombotic states, should be managed, there are no data to suggest initiation of antithrombotic agents in patients having migraine with aura [19].

Management of Migraine with Aura

Although migraine with and without aura are recognized as distinct entities, the management approach is typically similar, as there are no therapies proven to have better efficacy for migraine with aura versus without, with one exception. Single-pulse transcranial magnetic stimulation (sTMS) has been studied in migraine and is specifically indicated for migraine with aura as an abortive therapy. Of note, this is an FDA-approved treatment. The sTMS is proposed to interrupt propagation of CSD during an aura. A randomized, sham-controlled trial showed that there was a 2-hour pain-free rate of 39% versus 22% in the sTMS group versus sham group, respectively [20]. Daily use of sTMS has also been approved for migraine (with or without aura) for prophylaxis. There are no prophylactic treatments specifically approved for migraine with aura.

Several pharmacologic agents have been studied in migraine aura specifically. A study in rat cortex and chick retina showed that neuronal N-methyl-D-aspartate (NMDA) receptors are involved in the creation and propagation of CSD, and thus, NMDA-antagonists may have a role in migraine aura therapy [21]. Ketamine, memantine, topiramate, lamotrigine, and magnesium are all NMDA-antagonists that have been studied and show some promise as treatment for migraine aura but, aside from topiramate, lack strong evidence of efficacy. One case series and a retrospective study showed intravenous ketamine may be of benefit in refractory migraine [22, 23]. Another randomized controlled trial of intranasal ketamine showed benefit for reducing the severity of aura in migraine with prolonged aura [24]. Lack of clear evidence, along with difficulty of administration and potential for adverse effects, limit the widespread use of this medication.

Memantine is an activity-dependent NMDA receptor antagonist, and it has also been shown to have activity on the 5HT3 receptor and a subtype of the nicotinic acetylcholine receptor [25, 26]. One observational study found a reduction in migraine aura, as well as headache in patients treated with memantine [27]. A randomized, placebo-controlled study has been conducted for migraine patients; however, migraine with aura was excluded from the study [28]. Further research is needed regarding memantine's efficacy in migraine aura.

Among its numerous effects on ion channels and connexin channels, magnesium also serves as an activity-dependent NMDA receptor antagonist. It is widely used as a nonprescription prophylactic and acute therapy, largely due to its tolerability and availability. Reduced levels of magnesium have been found in the cerebrospinal fluid and serum of migraineurs [29]. In a randomized, placebo-controlled study, individuals having migraine with aura and receiving magnesium sulfate showed a statistically significant improvement of pain and of all associated symptoms

compared with controls; conversely, there was no statistical difference in pain levels of patients who had migraine without aura and were being treated with magnesium sulfate, versus those treated with placebo [30]. There is little evidence to support magnesium's efficacy as a prophylactic agent.

Several antiepileptic medications have been used and studied for their effectiveness in migraine with and without aura, with particular attention paid both to topiramate and lamotrigine for migraine aura. Both topiramate and lamotrigine are known to have multiple mechanisms of action and effects on multiple voltage-gated ion channels, including presynaptic voltage-gated calcium channels (VGCCs) and voltage-gated sodium channels (VGSCs) [31]. Their inhibition of VGCCs and VGSCs has been shown to have a net inhibitory effect on glutamate release in the CNS.

Topiramate, widely used for migraine without aura prophylaxis, has also been shown to have a beneficial effect on migraine aura. Multiple large randomized trials have shown statistically significant reduction in migraine (with or without aura) days with topiramate when compared with placebo [32, 33]. There are few studies that perform subgroup analyses on migraine aura. One such study, while it did not find statistical significance in headache reduction for migraine without aura, did find reduction in migraine with aura frequency [34].

Regarding lamotrigine, three open-label pilot studies and one retrospective study examining lamotrigine's effect on migraine with aura from 1999 to 2005 all showed excellent response in terms of reduction of aura frequency and duration [35–38]. While these open-label and retrospective studies showed promise in aura prophylaxis, a randomized clinical trial in 1997 showed that lamotrigine 200 mg did not have significant benefit in reducing migraine (with or without aura) frequency when compared with placebo. Of note, no subgroup analysis of migraine with versus without aura was performed, and migraine with aura comprised only 17 patients out of 77 in this study [39]. A later cross-over study in 2007 comparing low doses of topiramate (50 mg), lamotrigine (50 mg), and placebo found that low-dose lamotrigine did not meet the primary end points (reduction of migraine frequency by ≥50% and reduction of migraine intensity by ≥50%) when compared with placebo, but did show a statistically significant reduction in migraine frequency per month (by 1.13) when compared with placebo in their secondary end point analysis [40]. Again, migraine with aura was only represented by 19 out of 60 patients in this study. While lamotrigine does show promise as a prophylactic agent for migraine aura from multiple pilot studies focused exclusively on migraine aura, randomized and cross-over studies including migraine with and without aura have not shown significant benefit in reducing migraine frequency and intensity when compared with placebo, although migraine with aura had little representation in these studies.

Many health care providers avoid prescribing triptans in migraine with aura due to their vasoconstrictive effects and concern for migrainous infarction. However, a study with MR angiography demonstrated that although there is evidence of extracranial arterial vasoconstriction, there are no significant intracerebral vasoconstrictive effects with use of triptans [41]. There are no formal contraindications to use of triptans in migraine with aura.

In conclusion, visual aura is a heterogenous set of symptoms that can be seen in multiple settings, including migraine, ischemia, and focal seizures. Migraine is the most common cause of visual aura, and no further work up is required if the aura is consistent with typical migraine aura. Patients should undergo further evaluation with head imaging and potentially EEG in the atypical settings discussed in this chapter. The risk of stroke is elevated in migraine with aura for unclear reasons, and there seems to be further increased risk in young females, with cigarette smoking, and with use of CHCs. While there have been long-standing contraindications regarding the use of CHCs in patients with migraine with aura, controversy surrounding the risk has been increasing due to mixed evidence and multiple confounding factors. Potential risk of use of CHCs should be discussed with all migraine with aura patients, and an assessment for other vascular risk factors should be conducted. Treatment for visual aura in migraine is largely the same as migraine without aura, although there is some evidence that ketamine may be more beneficial for prolonged aura, and sTMS is the only FDA-approved therapy specifically for abortive use in migraine with aura.

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Part V

Pain

Migraine

20

Matthew V. Purbaugh and Amrita-Amanda D. Vuppala

Case

A 24-year-old Caucasian woman is referred to your clinic for refractory migraines. Her past medical history is significant for depression, obesity, tachycardia, and migraines since the age of twenty-two. Her current migraines are described as "pounding" and localized to the left temporal region of her head. There is associated photophobia, phonophobia, and nausea. She denies any change in the pain with change in position. Though her head pain was initially manageable the intensity has increased over time and is now associated with eye pain. She reports headache frequency of three times a week. Initial workup with primary care included an MRI brain scan with and without gadolinium that was unremarkable. Given the headache characteristics and normal MRI, the patient was diagnosed with episodic migraine and started on a preventative agent of amitriptyline and an abortive agent of sumatriptan. The amitriptyline was initiated at 25 mg nightly and titrated to 150 mg nightly. This medication decreased the intensity and severity of her migraine by half. She was also prescribed sumatriptan 100 mg orally as needed for severe migraine and, though this drug is effective as an abortive on severe headache days, she frequently runs out of her monthly limit of sumatriptan. The patient has normal neurologic and ophthalmologic exams, including a healthy appearing fundus in both eyes. She would like to reduce her headache frequency and severity. She states that she would like to avoid anything involving needles and has recently lost her

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insurance. She is not currently planning on becoming pregnant and is using a copper intrauterine device (IUD) as birth control.

What is the next best step in managing this patient's episodic migraine disorder?

A. Stop amitriptyline and start onabotulinumtoxinA (Botox)
B. Continue amitriptyline and add topiramate 50 mg nightly with titration to 100 mg twice a day
C. Discontinue amitriptyline and start valproic acid 500 mg twice a day
D. Discontinue amitriptyline and start topiramate 50 mg nightly with titration to 200 mg daily
E. Continue amitriptyline and start valproic acid 500 mg twice a day

We recommend *choice (b)*, however *choice (d)* would also be a reasonable option. The patient experienced 50% improvement of headache frequency and severity with the amitriptyline, with no significant side effects. Thus, the benefit of this medication outweighs the risk of adverse side effects, and the medication should be continued. In addition, the patient has depression, and the amitriptyline may also be helping her depression (even though it is being used as a migraine medication). We recommend initiating polytherapy by starting another evidence-based preventative agent as discussed in this chapter. In this case, topiramate is a better choice than valproic acid. Though both medications have class A level of evidence for migraine prevention per the American Academy of Neurology (AAN), valproic acid is generally avoided in young women of childbearing age due to teratogenic side effects, even if the patient is on birth control. Topiramate would also be of greater benefit in this patient as she is overweight, and topiramate may cause weight loss through appetite suppression. The starting dose of topiramate or any preventative agent should be low and gradually increased to a higher dose as needed and as tolerated. We will discuss the benefit of using polytherapy with multiple medications at a lower, tolerable dose later in this chapter. *Choice (d)* is also a reasonable option as the evidence for polytherapy over monotherapy is limited. Headache societies currently recommend monotherapy implicitly due to the lack of a large number of controlled trials for polytherapy.

Management

Migraine is one of the most common diseases in the United States. With a prevalence of 16.6% in adults 18 years and older, migraine is the fifth most common cause of emergency room visits and makes up 1.2% of all outpatient visits to medical providers [1]. Migraines occur in 17.6% of females and 5.7% of males, with a clear female predominance [1, 2]. Since many migraine patients have accompanying visual complaints such as eye pain, positive visual phenomenon, or photophobia, migraine is also a common presentation to neuro-ophthalmologists from both neurologic and ophthalmologic training backgrounds.

The diagnosis of migraine as indicated by the most recent guidelines from the International Headache Society requires at least five attacks of head pain lasting between 4 and 72 hours if untreated, with at least two of the following common pain characteristics: unilateral location, pulsating quality, moderate to severe pain intensity and aggravation or avoidance of physical activity. During the headache, one of the following must be present: nausea/vomiting, photophobia, or phonophobia [3]. Many migraineurs require both a preventative and an abortive agent for adequate pain relief. The goal of the preventative or prophylactic agent is to keep the head pain at bay. In contrast, the abortive agent is used episodically on an as-needed basis when the head pain has flared or increased in severity. Adequate migraine treatment with an efficacious preventative medication is important to prevent the transformation of episodic migraine into chronic migraine [4]. While many primary care providers feel comfortable making a preliminary diagnosis of migraine and starting a first-line agent, the question of what to do next if the first medication fails is less clear. Most patients have already been through a trial of a first-line preventative by the time they see a specialist (neurologist or ophthalmologist) and, thus, adequate knowledge of appropriate therapeutic interventions becomes vital.

We begin with a discussion of how to best initiate monotherapy. When choosing a preventative medication, several aspects must be considered. The patient's medication list and past medical history must be reviewed so that the physician is aware of other medical comorbidities and potentially interacting medications. It is also important to consider adverse reactions the patient may have had to other mediations in the same class. For example, patients with a history of depression may have already tried a tricyclic antidepressant or serotonin-norepinephrine reuptake inhibitor (SNRI). Next, it is important to follow the evidence-based guidelines for preventative agents as recommended by the AAN, The Canadian Headache Society and The American Headache Society (AHS) to guide appropriate medications and dosages [1, 5, 6]. We suggest starting with medications with the highest level of evidence (class A). Each of the medications has a recommended therapeutic dosage. A summary of the recommended starting and maximum medication dosages, treated co-morbid conditions, most common adverse events, and levels of evidence may be found in Table 20.1. Metabolism and medication response will vary among patients, and clinicians should start at a low dose and titrate slowly to a therapeutic dose to encourage medication tolerance and compliance. It should be noted that some patients might respond to a lower dose of the medication than recommended, and in these cases, the medication should only be increased if the patient again becomes symptomatic requiring a higher dose. Clinicians may also encounter situations in which the patient is reluctant to start a medication but willing to try a natural supplement. Natural supplements evaluated by the AAN can be found in Table 20.2, again with associated level of evidence and adverse effects. Unfortunately, none of the nutraceuticals have class A level of evidence for use in migraine. Anecdotally, we at our institution use magnesium the most and observe that while some patients have benefit with this medication, most of the time a pharmacologic agent will still be required a couple months down the line. Of note, some drug companies have provided combination nutraceutical agents such as the well known and often alluded to

Table 20.1 Preventative agents for use in chronic migraine

Medication	AAN class (if available) or level of evidence	Starting daily dose	Therapeutic dose	Treated comorbid conditions	Most common adverse effects	Black box warnings
Propranolol	A	40 mg	80–240 mg	HTN, tachycardia	Fatigue, dizziness, constipation, bradycardia, hypotension, depression	Severe angina exacerbations, myocardial infarctions, and ventricular arrhythmias in angina patients after abrupt discontinuation can occur
Metoprolol	A	20 mg	100–200 mg	HTN, tachycardia	Fatigue, dizziness, diarrhea, pruritus, rash, depression, dyspnea, bradycardia	Severe angina exacerbations, myocardial infarctions, and ventricular arrhythmias in angina patients after abrupt discontinuation can occur
Timolol	A	10 mg	20–60 mg	HTN, tachycardia	Bradycardia, fatigue, dizziness, headache, dyspnea	Severe angina exacerbations, myocardial infarctions, and ventricular arrhythmias in angina patients after abrupt discontinuation can occur
Nadolol	B	20 mg	20–160 mg	HTN, tachycardia	Bradycardia, fatigue, dizziness, impotence, pruritus, rash	Severe angina exacerbations, myocardial infarctions, and ventricular arrhythmias in angina patients after abrupt discontinuation can occur.
Atenolol	B	25 mg	50–200 mg	HTN, tachycardia	Bradycardia, hypotension, fatigue, dizziness, cold extremities, depression, dyspnea	Severe angina exacerbations, myocardial infarctions, and ventricular arrhythmias in angina patients after abrupt discontinuation can occur

Lisinopril	C	5 mg	10–40 mg	HTN	Dizziness, hypotension, BUN/Cr elevation, headache, URI, cough	Fetal/neonatal morbidity/mortality may occur when drugs that act directly on the renin-angiotensin system are used in pregnancy
Candesartan	C	4 mg	16–32 mg	HTN	Hypotension, Cr elevation, hyperkalemia, URI, dizziness, back pain	Fetal/neonatal morbidity/mortality may occur when drugs that act directly on the renin-angiotensin system are used in pregnancy
Verapamil	U	120 mg	120–480 mg	HTN	Constipation, dizziness, nausea, hypotension, headache, edema	
Amitriptyline	B	10 mg	10–200 mg	Depression	Drowsiness, xerostomia, dizziness, constipation, blurred vision, palpitations, tachycardia	Increased suicidality in children, adolescents, and young adults with major depressive or other psychiatric disorders
Venlafaxine	B	37.5 mg	75–225 mg	Depression	Headache, nausea, insomnia, dizziness, anorexia, somnolence	Increased suicidality in children, adolescents, and young adults with major depressive or other psychiatric disorders

(continued)

Table 20.1 (continued)

Medication	AAN class (if available) or level of evidence	Starting daily dose	Therapeutic dose	Treated comorbid conditions	Most common adverse effects	Black box warnings
Topiramate	A	25 mg	50–200 mg	Obesity/ overweight, seizures	Metabolic acidosis, cognitive dysfunction, paresthesia, somnolence, hyperammonemia, URI, dizziness, weight loss, fatigue, ataxia, anorexia, abdominal pain, dysgeusia, renal stones, teratogenicity	
Sodium valproate	A	250 mg	500–2000 mg	Seizures	Headache, nausea, vomiting, asthenia, somnolence, thrombocytopenia, dyspepsia, dizziness, diarrhea, abdominal pain, tremor, alopecia	Serious or fatal hepatic failure has occurred. Increased hepatotoxicity in patients with mitochondrial disorders. Increases the risk of major congenital malformations including neural tube defects and lowering IQ scores. Life threating pancreatitis, including hemorrhagic cases with rapid progression have occurred
Gabapentin	U	100 mg	600–3600 mg	Seizures, neuropathy	Dizziness, somnolence, ataxia, fatigue, fever, peripheral edema, nystagmus	

Onabotulinumtoxin A	A	N/A	155 units	None	Headache, migraine, facial paresis, eyelid ptosis, neck pain, stiffness, muscular weakness, myalgia, injection site pain	
Erenumab	Double-Masked Randomized Placebo-Controlled Trials	N/A	70 mg or 140 mg every 28 days subcutaneous injection	None	Constipation, HTN, injection site reaction, cramps, muscle spasm	
Eptinezumab	Double-Masked Randomized Placebo-Controlled Trials	N/A	100–300 mg every 3-month infusion	None	Nasopharyngitis, angioedema, urticaria	
Fremanezumab	Double-Masked Randomized Placebo-Controlled Trials	N/A	225 mg every 3-month subcutaneous injection	None	Urticaria	
Galcanezumab	Double-Masked Randomized Placebo-Controlled Trials	240 mg once	120 mg every 28 days after first dose	None	Injection site reaction, urticaria, dyspnea	

Abbreviations: *AAN* American Academy of Neurology, *HTN* hypertension, *BUN* blood urea nitrogen, *Cr* creatinine, *URI* upper respiratory infection, *IQ* intelligence quotient

Table 20.2 Nutraceuticals for use in migraine

Dietary supplements (nutraceuticals)	AAN class (if available) or level of evidence	Starting daily dose	Therapeutic dose	Potential improvement in comorbid conditions	Most common adverse effects
Coenzyme Q10	C	300 mg	80–300 mg	Statin-induced myalgias	Nausea, diarrhea
Magnesium citrate	B	400 mg	400–600 mg	Constipation	Diarrhea
Riboflavin	B	400 mg	400 mg	B2 deficiency	Urine discoloration
Feverfew	B	50 mg	50–300 mg	N/A	Nausea, diarrhea
Butterbur	No longer recommended				

"Migravent." This supplement can be purchased over the counter and includes a combination of magnesium, riboflavin, and Coenzyme Q10. A randomized, placebo-controlled, double-masked multicenter trial including 130 migraneurs found that the burden of disease and frequency of migraine were improved in patients taking Migravent compared with placebo [7]. It is reasonable to give a time-limited trial of a natural supplement in migraine patients reluctant to try a pharmacologic agent, either with one or a combination of the agents found in Table 20.2; however, if the patient remains debilitated by migraine attacks and unwilling to try a pharmacologic preventative agent, the risk of transformation from episodic to chronic migraine in poorly managed migraine patients should be discussed.

It is not uncommon for a seemingly ideal medication to provide inadequate relief of a patient's head pain. At this time, the clinician must decide the next best step in management. If the patient has developed intolerable side effects to an appropriate drug, the physician should move on to a different evidence-based preventative agent [8]. If a subtherapeutic dose of medication is prescribed, the physician should increase the dose to an appropriate level based on AAN/AHA guidelines [1, 5, 6]. If the patient has not been on the medication for at least 3 months, the therapeutic trial should be extended, and the patient should be encouraged to continue the medication and give it time. Monotherapy involves choosing an evidence-based medication, giving the drug a reasonable therapeutic trial, and continuing this drug or choosing a different single agent at a follow-up appointment. If there was absolutely no benefit from the first agent tried, it is an easy decision to stop the medication and start another. In some instances, however, the patient experiences some relief from the first agent, though inadequate, and adding another agent to the first (polytherapy) may be appropriate. Historically, the headache societies implicitly have recommended monotherapy [9, 10]. The 2019 AHS Guidelines on new therapies allow for consideration of polytherapy when starting a novel agent [11]. Despite the implicit recommendation for monotherapy and lack of high-quality evidence for polytherapy, polytherapy is a strategy often used in clinical practice as many patients have some, but inadequate, response without significant side effects when using

monotherapy, as seen in the case at the start of this chapter [8, 10]. The available evidence for polytherapy, as well as a proposed algorithm for when to consider this approach, are discussed further in the following paragraphs.

Polytherapy is defined as the concurrent use of two or more drugs to treat the patient's migraine disorder and may be further divided into true or false polytherapy. In true polytherapy both drugs are prescribed with the intention to treat migraine and, if present, a comorbid disease [10]. False polytherapy is defined as the current use of two or more drugs that *can* treat migraine, but one or more of these drugs is primarily being used to treat, with therapeutic independence, a comorbid condition such as epilepsy or depression [9, 10, 12]. Unfortunately, perhaps due to the large number of evidence-based medications that can be used in migraine, there is a lack of double-masked or statistically significant studies for the use of polytherapy in migraine. Likely because of this, prominent headache societies do not have guidelines for initiating polytherapy [10].

Several small, double-masked trials investigating various migraine medications and comparing mono- versus polytherapy have yielded variable results. One double-masked study with 38 total patients showed statistically significant benefit for polytherapy with topiramate and nortriptyline over monotherapy with either agent [13]. Interestingly the doses used in this study were lower than the maximal recommended dose for migraine prophylaxis, which seemed to increase tolerability [13]. A second double-masked study with 73 subjects evaluated topiramate and amitriptyline polytherapy compared with monotherapy with either agent [14]. In this study, both the polytherapy and monotherapy groups had significant migraine relief with no difference between the groups. The polytherapy group had higher satisfaction scores and used lower medication doses, with decreased side effects reported from amitriptyline use [14]. Other studies have shown no statistically significant difference between the effectiveness of mono- versus polytherapy [15, 16]. A small open-label study examined patients who had therapeutic benefit from either topiramate or valproate but had intolerable side effects at a therapeutic dose [17]. Combined therapy with topiramate and valproate at lower doses was shown to increase tolerability, decrease side effects and maintain antimigraine efficacy [17]. Though these studies have examined different combinations of evidence-based medications for migraine with variable conclusions, the common theme is that, overall, polytherapy leads to lower individual medication doses, increased tolerability, and higher patient satisfaction with therapy, and provides the additional benefit of treating migraine and comorbid illness at the same time [10, 12–14]. Figure 20.1 provides a stepwise approach for when to consider initiating polytherapy.

Recently complicating the clinical decisions about monotherapy versus polytherapy is the introduction of new oral, injectable, and nerve stimulating devices for both abortion and prevention of chronic and episodic migraine. Among these are the calcitonin-gene-related peptide (CGRP) inhibitors and electronic devices used to prevent and treat episodic migraine headaches. The first CGRP inhibitor, the human monoclonal antibody erenumab, was FDA approved for the treatment of migraine in 2018 after it was found to be effective in the prevention of both episodic and chronic migraine when compared with placebo in several large clinical trials [18,

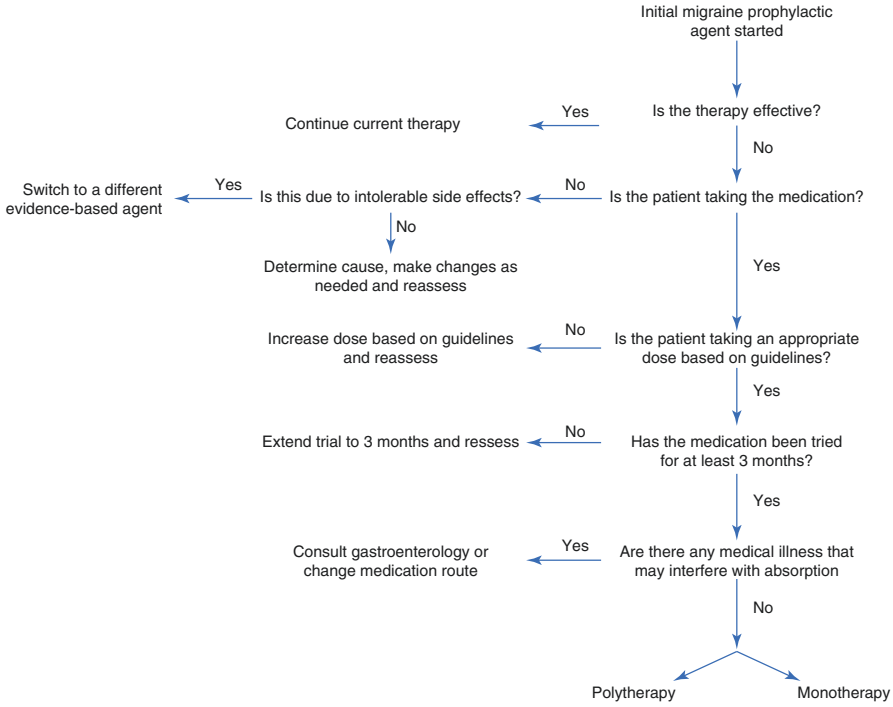

Fig. 20.1 Flow diagram of approach to migraine preventative therapy management

19]. Subsequently, several other human monoclonal antibodies that target CGRP have been approved, including eptinezumab, fremanezumab, and galcanezumab [20–23]. The CGRP inhibitors have become rapidly and widely used due to the strong data for good efficacy and favorable side effect profiles seen in their clinical trials. CGRP inhibitors are used on average every 28 days and are administered via subcutaneous injection, which may be of particular benefit in patients with absorption and/or compliance issues. Though there are limited data in the literature regarding the use of CGRP inhibitors with oral migraine medications, anecdotally, we frequently use CGRP inhibitors with oral migraine medications and have found that patients tolerate both therapies simultaneously. Additionally, the AHS position statement in 2019 recommended that it is reasonable to continue an existing oral antimigraine agent while starting a CGRP inhibitor and then decide on switching to monotherapy or continuing polytherapy [11]. Aside from these injectable anti-CGRP medications, another type of CGRP antagonist, the gepants, has been developed and recently approved, specifically for abortive treatment in migraine. Previously, prescription options for abortive treatment were mostly limited to the triptan medications, which carried significant side effects of numbness, tingling, flushing, gastrointestinal upset, fatigue, and chest pain and were contraindicated in patients with cardiovascular disease, hemiplegic migraine, and migraine with

brainstem aura [24, 25]. There has also been concern about using triptans in women with visual aura due to stroke risk in this population [26]. This novel gepant class of medications has been shown not to increase the risk of cardiovascular side effects in patients with migraine and significant cardiac history [27, 28]. Table 20.3 lists medications that can be used for acute abortion of migraine, level of evidence, common adverse effects, and black box warnings when applicable.

Novel nerve stimulating devices focus primarily on stimulation of the vagus and supraorbital nerves. Non-invasive stimulation of the vagal nerve via a device known as gammaCore™ gained FDA approval in 2017 for both acute abortion and prevention of migraine [29, 30]. Another stimulator known commercially as Cefaly® allows for transcutaneous stimulation of the supraorbital nerve as a method of migraine prophylaxis [31]. Finally, transcranial magnetic stimulation (TMS) has also been approved by the FDA for migraine prophylaxis and abortion. TMS, including a portable form commercially called Cerena, has been shown to be both safe and effective [8, 32].

Currently, these monoclonal antibodies and nerve stimulation devices have not made it into society guidelines. Their role as single agents in a monotherapy approach or as adjuvant agents has not yet been elucidated. The unique mechanisms of action and low side effect profiles that these novel interventions offer make them excellent options as either monotherapy or polytherapy in refractory migraine cases. We continue to recommend starting with evidence based, class A, oral agents before proceeding to a novel intervention.

In conclusion, patient-specific factors including comorbidities, degree of disability from migraine, number of prior medications tried, and patient wishes offer the best guide when considering monotherapy or polytherapy. The major benefit of monotherapy is medication simplicity for the physician and for the patient. For the physician, this simplifies the process of adjusting doses, testing efficacy, and identifying which medication is potentially causing side effects [10]. For patients, monotherapy decreases the total number of medications that they must remember to take, which is often a stated goal. When polytherapy is employed, the goal should be to increase therapeutic effectiveness and not to treat the side effects of the first antimigraine drug [8]. When using polytherapy, it is best to choose medications that have different mechanisms of action and work synergistically on different neurotransmitter systems [13, 33]. With both mono- and polytherapy, it is important to consider which comorbidities the patient has that may benefit from the migraine medication [13]. For example, mental health conditions, such as depression, may benefit from the addition of an antidepressant medication. In patients with multiple medical problems, consider a multidisciplinary approach, such as the involvement of a gastroenterologist in a patient with absorption issues, or the patient's psychiatrist if they have comorbid mental illness. Though we recommend starting with the older, evidence-based oral migraine medications for prevention, starting abortive therapy with a newer agent such as a gepant, rather than a triptan, may be safer due to their desirable side effect and safety profile. We recommend consideration of the new therapeutic interventions, including monoclonal antibodies and nerve stimulation

Table 20.3 Acute medications to abort migraine

Medication	AAN class (if available) or level of evidence	Dosage forms for migraine (oral route unless otherwise specified)	Most common adverse effects	Black box warning(s)
Acetaminophen	A	1000 mg	Nausea, rash, headache	
Aspirin	A	500 mg	Bleeding, dyspepsia, GI ulcers, nausea, and vomiting	
Ibuprofen	A	200 mg 400 mg 800 mg	Bleeding, GI distress, GI ulcers	NSAIDs increase the risk of serious and potentially fatal GI adverse events. NSAIDs increase the risk of serious and potentially fatal cardiovascular thrombotic events including MI and stroke
Naproxen	A	500 mg	Bleeding, dyspepsia, GI ulcers, nausea, and vomiting	NSAIDs increase the risk serious and potentially fatal GI adverse events. NSAIDs increase the risk of serious and potentially fatal cardiovascular thrombotic events including MI and stroke
Almotriptan	A	12.5 mg	Somnolence, dizziness, nausea, headache	
Eletriptan	A	20 mg 40 mg 80 mg	Somnolence, dizziness, nausea, headache	
Frovatriptan	A	2.5 mg	Somnolence, dizziness, nausea, headache, paresthesia	
Naratriptan	A	1 mg 2.5 mg	Nausea, paresthesia, chest pain	
Rizatriptan	A	5 mg 10 mg	Dizziness, somnolence, asthenia, fatigue, nausea	

Table 20.3 (continued)

Medication	AAN class (if available) or level of evidence	Dosage forms for migraine (oral route unless otherwise specified)	Most common adverse effects	Black box warning(s)
Sumatriptan[a]	A	25 mg 50 mg 100 mg	Paresthesia, hot sensation, cold sensation, malaise, fatigue, chest pain	
Zolmitriptan[b]	A	2.5 mg 5 mg	Nausea, dizziness, paresthesia, neck pain, jaw pain	
Dihydroergotamine[c]	A	2 mg (intranasal)	Dizziness, paresthesia, flushing, dyspnea, anxiety	Serious and/or life-threatening peripheral ischemia is possible when given in combination with potent 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Increased risk for vasospasm leading to cerebral ischemia is also possible
Ubrogepant	Double-Masked Randomized Placebo-Controlled Trials	50 mg 100 mg	Nausea, somnolence, xerostomia	
Rimegepant[d]	Double-Masked Randomized Placebo-Controlled Trials	75 mg	Nausea	

We strongly recommend against using opioid and butalbital containing medications for migraine treatment except in unusual circumstances. As such these medications were not included in this table although the AAN has assigned levels of evidence for these medications

Abbreviations: *GI* gastrointestinal, *NSAID* nonsteroidal anti-inflammatory drug, *MI* myocardial infarction, *AAN* American Academy of Neurology, *IV* intravenous, *IM* intramuscular

[a]Sumatriptan is also available in a subcutaneous injection form of 4 mg and 6 mg, and an intranasal form of 10 mg and 20 mg

[b]Zolmitriptan is also available in subcutaneous injection form of 2.5 mg and 5 mg

[c]Dihydroergotamine is also available in subcutaneous injection form at 1 mg (Level B AAN level of evidence) and IV and IM forms at 1 mg (Level B AAN level of evidence)

[d]Rimegepant cannot be re-dosed within 24 hours

devices, in patients who are refractory to more than one adequate trial of oral anti-migraine medication and in those patients with severe disability from migraine requiring a multifaceted approach.

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Trigeminal Autonomic Cephalgias

21

Daniel Crespo and Amrita-Amanda D. Vuppala

Case 1

A 55-year-old man presents to the clinic reporting episodes of light sensitivity and headaches. His past medical history includes migraine headaches without aura, hypertension, non-insulin-dependent type 2 diabetes mellitus, and a remote left cerebellar stroke without residual deficits. He takes topiramate for migraine prevention, lisinopril for hypertension, and aspirin and atorvastatin for stroke prevention. He reports that, for the past 2 months, he has been having short episodes of severe, stabbing, right-sided headache with associated photophobia in his right eye. The location of the head pain is always right temporal or right supraorbital. His spouse reports seeing him grab his face due to severe pain caused by these episodes. She has also noted his right eye tends to get red and teary with each episode. Each episode lasts up to 1 minute; however, they occur multiple times a day. His primary care provider increased his dose of topiramate 2 weeks ago, which has not helped. The patient has also tried acetaminophen, naproxen, and ibuprofen, but states that by the time he takes the pill, pain is gone. He denies any headache triggers aside from chewing.

Neuro-ophthalmologic examination shows visual acuity of 20/20 in both eyes with no relative afferent pupillary defect and normal color vision. Slit lamp exam reveals normal anterior segment and fundus exam in both eyes. Optical coherence tomography and Humphrey visual fields show no abnormalities in either eye.

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What is the primary differential diagnosis in this patient?

(a) Cluster headache
(b) Paroxysmal hemicrania
(c) Migraine headaches without aura
(d) SUNCT
(e) SUNA
(f) Hemicrania continua

What would be the first line of treatment for this patient?

(a) Indomethacin
(b) Subcutaneous sumatriptan
(c) Gabapentin
(d) Lamotrigine
(e) Oxygen

The diagnosis is *(d) SUNCT* due to the presence of severe short episodes of unilateral pain that are stabbing in character and associated with cranial autonomic symptoms such as lacrimation and conjunctival injection. The optimal or first-line treatment for SUNCT is *(d) lamotrigine*.

Discussion

The term "trigeminal autonomic cephalgias" (TACs) is used to refer to five headache syndromes with distinct clinical features and attack duration. These five headache disorders, considered primary headache disorders, include cluster headache (CH), short-lasting unilateral neuralgiform headache with conjunctival tearing and injection (SUNCT), short-lasing unilateral neuralgiform headache with cranial autonomic symptoms (SUNA), paroxysmal hemicrania (PH), and hemicrania continua (HC) [1]. Diagnosis and management of these headache syndromes may be challenging for both neurologist and ophthalmologist alike. Patients will often present to a neuro-ophthalmologist due to the presence of ocular manifestations such as periorbital pain, lacrimation, conjunctival injection, eyelid edema, and miosis. These ocular manifestations are thought to occur secondary to trigeminal-autonomic activation [2]. Appropriate diagnosis is critical to initiating the correct treatment, as the first-line agent for each of these syndromes may vary.

Updates in Pathophysiology

The pathophysiology of TACs is complex and not fully understood. Three key systems are suspected to play a role in trigeminal-autonomic activation: trigeminovascular system, hypothalamus, and cranial autonomic system. These systems are

connected through the trigeminal autonomic reflex and hypothalamic-autonomic and hypothalamic-trigeminal connections [3, 4]. The first player, the trigeminovascular system, is the proposed facial pain component of TACs. The ophthalmic branch of the trigeminal nerve receives pain input from various cranial structures including the dura, eye, cranial vessels, and the forehead. This trigeminal nerve branch then activates other pain areas in the brainstem and upper cervical cord, including the occipital nerve. These pain areas ultimately project to the thalamus and a collection of cortical and subcortical pain modulatory areas throughout the brain, known as the "pain neuromatrix," to cause facial pain [3]. The next player, the hypothalamus, is thought to contribute to the circadian nature and restlessness seen in some TACs, as the circadian system and aggression areas are controlled by the hypothalamus [4]. Support for hypothalamic involvement also comes from PET scan studies showing activation of the hypothalamus during the phases of acute pain in nitroglycerin-induced cluster headaches [5]. Finally, the cranial autonomic system contributes to the TAC pathophysiology through both parasympathetic overactivation and sympathetic inactivation of an important pathway from the superior salivatory nucleus in the brainstem to the sphenopalatine ganglion [6]. The sphenopalatine ganglion is responsible for innervating the lacrimal gland and paranasal sinuses, accounting for the autonomic symptoms (lacrimation and rhinorrhea, respectively) seen in TACs. Artificial activation of the sphenopalatine ganglion has been shown both to trigger and treat cluster headaches, providing further evidence of the importance of this pathway [7]. The role of the trigeminal nerve itself in autonomic activation is only partial, as trigeminal nerve resection does not seem to abort the headaches, nor the cranial autonomic symptoms [8]. Molecules involved in the autonomic pathway causing TACs are vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), both of which have been found to be elevated during attacks [4, 9, 10]. Based on recent studies showing alleviation of cluster headache with stimulation of the vagus nerve, it is also postulated that there may be some vagal involvement in TAC pathogenesis; however, the nature of this involvement remains to be discovered [11, 12]. TACs are not inherited in a Mendelian fashion, and thus far, no specific gene mutations have been consistently shown to increase susceptibility [13].

Updates to Clinical Criteria and Treatment

The most recent diagnostic criteria for TACs come from the International Headache Society (IHS) and are detailed in the third edition of the International Classification of Headache Disorders (ICHD-3), developed in 2018. The TACs are classified under five categories, including CH, PH, short-lasting unilateral neuralgiform headache attacks, HC, and probable TAC [14]. One of the most important updates to these new criteria is the inclusion of HC as a TAC. In addition, the list of included cranial autonomic features no longer includes ipsilateral flushing or ipsilateral ear fullness. Finally, the definition of a chronic TAC (excluding HC) includes an extended remission period of less than 3 months (compared with the previously suggested less than

Table 21.1 Types of TACs

	SUNCT and SUNA	Paroxysmal hemicrania	Cluster headache	Hemicrania continua
Epidemiology	Men > women, onset in late adulthood	Women > men, onset in mid-age	Men > women, onset in mid-age	Women > men, onset in mid-age
Severity of headache	Severe	Severe	Severe	Mild/moderate with severe flares
Duration of episode/ headache	1–600 seconds	2–30 minutes	15–180 minutes	>3 months
Frequency of episodes	At least 1 a day	5 or more per day	1 to 8 per day	Continuous
Presence of restlessness	+++	+	+	+
Autonomic symptoms	+++	++	++	+++
Circadian rhythmicity	No	No	++	No
Headache trigger	Cutaneous stimulation, neck movements	Neck movements, alcohol, nitroglycerin	Alcohol, nitroglycerin	Alcohol
1st line treatment	Lamotrigine	Indomethacin	High-flow oxygen and triptans	Indomethacin
2nd line treatments	Lidocaine, oxcarbazepine, carbamazepine, duloxetine, topiramate, gabapentin, steroids	Posterior hypothalamic stimulation, verapamil, sphenopalatine/ pericranial nerve block, celecoxib, topiramate	Octreotide, nasal lidocaine, vagus nerve stimulation, verapamil, lithium, topiramate, melatonin, baclofen, valproic acid	Gabapentin, verapamil, non-invasive vagal nerve stimulation, botulinum toxin, occipital nerve block, melatonin, celecoxib

1 month). In the following paragraphs, we will briefly review each TAC headache syndrome with associated treatment updates. A summary table comparing the TACs is detailed in Table 21.1.

Cluster Headache

CH is a severe type of headache that usually presents in middle-aged men. The headaches may be either chronic or, more often, episodic [15]. Episodes range from one every other day to eight episodes per day of unilateral headache lasting 15–180 minutes. CHs are associated with cranial autonomic symptoms or restlessness [15, 16]. Episodes may be clustered (occur in bouts) or occur without a remission period [15–17]. CH is the only TAC with clear circadian rhythmicity [15]. In the updated ICHD-3 criteria for CH, the definition of chronic CH was changed from

a remission period of less than 1 month to now less than 3 months [14]. Of the TACs, CH is one of the most debilitating due to the severe episodic pain that has been equated to "giving birth or passing a kidney stone" [9]. The first-line treatment of acute CH is high-flow oxygen (100% 6–12 L) along with sumatriptan or zolmitriptan [18]. While this regimen has been the classic first-line treatment for years, there are several novel second-line treatments that have been used successfully for acute management of CH. In a randomized placebo-controlled double-masked crossover study, subcutaneous octreotide showed a 52% response rate compared with a 36% response rate to placebo ($p < 0.001$) [19]. Robbins et al. [20] reported mild or moderate relief with intranasal 4% lidocaine in 30 patients with CH. In another double-masked placebo-controlled study, Costa et al. [21] found complete relief in nitroglycerin-induced CH with the use of 10% lidocaine application in the region of the sphenopalatine fossa under anterior rhinoscopy. Suboccipital steroid injections have also been shown to be useful for short-term prevention of acute CH and treatment of chronic CH in a randomized controlled trial [22].

Nonpharmacologic interventions such as transcranial stimulation and neuromodulation have also been tested in clinic trials. Transcranial direct current stimulation (tDCS) was studied in 31 patients with refractory chronic CH, with a significant decrease in attack frequency and duration [23]. Sphenopalatine nerve stimulation was studied in a randomized sham-controlled study with acute pain relief achieved in 67.1% of patients with full stimulation within 15 minutes [24]. Neuromodulation with non-invasive vagal nerve stimulation (nVNS) has also been shown to be a promising treatment for patients with CH. In a retrospective analysis of 30 patients with CH in the United Kingdom, Marin et al. used nVNS as adjunctive therapy for refractory CH with significant decrease in attack severity, frequency, and duration [25]. At this time, nVNS is approved by the FDA for acute prevention of episodic CH. There is limited evidence on occipital nerve stimulation for CH; however, the Occipital Nerve Stimulation in Medically Intractable Chronic Cluster Headache (ICON) trial is currently studying its clinical efficacy [26].

For preventive therapy of CH, verapamil is the drug of choice. The smallest effective dose based on a double-masked study by Leone et al. was documented as 360 mg daily (divided into three doses) [27]. Higher doses (up to 1200 mg daily) have been tried, but given the risk of symptomatic bradycardia and atrioventricular block, ECG monitoring prior to starting therapy as well as prior to increasing doses is recommended [27]. Second-line preventative treatments for CH are lithium, topiramate, and melatonin as an adjunctive therapy [16, 28, 29]. Lastly, baclofen and valproic acid have also been used, but evidence of their effectiveness is limited to case reports and series [3, 30].

Paroxysmal Hemicrania

PH tends to present more commonly in middle-aged women [31]. Patients will typically complain of sharp unilateral headaches lasting two to 30 minutes, associated with unilateral cranial autonomic symptoms and less frequently with restlessness

[17, 31, 32]. The frequency of these episodes is at least five per day. PH must be responsive to indomethacin as per the ICHD-3 criteria [14]. This requirement, however, has been debated by Prakash et al. who reported one case report of PH that did not respond to indomethacin [31]. This type of headache may also be episodic or chronic without a remission period [2, 14]. The treatment of PH begins with a trial of indomethacin, a nonsteroidal anti-inflammatory agent that has improved blood-brain-barrier penetration compared with other similar agents [33]. Indomethacin should be slowly titrated to achieve pain relief, after which it should be tapered to the lowest effective dose to prevent common side effects [33]. A histamine blocking agent or a proton pump inhibitor can be used to prevent nausea and gastroduodenal ulcers from the use of indomethacin [9, 33]. Interestingly, indomethacin itself can cause a new type of headache to develop [34]. Second-line treatments for PH have been tried, but there is limited evidence for their use. Successful treatment of PH with posterior hypothalamic stimulation and sphenopalatine endoscopic ganglion block have been reported by Walcott and Morelli, respectively [35, 36]. Although described in the literature with case reports, there is limited evidence of the use of acetylsalicylic acid, verapamil, topiramate, and rofecoxib [35, 37–39]. Antonaci et al. reported a series of cases of unsuccessful treatment of PH with repetitive anesthetic pericranial nerve blockade [40].

Hemicrania Continua

HC is characterized by chronic mild to moderate pain with flares of severe headaches associated with unilateral autonomic symptoms [14]. HC tends to present more often in middle-aged women and presents as a continuous headache lasting at least 3 months, associated with either unilateral cranial autonomic symptoms, or restlessness [14]. Just as with PH, HC must be responsive to indomethacin to be classified as such per ICHD-3 criteria. Migrainous features may be seen in HC, initially clouding the correct diagnosis [32, 41]. Patients with HC have episodes of headache exacerbation that are severe, disabling, and can last from minutes to days [32, 41]. HC benefits from similar treatments as PH, with the first line being indomethacin. [33] Second-line treatments for HC have only been studied in case series and case reports. Spears reported optimal response to gabapentin in four out of nine patients [42]. Partial to complete relief with melatonin has also been described [43]. HC seems to be less responsive to verapamil than PH [44]. Topiramate has been reported to relieve symptoms from HC in several case reports [37, 45, 46]. Porta-Etessam et al. reported four cases of HC that were completely responsive to COX-2 inhibitors [47]. A cohort of 16 patients with HC received bilateral occipital nerve stimulation with a response rate of 50% [48]. nVNS was a successful treatment in two patients who did not tolerate indomethacin. [49] There is minimal evidence for the use of botulinum toxin [50, 51].

Short-Lasting Unilateral Neuralgiform Headache

Short-lasting unilateral neuralgiform headache attacks are divided into SUNCT and SUNA. SUNCT and SUNA tend to present in men more often than women with onset in late adulthood [3, 32]. Episodes of SUNCT or SUNA usually occur as episodic attacks of moderate-to-severe stabbing unilateral headaches that last from one to 600 seconds [14]. SUNCT has both conjunctival injection and lacrimation, whereas SUNA only has one or neither [14, 32]. Though both these syndromes are quite short, they also carry the highest frequency among the TACs, with episodes occurring up to 100 times per day. First-line treatment for SUNCT and SUNA is lamotrigine, which is typically titrated to 50–100 mg twice daily [3]. Slow titration of lamotrigine is essential to prevent dermatological complications such as Stevens-Johnson syndrome [52]. The most effective medication is intravenous lidocaine, but its use warrants admission for cardiac monitoring and experienced providers to monitor for arrhythmias [9, 53]. Posterior hypothalamic brain stimulation has been reported to work in intractable SUNCT in case reports [54]. In a retrospective case series, one out of two patients with SUNA responded well to paresthesia-free cervical 10 kHz spinal cord stimulation [55]. Occipital nerve injections have been shown to be effective in a few case series of SUNCT and SUNA [56, 57]. Short courses of steroids have also demonstrated relief in acute exacerbations [32, 58]. Other medications suggested by case reports and series are carbamazepine [58], gabapentin [59], topiramate [60], and duloxetine [61].

In conclusion, TACs are an under-recognized group of primary headache disorders with a multitude of autonomic symptoms that may be overlooked if not directly elucidated by the clinician during history taking. The neural systems involved in their complex pathophysiology can be targeted by pharmacotherapy and emerging neuromodulation therapies such as tDCS, VNS, and spinal cord stimulation as discussed in this chapter. It is essential to distinguish the characteristics of each TAC as the treatment options are distinct, and patients may improve significantly when the appropriate therapy is applied.

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Photophobia in Post-Concussive Syndrome

22

Meleha T. Ahmad and Eric L. Singman

Case

A 30-year-old woman presents for neuro-ophthalmic evaluation after a recent concussion. Two months prior, while working as a warranty manager for a boat dealership, she stood up quickly and hit her head on the bottom of a sailboat. She had no past medical history prior to the accident. She describes a wide constellation of symptoms, including carsickness, nausea with attempted reading, "brain fog", slowed speech, and stuttering at the end of the day. She reports constant head pressure as well as intermittent headaches. Most distressing to her is constant photophobia, which interferes with her ability to work since the accident. She wears dark sunglasses at all times, both indoors and outdoors, and prefers to spend time in the dark. Her ophthalmic examination demonstrates distance visual acuity of 20/20 in both eyes, as well as near acuity of J1+ in both eyes. Color vision, extraocular movements, and confrontation visual fields are full, and the pupils are equal, round, and briskly reactive with no relative afferent pupillary defect; however, the patient demonstrates clear discomfort during pupil testing. There is a 0.5 prism diopter exophoria at near, but the remaining strabismus exam is normal. Slit lamp examination is normal, and the optic nerves appear healthy with no edema or pallor. Dilated exam is deferred due to significant photophobia.

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What is the most appropriate management plan for this patient?

(a) Observation
(b) Prescribe tinted glasses and offer an automobile window-tint waiver
(c) Prescribe gabapentin
(d) Perform cervical ganglion blockade

Management

This patient has debilitating photophobia after mild traumatic brain injury (mTBI), which is interfering with her daily functioning. Although there is no definitive treatment for photophobia after TBI, *(b) tinted glasses* can help mitigate some of her symptoms and would be the most appropriate treatment option in this case.

mTBI, colloquially known as concussion, accounts for 70–80% of TBIs that occur each year in the United States [1] and can result in acute and chronic visual changes [2]. TBI is defined by the National Institutes of Health (NIH) as "a form of acquired brain injury, (that) occurs when a sudden trauma causes damage to the brain" [3]. Although no broadly accepted diagnostic criteria for mTBI exist, descriptions of mTBI generally involve brief (<30 min) loss of consciousness and limited duration of post-traumatic amnesia (<24 h) from the time of injury, with best Glasgow Coma Scale (GCS) score of 13–15 within the 24 h after injury and normal neuroimaging [4]. Common symptoms in mTBI include headache, confusion, lightheadedness, dizziness, fatigue or lethargy, change in sleep patterns or mood, and difficulty concentrating or with memory [5]. Blunt trauma is the most common cause for mTBI, whereas penetrating brain injuries most often fall under moderate or severe TBI as they typically cause structural abnormalities seen on neuroimaging [4].

The association of mTBI with visual dysfunction has been attributed to the fact that so much of the brain subserves vision [6]. mTBI results from the brain hitting the skull, resulting in either coup or contrecoup impact. At the cellular level, damage arises from axonal stretching and sterile inflammation associated with increased intracellular calcium concentration, followed by proteolysis and neuronal depolarization [2]. The localized acidosis and edema can secondarily extend to worsening axonopathy and subsequent neuronal damage [2]. While the majority of patients will have a return to baseline neurophysiological state by 30–45 days [7], up to 15% suffer lasting deficits [8], and some can have ongoing cellular damage for years [9]. Aspects of visual function that can be affected after mTBI include afferent functions such as acuity, color vision, light tolerance, stereopsis, contrast sensitivity, and visual field; efferent functions including accommodation, ductions, saccades, and pupillary function; as well as those served by visual association areas such as visual memory and reading [2].

Photophobia, also termed photosensitivity or photo-oculodynia, is defined as "mild-to-extreme visual discomfort experienced by an individual in the presence of normal light levels" [10]. It is a common complaint with many etiologies, including ophthalmic, neurologic, and psychiatric. Ophthalmic causes for photophobia include dry eye syndrome and corneal neuropathy, uveitis, and retinal degenerations. The most common neuro-ophthalmic causes for photophobia are migraine or autonomic

cephalgias, benign essential blepharospasm (BEB), and TBI [11]. Less common, but more serious, neurologic causes for photophobia include pituitary tumor, progressive supranuclear palsy, and meningitis [11]. Migraineurs often report photophobia during headaches, although a number also report chronic photosensitivity [12]. Trigeminal autonomic cephalgias have been linked to unilateral photophobia, which is rare in traditional migraine [13]. Patients with BEB tend to complain of increased light sensitivity; however, it is unclear whether this is partially due to dry eye, since BEB often coexists with this condition [14]. In the past, some have thought that photophobia was derived from a functional rather than organic etiology [15]; however, more recent studies suggest a physiologic basis [10, 16, 17].

The pathophysiology of photophobia remains poorly understood but likely involves the trigeminal afferent nerves, which are closely associated with blood vessels of the globe and the orbit and are the primary mediators of pain sensation to the head [10]. It is likely that more than one neurologic circuit, including ones currently undiscovered, activate photophobia. Studies employing functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to evaluate patients with photophobia caused by various neurologic conditions have shown increased activity in the trigeminal nucleus [18], superior colliculus [19], and cerebral cortex [20]. Three potential neural circuits transforming light into a painful sensation have been identified. Specifically, light activates:

1. Retinal photoreceptors, which in turn activate retinal ganglion cells projecting to the superior salivatory nucleus. This nucleus then sends signals to ocular blood vessels, which lead to vasodilation and stretching of pain-sensing neurons in those blood vessels [21].
2. Melanopsin-containing intrinsically-photosensitive retinal ganglion cells (ipRGCs), which project to pain centers in the thalamus [22].
3. Retinal ganglion cells (RGCs), which connect directly to trigeminal afferents. These RGCs do not send axons into the optic nerve or the central visual system [23].

Concerning the biochemical signaling involved in photophobia, at least two trigemino-vascular system neuropeptides, calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), have been implicated [24]. Physiologic studies of patients with TBI and photophobia have reported increased dark adaptation thresholds in the absence of identifiable retinal dysfunction, possibly due to a cortical-based maladaptive mechanism in response to hyperexcitability caused by cortical damage [25].

The link between photophobia and TBI seems to be indisputable, with photophobia present in up to 59% of veterans with polytrauma and TBI [26, 27]. This number is nearly as high in veterans with mTBI due to blast injuries (50–55%, compared with 10% in controls) [8, 28]. Patients with TBI have been shown objectively to tolerate a lower mean luminance compared with healthy controls 1–3 weeks following closed head injury [16], and this difference seems to persist in those with post-concussive symptoms 6 months after mild trauma [17]. The presence of photophobia on initial evaluation after head trauma may be one of several factors predicting persistent post-concussive symptoms [29]. Moreover, the psychosocial effects of

photophobia can be profound. In a study of 111 adults with photophobia, 50% were found to be unemployed, and 25% stated that this symptom greatly affected their quality of life [30]. Constant photophobia at work can contribute to end of day fatigue, headache, and nausea and can impair screen work and reading [31]. Although there is evidence that photophobia after TBI may improve over the first year [30], patients with significant symptoms should be offered treatment and not simply observed *(choice A)*.

Photophobia has been called one of the most challenging neuro-ophthalmic conditions to treat, in part due to the lack of rigorous data on which to base treatment regimens [10]. It is perhaps surprising that there are no randomized controlled trials in the treatment of photophobia. Most clinical evidence consists of case reports and small cohort studies. The treatment of photophobia in any patient, with or without mTBI, starts with a complete ocular examination to identify underlying ophthalmic conditions such as dry eye and BEB. Special attention should be paid to patient description of symptoms, particularly because observer judgment of the presence and degree of photophobia based on patient's response to light has been shown to have poor correlation with the patient's described symptoms [32]. Photophobia questionnaires have been developed by several groups, although these typically are only used in research settings [33–35]. If no identifiable cause for photophobia is found on exam, palliative measures should be introduced.

Optical treatments are the first line of treatment for photophobia due to their noninvasive nature (*choice B)*. These therapies exist in the form of either neutral density lenses (such as sunglasses) or spectral filter lenses (such as colored lenses) [31]. Although neutral density lenses have the advantage of ease of procurement, they can significantly decrease luminance by blocking out all wavelengths. In addition, there is a suggestion that darkly tinted glasses, especially when worn indoors, can lead to increased dark adaptation and worsening aggravation to light in the long run [10, 11]. Indeed, constant indoor sunglass wear was reported to be a risk factor for persistent photophobia after mTBI [30]. When neutral density lenses are employed, it may be worthwhile to titrate the tint density over time [30]. Paradoxically, light therapy tended to decrease light sensitivity in patients with seasonal affective disorder [36], and it would be reasonable to explore this approach in patients with mTBI. It should be mentioned that patients might prefer to have their home and automobile windows tinted rather than wear spectacles all of the time. While most states limit the density of automobile window tints, many provide waiver forms that a physician can complete on behalf of the patient [37].

Chromatic lenses also have been offered as treatment for patients with photophobia [31, 38]. There may be a benefit to altering the spectral composition of incoming light through colored lenses. For example, because blue light is focused in front of the retina, filters that preferentially transmit blue light can decrease accommodative demand in those with accommodative insufficiency. In addition, studies of patients with migraine indicate that certain wavelengths might be less tolerated than others [39]. A commercially popularized lens tint to treat photophobia associated with migraine is FL-41 tint, which was formulated in Birmingham, England in the 1980s [40]. FL-41 is a rose-colored tint that filters 80% of short wavelength light [10].

Spectacle lenses tinted with FL-41 have been shown to be helpful with migraine treatment [41] and in reducing the number and intensity of blinks (an objective measure of photophobia) in patients with BEB [42]. In addition, patients with BEB prefer FL-41 tint over gray (neutrally tinted) lenses [42]. There have been studies exploring TBI-patients' perceived efficacy of different colored spectacles [31, 38]. Clark et al. found that 85% of patients presenting with photophobia after mTBI had relief with at least one color of glasses [38], where blue was the tint most likely to provide relief, followed by green, red, and purple lenses. Interestingly, in 33 patients, yellow-tinted lenses never provided relief. The relief from blue lenses was supported in another study [43]. There is no evidence that colored lenses are effective in treating other visual problems in patients with mTBI; indeed, one report showed that neither red, blue, nor neutral density lenses provided any help for reduced reading speed in these patients [31]. Furthermore, when patients were allowed to use a system called the Intuitive Colorimeter System in order to find any tint that might provide comfort while reading text, colored lenses of their choosing appeared to offer no benefit [31].

Medical treatment for photophobia specific to TBI has not been extensively studied. However, medical management of photophobia in mTBI generally mirrors medical management of migraine [44]. Treatment of migraines with beta blockers, calcium channel blockers, and anticonvulsants has been shown to reduce photophobia associated with a migraine attack but has not been widely explored for use in patients with TBI [45]. A randomized trial offering high dose magnesium intravenously to patients with migraine showed that this intervention reduces photophobia during the migraine attack [46], but this has not been extended to patients with persistent photophobia.

Gabapentin (*choice C*) and melatonin anecdotally have been reported to reduce discomfort associated with photophobia [10]; however, evidence supporting these as primary treatments is lacking. CGRP has been implicated in photophobia in mouse models, and CGRP monoclonal antibodies are currently approved for treatment of chronic migraine [47, 48]. It would seem reasonable to consider exploring CGRP monoclonal antibody therapy for photophobia.

Local nerve blocks for photophobia have also been reported. Injections to the supraorbital nerve [49], trigger point injections [50], and onabotulinum toxin A (Botox™) [51, 52] have been used to treat photophobia due to migraines and post-traumatic headache. In addition, sympathetic blockade *(choice D)* with anesthetics has been shown to improve light sensitivity in some patients with photophobia due to anterior segment injury [53], although the relief obtained only lasted several hours to a few days.

Conclusion

In summary, photophobia is a common symptom after mTBI, although its pathophysiology has not been clearly elucidated. In many patients, photophobia improves over weeks to months after the mTBI, but a significant minority are left with

debilitating photophobia. While no definitive treatment for photophobia in this setting is known, tinted lenses, specifically with colored lenses (e.g., FL-41 or blue tinted lenses) for indoor use and neutral density filters (i.e., sunglasses) for outdoor use, are noninvasive and may help control symptoms in some patients. Medical treatments may be considered in refractory cases.

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Part VI

Systemic Disease

Giant Cell Arteritis

23

Andrew R. Carey

Case

A 67-year-old Caucasian male was referred by rheumatology for 2 weeks of fever, fatigue, and leg cramps. He denied cranial or vision symptoms. His medical history was significant for type 2 diabetes mellitus. Labs showed erythrocyte sedimentation rate (ESR) of 119 mm/h, c reactive protein (CRP) 20.1 mg/dL (upper limit of normal 0.5), and platelets 523 K/mm^3 with normal hemoglobin. His eye exam was normal. Bilateral temporal artery biopsies (TAB) of 1.5 cm each were negative. Rheumatology initiated prednisone 80 mg per day, which was tapered over 5 months to 20 mg, along with methotrexate. At a dose of prednisone 20 mg per day, ESR increased from 57 to 98 and CRP from 2.8 to 10.7. When prednisone was tapered to 13 mg daily, he developed eye pain and recurrent amaurosis fugax. Eye exam remained normal.

What is the most appropriate next step in management?

(a) Increase methotrexate dose
(b) Increase prednisone dose with no other change in treatment
(c) Change methotrexate to mycophenolate
(d) Add tocilizumab subcutaneous injections
(e) Add intravenous (IV) tocilizumab infusions

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Management

The likely diagnosis in this patient is GCA with cranial involvement and relapse on an unacceptably high dose of prednisone. The FDA approved *(d) subcutaneous tocilizumab* in 2017 for treatment of GCA based on results from the phase 3 randomized controlled GiACTA trial, which showed a higher rate of remission at 1 year, as well as lower cumulative prednisone dose, with the addition of tocilizumab to the treatment regimen compared with prednisone alone. Tocilizumab is, as such, the first medication approved by the FDA for treatment of GCA [1, 2].

GCA is a vasculitis affecting large and medium muscular arteries almost exclusively in patients age 50 and over and is more common among women with a 3–5:1 female to male ratio [3]. The annual incidence ranges from 2 to 29 (with 77 reported in one county in Denmark) cases per 100,000 people over age 50 years. Incidence varies geographically, with highest rates in people of Northern European descent. Incidence increases with each decade of life (in Norway 2 per 100,000 aged 50–60 and 34.5 per 100,000 aged over 70) [3, 4]. GCA can affect any muscular artery but has a penchant for the aorta, its major branches, and cranial vessels. Up to 25% of GCA patients develop vision symptoms, and 8–15% suffer permanent vision impairment in at least one eye, with anterior ischemic optic neuropathy occurring in 7% (84% of patients with vision loss), central retinal artery occlusion occurring in 2% (20% of patients vision loss), and cilioretinal artery occlusion occurring in 0.4% (5% patients with of vision loss) [5]. Posterior ischemic optic neuropathy is a rare cause of vision loss in these patients but is highly specific for GCA, and patients may have more than one simultaneous ocular ischemic insult [3, 5].

Diagnosis of GCA can be a challenge with no true gold standard diagnostic test. The American College of Rheumatology (ACR) developed classification criteria; however, these were designed specifically to distinguish among various types of vasculitis, rather than to diagnose GCA [6]. As such, the ACR criteria may miss up to 25% of patients with vision loss and positive TAB [7]. Many clinicians depend on the TAB, but due to the frequency of skip lesions, sensitivity is limited. A systematic review from 2019 estimated sensitivity at 77%, and it was reported as only 62% among patients in the GiACTA study [8, 9]. Bilateral TAB may increase sensitivity by 3–5% [10]. There are mixed data on importance of biopsy length with high heterogeneity found in a systematic review, but longer biopsies generally have higher likelihood of being positive with a cutoff of 15 mm on pathologic specimen. Most surgeons aim for a 20–30 mm specimen at time of biopsy [11, 12]. A risk calculator for positive TAB based on 1200 biopsies from 14 medical centers was developed to determine which patients benefit from a TAB. Using the interactive online tool, age, sex, presence of new headache, temporal artery tenderness or reduced pulse, jaw or tongue claudication, permanent vision loss from ischemic optic neuropathy or central retinal artery occlusion, diplopia, ESR, CRP, and platelet count can be input, resulting in a calculated approximate risk for GCA for the individual patient. Area under the receiver operator curve of the model was shown to be 0.86. Additionally, the calculator outputs 95% and 99% sensitivities based on individual patient characteristics [13, 14]. A prospective trial comparing temporal artery ultrasound

(TAUS) and TAB showed similar diagnostic accuracy of 0.44 and 0.46, respectively, in isolation and 0.77 and 0.71, respectively, when combined with physical and clinical characteristics; however, a systematic review of 20 studies comparing TAUS to TAB showed TAUS sensitivity of 68% and specificity of 81%. As experience with TAUS increases, specificity also may increase, with newer studies reporting 90–100% specificity [15–17]. Benefits of TAUS include ability to evaluate a larger sample size of the temporal artery as well as other extracranial arteries, along with easy repeatability for possible relapses.

Among patients enrolled in the GiACTA trial at baseline, 20% had polymyalgia rheumatica symptoms without cranial manifestations, and 37% were diagnosed by cross-sectional imaging findings rather than a positive TAB [9]. In addition to TAUS, several other imaging modalities have been used for the diagnosis of GCA and its complications. MRI of the cranial arteries in early disease showed a 78% sensitivity and 90% specificity for clinical diagnosis but lower sensitivity (57%) in patients with a positive TAB [18]. A prospective, double-masked study showed PET-CT sensitivity of 92% and specificity of 85% when compared with TAB, and 71% sensitivity and 91% specificity when compared with clinical diagnosis, while identifying aortitis in 42% of those patients with a positive TAB, and an alternate diagnosis including infection in 10% and malignancy in 8%. Additionally, the presence of PET-positive aortitis at baseline increased the risk of aortic complications [19, 20]. MRA of the chest may identify additional areas of inflammation, with reports of involvement ranging from 10% to 70%, and may recognize additional areas of involvement not identified on PET scans [21, 22]. As of 2018, the European League Against Rheumatism recommends baseline imaging with either ultrasound or MRI to assess for extracranial involvement. While there are no clear recommendations for follow-up imaging, it may be useful in suspected relapses [23].

Corticosteroids have long been the mainstay of treatment for GCA. Steroid sparing therapies are frequently used in chronic inflammatory conditions to reduce the need for and complications from steroids, but a meta-analysis of studies of large vessel vasculitis did not show any improvement over steroids alone and possible harm from alternate day steroids, hydroxychloroquine, infliximab, adalimumab, and dapsone. Additionally, no definite benefit was demonstrated from loading IV steroids compared with oral administration [24]. Data on methotrexate are mixed, with some studies showing benefit, with steroid doses reduced by approximately 33% and relapses by 40%, although results may be skewed by its benefit for polymyalgia rheumatica symptoms [25]. Aspirin has been shown in meta-analysis to decrease the risk of severe ischemic events in combination with corticosteroids [26]. Many clinicians favor administration of at least one dose of IV steroids in patients with visual loss in GCA, and some advocate continuing IV steroids until a significant reduction (halving) of baseline ESR and CRP is attained, although strong evidence is lacking.

As previously mentioned, the GiACTA study was a phase 3 randomized controlled trial evaluating the effectiveness of tocilizumab (an anti-interleukin 6 monoclonal antibody), given subcutaneously either weekly or every 2 weeks in addition to prednisone on a 26-week taper, compared with prednisone monotherapy on either a 26-week or 52-week taper. Prednisone was started at 60 mg (or previous dose in

the relapsing group) and tapered weekly [2]. Two hundred fifty-one patients were enrolled. At 1 year, 52–56% of patients in the tocilizumab group had sustained remission (without any flare or deviation from prednisone taper) compared with 14–18% in the prednisone-only group, and cumulative prednisone dose at 1 year in the tocilizumab group was 49–56% of that in the prednisone-only group [2]. One hundred thirty-one patients had relapsing GCA at enrollment, and of this subset, reduced rate of flares occurred in the weekly tocilizumab group compared with prednisone-only groups (HR 0.23) but not in the biweekly tocilizumab group. In the subset of 120 patients with a new diagnosis of GCA, both the weekly and biweekly groups showed a reduced rate of flares (HR 0.20–0.25) compared with the 26-week but not 52-week prednisone taper groups [2]. One patient developed vision loss during the study, attributed to anterior ischemic optic neuropathy during a flare. This subject was in the biweekly tocilizumab group. Two patients developed diplopia during a flare, both of whom were in the prednisone-only groups (one on each taper schedule); one patient in the 26-week taper group developed amaurosis fugax during a flare; and seven patients developed blurred vision during flares (one in tocilizumab biweekly group, four in the 52-week taper, and two in the 26-week taper prednisone-only groups). No patients in the weekly tocilizumab group had any vision symptoms during flares [2]. Adverse events and infections were similar between the tocilizumab and prednisone-only groups [2].

With regard to the use of tocilizumab in clinical practice, patients on tocilizumab require monitoring of complete blood counts for neutropenia and liver function tests for transaminitis. Although tocilizumab reduces the risk of flares and overall need for prednisone, it does not eliminate the risk for flares, as 23% of patients in the GiACTA trial still had clinical flares, 64% of which occurred while on prednisone. Therefore, tocilizumab is likely not appropriate for monotherapy from the start and, from a more practical standpoint, insurance approval of the drug may take weeks in instances in which this is required. Therefore, initial treatment with prednisone remains advisable [2]. Additionally, it is unclear how to manage tocilizumab after successful tapering off of prednisone. One small study of 20 patients showed a 50% relapse rate after stopping tocilizumab, at a mean of 6.3 months and median of 5 months, ranging from 2 to 14 months, after cessation [27].

While tocilizumab has many benefits, it may not be required in all cases of GCA. Many patients do well on prednisone alone, as demonstrated in the GiACTA trial, in which 51% of patients in the 52-week taper prednisone alone group had no flares, and none developed permanent vision loss [2]. The potential benefits of tocilizumab should be weighed against its high cost (without insurance it costs approximately $1050 per treatment, amounting to approximately $54,600 in the first year for weekly dosing) in individual cases. However, some patients are at high risk of complications from prednisone, particularly those with poorly controlled diabetes mellitus, psychiatric disease, and those at risk for fluid overload such as from congestive heart failure or renal failure.

Monitoring patients for recurrence or flare of disease during prednisone taper and after cessation is crucial and can be challenging, as treatment may mask some of the typical features that clinicians use for gauging disease activity. Particularly,

tocilizumab suppresses the inflammatory pathway responsible for CRP elevation [28]. In the event of relapse, escalation of immunosuppressive therapy is indicated, usually by restarting or increasing the dose of prednisone.

To date, there is no available treatment to restore lost vision in the setting of GCA. Therefore, early detection of GCA, which remains a clinical diagnosis, is key, followed by aggressive treatment to prevent visual complications and close monitoring during tapering of immunosuppressive therapies.

Case Resolution

The patient was started on weekly subcutaneous tocilizumab. He had resolution of amaurosis fugax and morning headaches. His ESR subsequently reduced from 57 to 13 and CRP from 2.8 to 0.2 within 1 week. Prednisone was subsequently tapered to 2.5 mg per day by rheumatology, and methotrexate was discontinued due to transaminitis. He did have a relapse of headache and blurred vision lasting minutes when tocilizumab was reduced to biweekly administration, which resolved after weekly administration was reinstituted.

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Myasthenia Gravis

24

Andrew R. Carey

Case

A 54-year-old man with fatigable ptosis and diplopia with negative acetylcholine receptor antibodies and negative CT chest is controlled on prednisone 15 mg daily but recurs on tapering prednisone to 10–13 mg multiple times over a 9-month period. He has never had dysphagia, dyspnea, fatigue, or generalized weakness.

Which of the following is the most appropriate next management step for symptom control?

(a) Continue prednisone at 15 mg daily indefinitely
(b) Add pyridostigmine 30–60 mg 3–4×/day
(c) Add IVIG infusions or plasmapheresis
(d) Add rituximab infusions
(e) Add eculizumab infusions
(f) Add mycophenolate or azathioprine
(g) Refer for thymectomy

Management

This patient most likely has seronegative ocular myasthenia gravis (OMG) that is steroid dependent at a dose unacceptable for long-term maintenance, given the risk of side effects. While steroid-sparing therapies such as IVIG, plasmapheresis, rituximab, eculizumab, and thymectomy have been shown to be helpful for antibody positive systemic disease, their efficacy has not been proven for antibody negative

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ocular disease. Future research may prove otherwise, although the risk-benefit ratio and cost effectiveness of these therapies will have to be balanced, since ocular myasthenia is not life threatening. Pyridostigmine has little benefit for ocular disease with diplopia. Therefore, the correct option is *(f) mycophenolate or azathioprine*.

Myasthenia gravis is an autoimmune disease with generalized, bulbar, and ocular phenotypes. It is thought to be a type 2 autoimmune disease characterized by autoantibodies [1]. Acetylcholine receptor antibodies are the most common, followed by antibodies to muscle-specific kinase (MuSK), and less commonly lipoprotein receptor-related protein 4 (LRP-4), striated muscle, and agrin [1]. While 93% of patients with generalized myasthenia will have identifiable antibodies, antibodies are typically only identified 50% of the time in OMG [1]. However, a study in 2012 found complement-activating antibodies to clustered acetylcholine receptor proteins in 50% of seronegative OMG patients, suggesting that "seronegative" cases have autoantibodies that have not yet been identified [2].

OMG can progress to generalized myasthenia, although the precise rate of generalization is unclear. Some single-center studies report rates as high as 50–80% without immunosuppressive therapies [3, 4], but a multicenter study from 2015 showed the rate to be 21% in a mixed group of immunosuppressed and non-immunosuppressed with a 19% rate at 2 years in the non-immunosuppressed group [5]. Ninety percent of conversions occur within 3 years of diagnosis and 95% within 5 years [4]. Risk factors predicting generalization are unclear, with mixed results regarding single fiber electromyogram (sf-EMG) results and antibody seropositivity [6, 7].

Pyridostigmine was reported as MG treatment in 1954 [8]. The Efficacy of Prednisone for the Treatment of Ocular Myasthenia (EPITOME) study was a randomized controlled trial comparing pyridostigmine+prednisone to pyridostigmine+placebo in the treatment of OMG. The trial failed to meet its enrollment goal, randomizing only 11 of the planned 88 patients. Results from this small group showed 100% treatment failure in the placebo group compared with 17% in the prednisone group (starting 10 mg every other day for 1 week, then 10 mg daily for 1 week, and titrating by 10 mg every other day weekly until minimal manifestation status, up to 40 mg daily) with $p = 0.02$ [9]. Mean time to response to steroid treatment has been reported to be 2–3 weeks, with a 21% recurrence rate in patients who had full resolution of symptoms within 6 months after discontinuing steroids [10]. Multiple retrospective studies have suggested that treatment with steroids can delay or reduce the risk of progression to generalized myasthenia with an odds ratio of 0.13–0.26 and absolute rates of 9–13% at 2 years [7, 11–13], although no prospective studies have confirmed this, and the optimal dose and duration of steroid treatment has not been determined. Some providers opt to maintain patients on a prednisone dose of 5–7.5 mg daily (or an equivalent dose on an alternating day regimen) for prevention.

Studies in rheumatoid arthritis have shown increased adverse events, including fractures, gastrointestinal bleed or perforation, and infection, from long-term steroids when daily dose exceeds 10 mg (OR 32). While risks were reduced with doses

below 10 mg, and further reduced at less than 8 mg, the risk was not nullified until the dose reached 5 mg [14]. The prednisone dose threshold for increased mortality is 8 mg per day, or cumulative dose of 40 g [15]. Milder side effects, including cushingoid features, ecchymoses, ankle edema, fragile skin, cataract, nose bleeds, and weight gain, still occur at more than double the rate with daily doses at or below 7.5 mg compared with no steroids [16]. Bruce and Kupersmith looked at adverse events in OMG patients on prednisone for a minimum of 1 month and found that 35% of patients developed a mild complication with a rate of 6.6 complications per 100 person-years with 0.7 serious complications per 100 person-years; however, there was no control group [17]. An additional concern with long-term prednisone use is muscle wasting in patients already at risk for generalized weakness. Most patients can be tapered to prednisone 7.5 mg daily (or equivalent alternate day dosing) within 3 months, thus decreasing their risk of steroid-related adverse events. In patients who cannot be maintained on a sufficiently low dose of prednisone to limit adverse outcomes or side effects, steroid-sparing therapies should be instituted.

Acetylcholinesterase Inhibitors

In the EPITOME trial, all patients were treated with pyridostigmine monotherapy prior to randomization. Of the 15 patients initially enrolled, 27% responded to pyridostigmine alone [9]. In a large retrospective cohort, diplopia persisted in 57% of OMG patients treated with pyridostigmine [11]. A retrospective study out of Thailand showed pyridostigmine was more likely to work in patients presenting with ptosis alone, with a trend toward less success in patients presenting with diplopia alone, and a significant failure rate (6.3 fold) in patients presenting with both diplopia and ptosis [18]. The major limiting factor for pyridostigmine treatment is gastrointestinal side effects, including diarrhea and bloating. An extended release version is available and may be better tolerated [19].

Thymectomy

Evidence for thymectomy for the treatment of myasthenia originated in the association of myasthenia with thymoma. Trans-sternal thymectomy was shown to be beneficial in generalized myasthenia with non-thymoma pathology, leading to improved symptoms, lower doses of prednisone, reduced need for steroid-sparing therapy, and reduced hospitalizations for exacerbations in a randomized controlled trial [20]. A retrospective comparison suggested trans-sternal and video-assisted thoracoscopic surgical approaches both were beneficial, although the thoracoscopic approach had lower needs for postoperative ventilation, reduced admission times, and higher rates of prednisone cessation [21]. A meta-analysis of thymectomy in non-thymomatous OMG, including studies published from 1996 through 2014, suggested a complete remission rate of 50% [22]. However, a more recent retrospective comparison of prednisone versus thymectomy for OMG failed to show a benefit [23]. A

randomized controlled trial is needed to compare risks and benefits of medical versus surgical treatment for OMG for primary therapy, but thymectomy remains a reasonable option for patients with low surgical risk who cannot obtain symptomatic control on an acceptable dose of prednisone [24].

Intravenous Immunoglobulin and Plasmapheresis

Intravenous immunoglobulin (IVIG) is used in type 2 autoimmune (autoantibody) disease and is thought to dilute the autoantibodies and reduce severity of disease. A randomized controlled trial evaluated use of IVIG given over 2 days and showed statistically significant and clinically meaningful improvements in disease severity for patients with generalized myasthenia at 14 and 28 days, with greater gains in more severe patients. However, patients with OMG in the same study did not improve [25]. IVIG is currently used for patients with generalized myasthenia and acute exacerbations requiring rapid induction, particularly in patients at high risk for adverse outcomes with steroids, either from worsening of myasthenia or other systemic side effects. Plasmapheresis, also referred to as plasma exchange, is a process that filters the patient's blood and is used in autoimmune diseases to remove the disease causing molecule, often an autoantibody. While plasmapheresis has been thought to be equivalent to IVIG based on a meta-analysis for generalized myasthenia [26], it has not been investigated for treatment of OMG.

Oral Steroid-Sparing Immunotherapies

Steroid-sparing immunotherapies may be beneficial in patients unable to tolerate steroids and in those at high risk of adverse effects from steroid treatment, either due to underlying health conditions or requirement of a high dose of prednisone to mitigate myasthenia symptoms. The use of steroid-sparing agents may allow symptom control with lower doses, and sometimes complete cessation, of prednisone. Several medication options may be considered when initiating steroid-sparing immunosuppression in patients with OMG, with no strong evidence available to support the use of one agent over the others. Methotrexate has well-documented effectiveness in the treatment of another autoantibody disease, rheumatoid arthritis. However, a randomized controlled trial of methotrexate 20 mg weekly versus placebo did not show any steroid-sparing benefit for generalized myasthenia over 12 months. There have not been any studies of methotrexate specifically for OMG [27]. Both azathioprine and mycophenolate mofetil have been used for the treatment of myasthenia with some success. Azathioprine has been used in the United States for over 50 years. It is often started at doses of 50–100 mg daily and titrated to 150–300 mg per day, while monitoring blood counts for leukopenia and complete metabolic panel chiefly for transaminitis [24]. Prior to starting azathioprine, genetic testing of the thiopurine methyltransferase gene, which increases risks for myelosuppression among other side effects, should be considered [24]. Mycophenolate

mofetil may be better tolerated than azathioprine as a steroid-sparing therapy. Mycophenolate's usual starting dose is 500–1000 mg per day, with titration to 1500–3000 mg per day, while monitoring blood counts and a complete metabolic panel for bone marrow suppression and transaminitis, which is more common than renal impairment [24]. Tacrolimus failed to show a significant steroid-sparing effect but demonstrated a mild improvement in activities of daily living score for generalized myasthenia, but its utility in OMG has not been documented [28]. Neither cyclosporine nor cyclophosphamide has been specifically investigated for OMG [24, 29].

A major limiting factor of steroid-sparing therapies is the time to onset of benefit, which often takes 3–10 months; therefore, they are not reasonable as primary therapy. However, addition of steroid-sparing agents to prednisone treatment should be considered in patients at high risk for steroid side effects and in patients who relapse while on steroids, thus indicating need for additional therapy or a higher steroid dose. Mycophenolate may have a faster onset of clinical response than azathioprine [24]. Retrospective data suggest that azathioprine and mycophenolate both may reduce the risk of progression of OMG to generalized myasthenia [24]. Of note, immunosuppressive therapies have been associated with a small but real increased risk in cancers, presumably due to reduced immune surveillance [29], and this risk should be weighed prior to initiation of steroid-sparing immunosuppression in patients with OMG.

Rituximab and Eculizumab

Rituximab is a monoclonal antibody that targets CD-20, which is found on the antibody producing B-cells. It has been used in a number of autoantibody diseases and has been shown to be efficacious in antibody positive generalized myasthenia [30]; however, its use has not been studied for OMG, which has a lower rate of seropositivity. Histopathologic studies have implicated the complement pathway and membrane attack complex in the pathologic development of generalized myasthenia [31]. Eculizumab is a monoclonal antibody targeting C5 in the complement cascade and was shown in the phase 3 randomized controlled REGAIN study to reduce rates of myasthenic exacerbation and decrease the need for rescue therapy, although there was no difference compared with placebo in myasthenia gravis activities of daily living in antibody positive generalized myasthenia [32]. Results from a placebo controlled phase 2 study for zilucoplan, a macrocyclic C5 inhibitor, showed positive results with a dose-escalation response for generalized myasthenia [33]. Neither eculizumab nor zilucoplan have been investigated specifically in OMG.

Lifestyle Modifications

Smoking was correlated with poorer activities of daily living function among patients with OMG in a cross-sectional study [34]. Additionally, obstructive sleep

apnea and excessive daytime sleepiness have been reported to be more common in myasthenic patients than in controls [35, 36]. Respiratory weakness in generalized and bulbar myasthenia may compound disordered sleep breathing, and, conversely, hypo-oxygenation and hypercapnia may worsen myasthenic symptoms. While there are case reports showing improvement in myasthenia with treatment of sleep apnea [37, 38] and improvement in sleep apnea with treatment of myasthenia [39], further studies are needed to confirm these benefits.

Special Scenarios

Pregnancy

Patients can experience myasthenia exacerbations in pregnancy, often in the first trimester, or postpartum during the first month after delivery, which may be related to shifts in cellular and humoral immunity, biomechanical changes in respiration, infections, medications, and the stress of labor [40]. Medications commonly used in pregnancy can worsen myasthenia, including labetalol, which is a drug of choice for hypertension in pregnancy; magnesium, which is used for preeclampsia and hypertension; antibiotics; and anesthetics used for caesarian section [40]. Further, many medications used for the treatment of myasthenia are contraindicated in pregnancy. Methotrexate is pregnancy category X; azathioprine, mycophenolate, and cyclophosphamide are category D, although azathioprine is the drug of choice in Europe during pregnancy; cyclosporine, rituximab, IVIG, and steroids are category C; and pyridostigmine is category B [40]. Additionally, autoantibodies can be passed from mother to neonate in utero, causing congenital myasthenia [40].

Children

OMG constitutes about 80% of myasthenia in children. [41] Mean age of onset from 62 patients under age 15 years was 4 years with ptosis occurring in 97% and abnormal extraocular motility in 45% (total ophthalmoparesis was the most common, occurring in 24% of patients with motility deficits) [41]. Children can be treated with pyridostigmine, but the maximum dose is 7 mg/kg [19]. While all of the treatments discussed above have been employed for pediatric OMG, children are at increased risks from steroids including decreased bone mineralization and growth failure [42]. Children are at risk of amblyopia due to either strabismus or ptosis from OMG; therefore, visual function needs to be monitored and amblyopia treated when it occurs [42]. Children may have residual or additional strabismus that may require surgery once OMG is controlled [42].

Myasthenia in the Setting of Cancer

Myasthenia can occur from a paraneoplastic cause, most commonly associated with thymoma, while Lambert-Eaton syndrome (which rarely has ocular involvement and almost never isolated ocular involvement) is more typically associated with small cell carcinoma of the lung [43]. A more classic myasthenic picture can present in the setting of ovarian cancer [44] and lymphoma [45], as well. Striational and

ganglioside antibodies in addition to titin and ryanodine receptor antibodies can suggest a paraneoplastic process, particularly with high titers [46]. If cancer is known at the time of presentation of myasthenic symptoms, initial treatment with acetylcholinesterase inhibitors is recommended, while avoiding immunosuppression until the cancer is at a minimum responding to treatment and resected, if possible [46]. If significant symptoms are not responding to acetylcholinesterase inhibitor therapy, low-dose steroids (less than 20 mg daily) are considered the next step [46]. However, discovery of a related cancer may lag behind myasthenia diagnosis by up to 2 years [46].

Case Resolution

The patient was started on mycophenolate, titrated to 500 mg twice per day. After 2 months, he had resolution of symptoms, and his prednisone was tapered to cessation. He remained stable for 1 year, at which point his mycophenolate was stopped after a taper. Eighteen months later, he had recurrence of ptosis. Prednisone and mycophenolate were restarted with successful resolution of symptoms. He was maintained on mycophenolate alone.

Summary

A number of treatment options are available for the treatment of OMG and can be tailored to a patient's severity, comorbidities, and preferences. For patients with intermittent ptosis, pyridostigmine is a reasonable first option. However, most patients with diplopia will not respond to pyridostigmine and require immunosuppressive therapies. OMG is highly sensitive to corticosteroids with rapid response even to low doses within a few weeks. Patients who cannot be controlled on low-dose steroids should be considered for steroid-sparing therapies including azathioprine, mycophenolate, or possibly thymectomy. Patients are at risk of generalization, which may be life threatening. Smoking cessation as well as evaluation and treatment of sleep apnea can help with control. Children and patients with pregnancy or cancer require special consideration.

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Graves Ophthalmopathy

25

Emma C. McDonnell and Timothy J. McCulley

Case

A 70-year-old woman with a history of hyperthyroidism presents with worsening vision. She was diagnosed with hyperthyroidism 3 years ago and recently underwent radioactive iodine (RAI) ablation of her thyroid gland. She reports a 6-week history of eye swelling, diplopia, and progressive blurring of her vision.

On examination, she has a visual acuity of 20/30 in the right eye and 20/150 in the left. Intraocular pressures are 16 mmHg and 19 mmHg in the right and left eyes, respectively. Her pupils react sluggishly to light bilaterally, with a 2+ left relative afferent pupillary defect. Color vision is 6.5/10 and 1/10. Ocular motility is restricted in all directions, most notably with limited supraduction, left slightly greater than right. External examination is notable for retraction of all four eyelids and marked proptosis. Slit lamp examination shows superficial punctate epitheliopathy of the inferior half of both corneas and moderate chemosis. There is bilateral fullness and slight hyperemia of the optic nerves.

Automated visual field testing demonstrates bilateral field loss, more prominent inferiorly, worse in the left eye. Mean peripapillary retinal nerve fiber layer thickness, as measured by ocular coherence tomography (OCT), measures slightly greater than normal in both eyes (Fig. 25.1). Orbit computed tomography (CT) demonstrates bilateral tendon-sparing enlargement of the extraocular muscles

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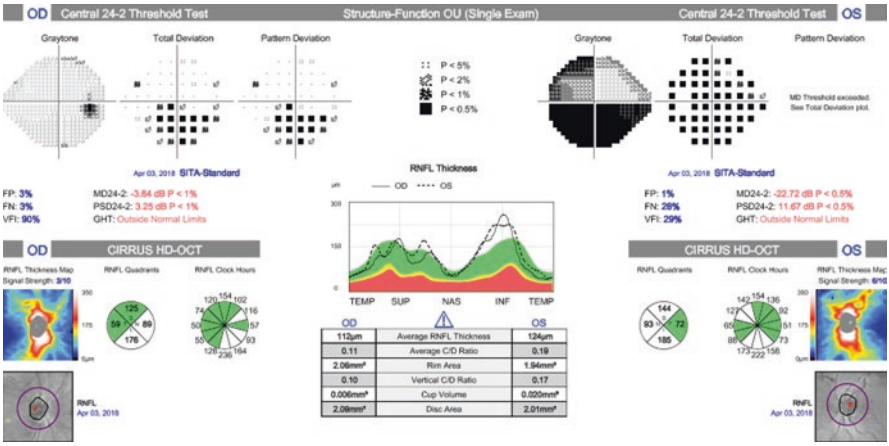

Fig. 25.1 24-2 Humphrey visual fields and Cirrus HD-OCT of both eyes demonstrate left greater than right visual field defects, more prominent inferiorly, and bilateral thickening of the retinal nerve fiber layer. (© TJ McCulley 2020. All Rights Reserved)

(Fig. 25.2) with crowding of the orbital apices, consistent with compression of the optic nerves.

What is the best next step in management of this patient?

(a) Corticosteroids
(b) Radiation therapy
(c) Surgical orbital decompression
(d) Intravenous teprotumumab

Management

In this patient presenting with evidence of compressive optic neuropathy in the setting of Graves ophthalmopathy (GO), *(a) corticosteroids* should be started urgently. Further long-term management options, including orbital radiation, surgical decompression, and teprotumumab treatment, may be appropriate for more definitive disease control.

When approaching patients with GO, a basic understanding of pathophysiology is important to provide a framework for management. GO is the result of an underlying abnormality of the immune system. Autoantibodies target various tissues including the thyroid gland, often resulting in hormonal abnormalities, most commonly hyperthyroidism [1, 2]. Antibodies targeting the skin may cause myxedema, and involvement of the orbital tissue produces ophthalmic findings. While orbital disease and thyroid abnormalities often coexist, the orbital disease is a direct result of abnormal autoantibodies, and severity of the ocular manifestations does not directly correlate with thyroid hormone levels. In our patient, thyroid hormone

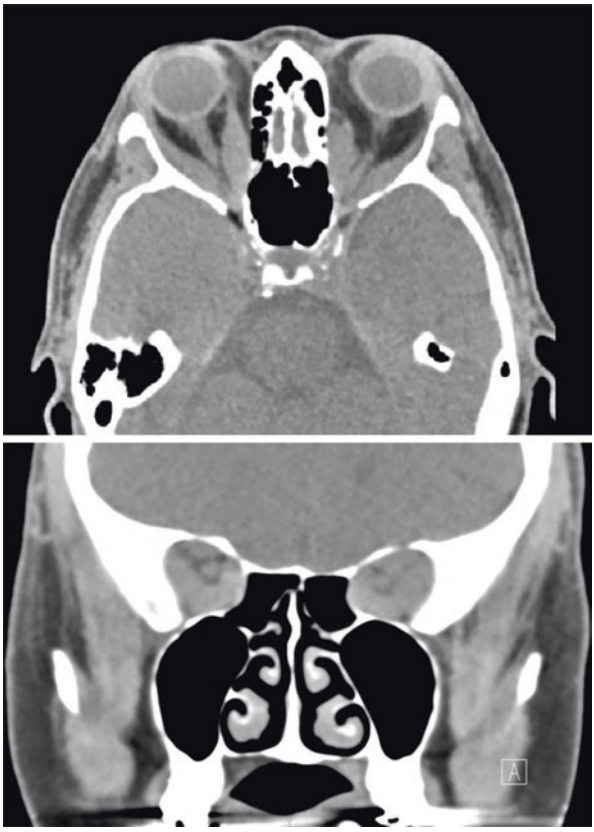

Fig. 25.2 Computed tomography (CT): Axial and coronal views show marked enlargement of the extraocular muscles bilaterally, sparing the tendons, with compression of optic nerves at the orbital apex. (© TJ McCulley 2020. All Rights Reserved)

levels were normal after the RAI treatment and subsequent oral levothyroxine. Clarification of this common misconception helps patients with orbital manifestations despite normal or treated thyroid function understand their diagnosis and the treatment strategies they are offered. Although the natural history of GO is highly variable, most individuals follow a similar progression through an "active" or "inflammatory" phase, which peaks in severity, slows, then ultimately quiets. The disease will stabilize into what is commonly referred to as the "fibrotic" phase. There will no longer be changes in the clinical manifestations; however, patients will not return to their baseline appearance or functional status (Fig. 25.3) [3].

The lack of uniformity in terminology can be confusing for patients and physicians. The term *Graves disease* is most commonly used to describe autoimmune hyperthyroidism associated with thyroid-stimulating immunoglobulin (TSI). Orbit involvement goes by a number of synonyms: *Graves orbitopathy*, *thyroid eye disease*, and *thyroid-associated ophthalmopathy* (TAO). Our preference is *Graves ophthalmopathy* (GO). Avoidance of the term "thyroid" reduces the semantic association of orbital disease with thyroid hormone levels.

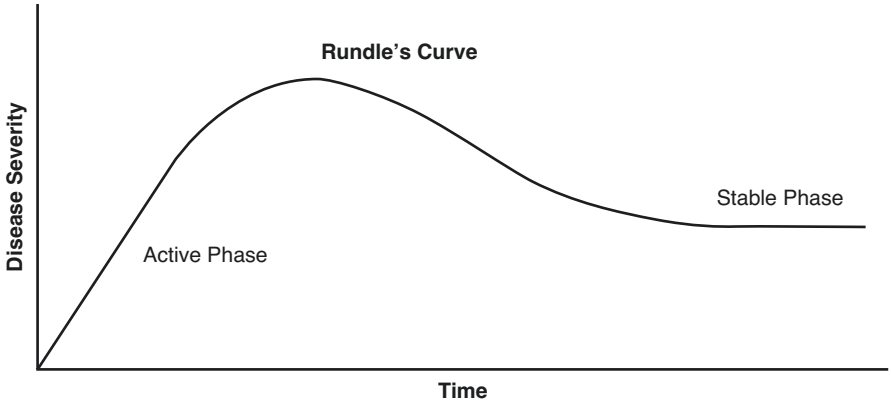

Fig. 25.3 Modeling disease activity with Rundle's curve. (Adapted from Mourits et al. [16])

Table 25.1 Clinical findings of Graves ophthalmopathy

Clinical features	Relative frequency
Eyelid retraction	90.8%
Exophthalmos[a]	62.4%
Restrictive extraocular movements	42.5%
Enlarged extraocular muscles	54.5%
Optic neuropathy	5.8%
Clinical evidence of thyroid dysfunction	92.5%

[a]Exophthalmos defined as Hertel >20 mm
Cited from: Bartley [1]
Bartley et al. [11]

Graves hyperthyroidism affects approximately 1–2% of the adult population worldwide and is about six times more common in women than men. Onset can be at any age but occurs most commonly between ages 30 and 50 [4]. Of those with Graves hyperthyroidism, about 25% will develop ophthalmopathy [5–7]. Manifestations of the orbital disease are highly variable with roughly 5% having disease severe enough to cause permanent vision loss [8, 9].

In GO, antibodies are thought to "activate" orbital fibroblasts leading to expansion of orbital soft tissues. Upregulation of expression of the insulin-like growth factor 1 receptor (IGF-1R) and thyrotropin receptors with loss of tolerance to these self-antigens is thought to be a major mechanism in disease pathogenesis [10]. These orbital changes can result in ocular surface disease, abnormal extraocular motility, optic neuropathy, and cosmetic anomalies. Table 25.1 summarizes the relative frequencies of more common GO-related clinical findings. Therapeutic options fall within three main categories: supportive management of symptoms, treatments that address the underlying abnormality of the immune system and resultant inflammation, and reconstructive therapies.

Ocular surface disease, manifesting as conjunctival injection, chemosis, and dry eye findings, results from the combination of proptosis, eyelid retraction and reduced ocular motility. The most common manifestation of GO is upper eyelid retraction [11]. Eyelid retraction is such a common manifestation that in patients lacking eyelid retraction, one should consider alternate etiologies for the orbital disease, or concurrent myasthenia gravis (MG). Proptosis, a consequence of expansion of the orbit tissues, also contributes to exposure. An often-overlooked contributor to corneal drying is the loss of a Bell's response seen with inferior rectus restriction. Another finding worth mention is lower eyelid epiblepharon most commonly seen in Asian populations, which has been reported in roughly 15% of Asian patients with GO [12]. Conservative measures for the treatment of ocular surface disease include topical lubrication and moisture chambers. The combination of lagophthalmos and loss of Bell's phenomenon creates a precarious situation when sleeping, so ointment use is strongly advised. Humidifier use also may mitigate nocturnal corneal drying. Surgical correction of eyelid retraction ideally is performed after the disease is stable, but if severe corneal disease threatens vision, repair may be needed on an urgent basis [13]. Epiblepharon usually requires urgent surgical correction as well.

Abnormal ocular motility results in diplopia and also may contribute to ocular surface disease. Fibrosis and scarring of the extraocular muscles cause restriction of eye movement opposite the involved muscle. Failure of extraocular muscle relaxation with pulling on the globe may cause elevated intraocular pressure that worsens upon attempted gaze in the restricted direction. Measurement of an increase in intraocular pressure upon attempted ocular elevation, in the setting of inferior rectus involvement, is suggestive of GO [14]. Documentation of the degree of restriction and alignment in primary gaze is useful in monitoring disease activity. Diplopia in the setting of GO may be quite difficult to control during the active disease phase. Progression of disease, and thus, of the degree of misalignment often precludes the use of prisms. Temporary measures are largely limited to monocular occlusion. For patients who wear glasses, placing frosted tape over one lens is often the preferred technique. Patients without glasses can wear a "pirate" patch or bandage. While patients with diplopia commonly become frustrated while waiting for ocular alignment to stabilize, it is appropriate to reassure them that once stability is demonstrated for at least 6 months, then strabismus surgery to correct the diplopia becomes an excellent treatment option.

Optic neuropathy, the most dreaded complication of GO, occurs in 6% of patients with GO and, in our experience, much more commonly in smokers [1]. There are three mechanisms for this: (1) compression by extraocular muscles in the orbital apex, (2) stretching of the optic nerve with severe proptosis, and (3) compression of the optic nerve along its length from increased orbital pressure. Monitoring for optic neuropathy with tests of acuity, color vision, afferent pupillary responses, clinical ophthalmoscopy, and perimetry, and aggressively treating optic nerve dysfunction are essential to avoid permanent visual loss in patients with GO.

The *cosmetic* impact of GO should not be underestimated. Proptosis and eyelid retraction result in a startled, bug-eyed appearance. Injection and chemosis of the

conjunctiva and the ocular misalignment can be striking. Hypertrophy of the orbital fat results in "baggy" eyelids, but fat hypertrophy is not limited to the orbit. Variable hypertrophy of fat surrounding the eyes may include the subcutaneous brow fat, and involvement of multiple areas of fat can be disfiguring, hindering patients' abilities to function normally in society and at home.

There have been a number of grading systems devised to quantitate disease severity [14, 15, 16]. These grading schemes can help the clinician monitor progression over time but do not necessarily indicate when or what treatment is needed. In our experience, the Clinical Activity Score (CAS) is the most practical and useful. Components and calculation of the CAS are shown in Table 25.2.

GO remains a *clinically based designation*, based on the signs shown in Table 25.1. Orbital imaging can be helpful to evaluate for characteristic tendon-sparing extraocular muscle enlargement and exclude alternate pathology, if the diagnosis is in question. While not always necessary for diagnosis, imaging is required when planning orbital decompression surgery. Opinions vary regarding the utility of ultrasonography. We have found ultrasonography to be of negligible use, and occasionally misleading. In the absence of known thyroid disease, serologic evaluation of thyroid-stimulating hormone (TSH) and free thyroxine (T4) is important to identify and treat hormonal abnormalities. Antibody tests can be performed if results of the standard tests are normal or to confirm the diagnosis and establish a baseline level to quantify disease activity. The presence of elevated thyroid-stimulating immunoglobulin (TSI) on serum evaluation is highly predictive of Graves disease [17, 18]. Elevated levels of TSI have been detected in up to 98% of patients with GO [17, 19]. In atypical cases assessing TSI can be helpful for diagnosis, but we do not find monitoring serum levels helpful in management.

Smoking cessation is essential. Regardless of disease stage, all patients should be counseled on smoking cessation. Smoking has been well documented to worsen the disease course. Although data on marijuana and e-cigarettes are lacking, we also counsel against their use [20, 21].

Table 25.2 Components of clinical activity score

Pain
Spontaneous orbital pain (1)
Pain with EOMs (1)
Erythema
Eyelid (1)
Conjunctiva (1)
Edema
Eyelid edema (1)
Chemosis (1)
Swollen caruncle (1)
Measurement changes 1–3 months
Increase in proptosis ≥2 mm (1)
Decrease of VA by 1 or more lines (1)
Restriction of EOMs by >5 degrees (1)

Abbreviations: *EOM* extraocular movement, *VA* visual acuity

Selenium is a trace element thought by some to have an antioxidant effect. Data from European populations suggest that selenium supplementation may reduce GO severity [22]. It remains unclear if this finding is applicable to populations in other parts of the world where selenium is more plentiful in the soil and food supply. We inform patients with active disease that it may have some benefit. As multivitamins may contain selenium, patients should be asked about supplements they are taking already, to avoid inadvertent overdose, which may result in diarrhea, fatigue, hair loss, joint pain, nail discoloration or brittleness, and nausea.

Immunosuppression and immunomodulation are options for managing the underlying autoimmune disorder. *Glucocorticoids* are commonly used for moderate-to-severe active GO. Steroid can be administered orally (PO), intravenously (IV), or by local injection [23, 24]. The use of PO steroids has fallen out of favor in recent years. Although most patients enjoy some degree of short-term benefit, data suggest little to no sustained benefit. Despite this, oral steroids still play specific roles in our practice. Oral steroids can be used in patients undergoing thyroid ablation, either surgically or with RAI. Concurrent use of steroids has been shown to decrease the rate of activation or worsening of disease in such patients. Oral prednisone also can be used as a temporizing measure in patients with vision threatening disease, while arranging for surgery or more definitive anti-inflammatory treatment.

IV steroid administration may be more effective in shortening of the active phase with long-term gains [23, 24]. There is no clear consensus on the optimal dosing regimen; however, most clinicians follow some version of the European Group on Graves' Orbitopathy (EUGOGO) protocol, administering 500–1000 mg of IV methylprednisolone weekly for 4–8 weeks. For patients such as the one presented, with active disease and progressive visual loss, a typical approach is to start PO prednisone (1 mg/kg daily) while arranging IV treatment, unless IV treatments are available immediately.

Orbital steroid injection has been described and advocated by some on the basis that systemic side effects are avoided. However, little more than anecdotal evidence supports the use of local steroid injection [23, 24].

Targeted immunotherapy is one of the most impactful recent developments in clinical medicine. Commercially available recombinant monoclonal antibodies are engineered to target specific antigens, most commonly on tumor or inflammatory cells. For example, the monoclonal antibody rituximab, which targets CD-20, has found an invaluable role in the treatment of lymphoproliferative disease. Some anecdotal success with rituximab has been described in the treatment of other diseases including GO [25–27]. Tocilizumab, an interleukin-6 (IL-6) monoclonal antibody approved in 2017 as a treatment for giant cell arteritis, also has been studied in GO with variable results [28, 29]. Teprotumumab, a monoclonal antibody targeting IGF-IR, has shown promise in reducing orbital involvement in patients with GO [25, 30–33]. In a randomized placebo-controlled double-masked clinical trial, patients with active GO treated with teprotumumab had a mean improvement of CAS and even a reduction of proptosis [32]. Our early clinical experience with teprotumumab largely supports these conclusions.

Orbital radiotherapy is thought to suppress the inflammatory cascade that follows fibroblast activation. Many publications, mostly descriptions of nonrandomized site-specific experiences, allege benefits from radiation in the treatment of GO. The use of radiation therapy in the treatment of GO was widespread until a prospective study in 2004 reported no clinically or statistically significant differences between treated and untreated orbits [33]. The study was criticized for including patients not in the active phase, and therefore, unlikely to benefit from radiation. Despite limitations, following publication of this study, radiation therapy became less popular. Radiation has regained some popularity in recent years, and recent data suggest that radiation is more beneficial when used in conjunction with IV methylprednisolone [34–40]. In our practice, we largely reserve radiation therapy for patients with active disease who continue to progress following a course of IV methylprednisolone.

Reconstructive surgical treatment is usually delayed until the disease stabilizes unless there is a sight-threatening issue such as corneal exposure or compressive optic neuropathy. For corneal exposure that is inadequately controlled with medical therapy alone, tarsorrhaphy may be required in the active phase. More "permanent" eyelid repositioning procedures are typically avoided during the active phase, due to concern that eyelid position could continue to change due to both active disease and future reconstructive surgical procedures. For optic neuropathy due to compression of the nerve at the orbital apex, medial orbital wall decompression with steroid coverage pre- and postoperatively may be useful to prevent permanent vision loss. This operation causes much less inflammatory reaction than an external approach and allows direct access to the orbital apex. Although opinions vary, it is our practice to avoid elective surgery until the disease has not progressed for a period of 9 months. Traditionally, orbital decompression surgery is performed first, followed by strabismus surgery, then eyelid surgery to address retraction [41–43].

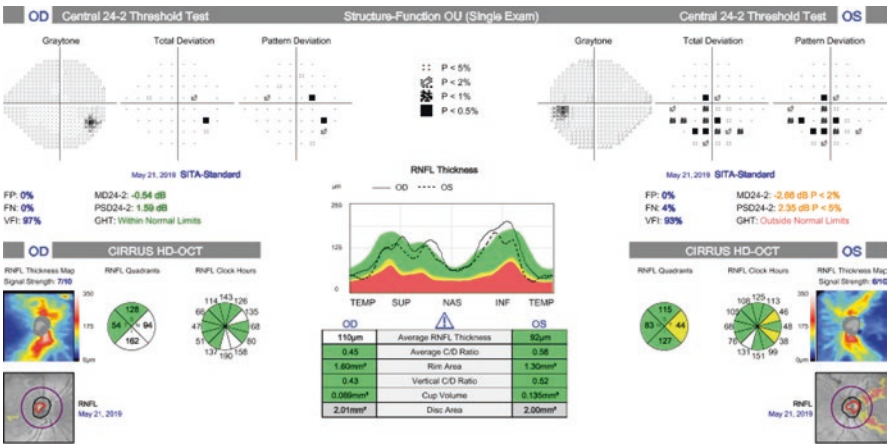

Fig. 25.4 24-2 Humphrey visual fields and Cirrus HD-OCT 4 months postoperatively show improvement in visual field defects in both eyes and mild focal thinning of the temporal RNFL OS. (© TJ McCulley 2020. All Rights Reserved)

Case Resolution

Our patient was placed on PO prednisone as a temporizing measure, while arranging for orbital decompression and IV methylprednisolone. One week after the decompression, her vision, visual fields, and OCT improved (Fig. 25.4). Methylprednisone infusions were continued for 8 weeks. Two years later, she remains stable with visual acuity of 20/25 in both eyes.

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Sarcoidosis

26

Amanda D. Henderson

Case

A 65-year-old man with a past medical history of type 2 diabetes mellitus, hypertension, and a single episode of unilateral anterior uveitis presented with bilateral vision loss for 2 weeks. On examination, visual acuity was counting fingers in the right eye and hand motion in the left with no relative afferent pupillary defect. His ocular examination and optical coherence tomography (OCT) were otherwise normal with no cause for the vision loss identified. Magnetic resonance imaging (MRI) of the brain and orbits showed a small dural-based enhancing mass arising from the wall of the right cavernous sinus but was negative for ischemia, optic nerve enhancement, and compressive lesions (Fig. 26.1). Erythrocyte sedimentation rate was elevated, and due to initial concern for giant cell arteritis, the patient was admitted urgently for evaluation and treatment with intravenous methylprednisolone. However, unilateral temporal artery biopsy and serum laboratory testing for potential infectious and inflammatory causes of bilateral vision loss were unremarkable. Chest X-ray showed no abnormalities. During his steroid treatment, he experienced dramatic improvement of his vision to 20/20 in both eyes with full color vision and fields. Repeat MRI demonstrated a decrease in the size of the enhancing dural-based lesion.

What test most likely would identify an underlying cause for his vision loss?

(a) Lumbar puncture with cerebrospinal fluid (CSF) studies
(b) Serum angiotensin converting enzyme (ACE)
(c) MRI spinal cord
(d) CT chest
(e) Contralateral temporal artery biopsy

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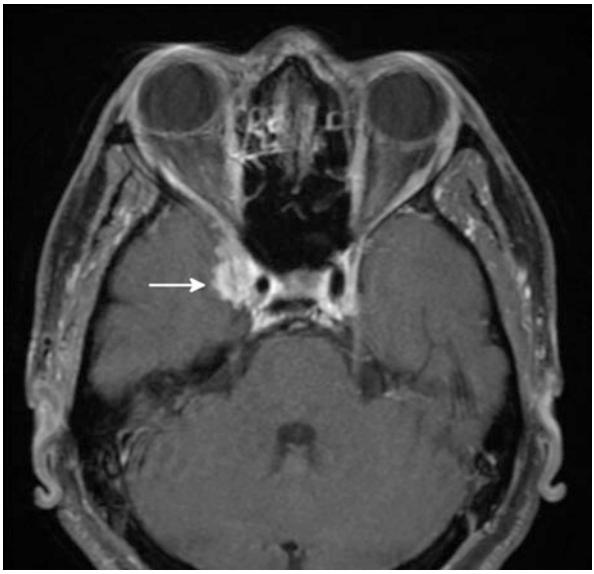

Fig. 26.1 Axial T1-weighted post-contrast MRI demonstrates a dural-based enhancing mass with indistinct borders (arrow), arising from the wall of the right cavernous sinus (Reprinted with permission from: Solyman et al. [49]. https://journals.lww.com/jneuro-ophthalmology/pages/default.aspx)

Management

Due to the marked steroid response, with striking visual improvement and decreased size of the enhancing dural-based mass lesion on MRI, as well as the history of uveitis, there should be high suspicion for sarcoidosis in this case. Choice *(d) CT chest* may show findings suggestive of sarcoidosis, including hilar and/or mediastinal lymphadenopathy, and also may provide a lesion amenable for biopsy. While an elevated ACE level may suggest sarcoidosis, it is not sensitive for the diagnosis.

Sarcoidosis is an idiopathic, multisystem disease, characterized pathologically by noncaseating granulomatous inflammation. Clinically, central nervous system involvement occurs in 5–15% of patients with sarcoidosis, with about half of those cases initially presenting with a neurologic manifestation [1–4]. Patients with neurosarcoidosis may present initially with visual symptoms, including vision loss or diplopia. Prior studies of neuro-ophthalmic sarcoidosis have reported that a neuro-ophthalmic presentation led to the primary sarcoidosis diagnosis in 31–88% of these cases, emphasizing the importance of consideration of this diagnosis, even in patients without a known history of sarcoidosis [2, 5–9]. The key to appropriate management of neuro-ophthalmic sarcoidosis is identifying the correct diagnosis. Disease presentation can resemble other inflammatory, infectious, and neoplastic conditions. MRI findings often mimic the appearance of other central nervous system diseases, including meningioma, infectious or carcinomatous meningitis, demyelinating disease, tuberculosis, granulomatosis with polyangiitis, lymphoma, or other neoplastic disease [10]. Therefore, the diagnosis can, at times, be challenging. However, certain clinical characteristics can increase suspicion for neurosarcoidosis and prompt appropriate evaluation. For instance, atypical behavior of an

enhancing mass (e.g., presumed meningioma), such as accelerated growth, unusual appearance (e.g., feathered margins), or decrease in size with steroid treatment, should heighten suspicion for an inflammatory process.

Optic neuropathy, which commonly but not exclusively is associated with optic disc swelling, may be a feature of neurosarcoidosis. No light perception visual acuity is not uncommon in these cases, and the presence of no light perception vision does not preclude visual recovery [6, 8, 11]. Variable visual field defects have been reported, including blind spot enlargement, nasal step, arcuate scotoma, central and cecocentral scotoma, paracentral scotoma, superior depression, altitudinal defect, diffuse depression, and hemianopic defects [2, 8, 11, 12]. Therefore, there is no particular field defect that suggests sarcoid optic neuropathy. Optic neuropathy may be subacute or chronic with a slower progression [11, 12]. Other reported findings include single or multiple cranial nerve palsies, tonic pupil, nystagmus, Parinaud syndrome, cavernous sinus syndrome, Horner syndrome, homonymous visual field defects due to optic tract or occipital lobe involvement, and visual perceptual abnormalities [2, 6–8, 13–16]. Seventh nerve palsy is the most commonly reported manifestation of neurosarcoidosis [4]. Cranial nerve involvement may occur due to direct infiltration or indirectly due to granulomatous leptomeningitis or increased intracranial pressure [17].

Ophthalmic involvement also is common in sarcoidosis and has been reported in 22–60% of cases [17]. Therefore, a thorough ocular examination may add valuable information to the overall clinical picture of a patient with sarcoidosis. Common eye findings in sarcoidosis include dry eye secondary to lacrimal gland involvement, conjunctival nodules, granulomatous anterior uveitis, cystoid macular edema, choroidopathy that can present with punched-out lesions or with granuloma formation, and periphlebitis [17, 18] (Fig. 26.2).

MRI should be performed early in the evaluation of any patient with an unexplained optic neuropathy and most other neuro-ophthalmic signs that are unexplained based on the clinical exam and ancillary clinic testing. Gadolinium-enhanced MRI sequences can offer valuable clues for diagnosis and may help to increase clinical suspicion, although no MRI finding is specific for neurosarcoidosis.

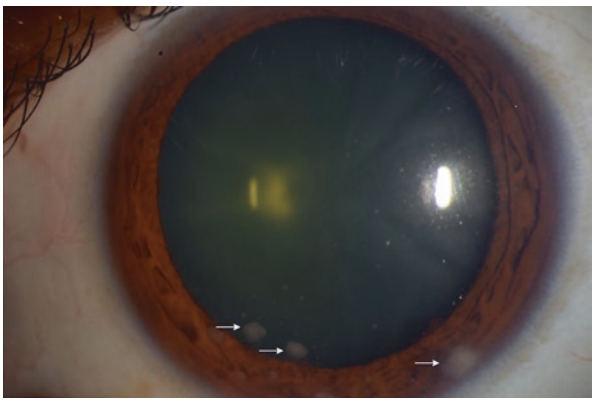

Fig. 26.2 Slit lamp photograph demonstrates "mutton fat" keratic precipitates (arrows) in a patient with granulomatous anterior uveitis in the setting of biopsy-proven sarcoidosis. (© AD Henderson 2021. All Rights Reserved)

Reported MRI findings in patients with neuro-ophthalmic sarcoidosis include enhancement of the optic nerves, optic nerve sheaths, chiasm, optic radiations, cavernous sinus, pachymeninges, leptomeninges, and cortical parenchyma [2, 6, 7, 11, 19–24]. Additionally, MRI may show orbital masses that mimic other neoplastic or inflammatory processes, including meningioma, glioma, and orbital pseudotumor [11, 19, 22, 23, 25]. While noncontrasted MRI may show optic nerve thickening in cases of anterior visual pathway involvement, the use of gadolinium greatly increases the sensitivity of MRI for neurosarcoidosis and should be used routinely unless there is a strong contraindication to gadolinium administration [19, 26]. Response to treatment can be monitored using MRI, as well [23]. Interestingly, 43–95% of patients with neuro-ophthalmic findings attributed to neurosarcoidosis have been reported to have abnormal brain imaging [2, 5–9]. As MRI technology has improved, specifically with stronger magnets and three-dimensional high-resolution skull base protocols, improved characterization of cranial nerve lesions may be expected [27].

As sarcoidosis is a systemic disease, it often is a constellation of clinical and neuroimaging characteristics, rather than one isolated finding, that heightens suspicion for the condition. Familiarity with typical features of neuro-ophthalmic sarcoidosis, their potential appearances on MRI, associated findings that are common in other body systems, and the additional evaluations required to confirm the diagnosis, is helpful to avoid missing this diagnosis and to allow for appropriate treatment in a timely manner.

As the locations of neuro-ophthalmic sarcoidosis involvement often are not amenable to low-risk biopsy, a search for other system involvement, specifically pulmonary, ocular, or cutaneous, is prudent to facilitate histopathologic diagnosis [28]. Thorough evaluation may require a multidisciplinary approach. The pulmonary system most commonly is affected in sarcoidosis; therefore, chest imaging, to assess for characteristic findings of hilar lymphadenopathy, should be performed to identify a site amenable to bronchoscopic biopsy [29]. Among patients with neurosarcoidosis, about 60% have chest X-ray findings suggestive of pulmonary sarcoidosis, and 70% have suggestive chest CT findings [3]. When hilar or mediastinal lymphadenopathy is identified, then bronchoscopy or mediastinoscopy can be used for biopsy of the involved lymph nodes [30]. Additionally, bronchoalveolar lavage fluid may be analyzed for CD4/CD8 ratio, which has been shown to be elevated in pulmonary sarcoidosis [31]. If CT chest is unremarkable, but suspicion for sarcoidosis remains high, then full body fluorodeoxyglucose positron emission tomography (FDG-PET) scan may be a more sensitive test to evaluate for sarcoidosis involvement elsewhere in the body and potentially locate an active site of inflammation in which biopsy may be pursued. FDG-PET also may be used to detect cardiac sarcoid, which can cause life-threatening arrhythmia and may be missed on chest CT [3]. While gallium scanning historically was used to evaluate for active sarcoid lesions, FDG-PET has been shown to be more sensitive, and, therefore, is preferred [32].

The skin and the eyes also frequently are involved in sarcoidosis. Cutaneous lesions occur in 20–35% of sarcoidosis cases [33]. While there is no “typical”

appearance of the cutaneous lesions of sarcoidosis, the presence of skin findings may provide a potential low-morbidity biopsy site. Due to potential for visual morbidity, direct pathologic confirmation of ocular sarcoidosis often is avoided. Vitrectomy may assist with diagnosis in some settings in which ocular involvement is prominent, particularly when therapeutic vitrectomy is indicated for visually significant nonresolving vitreous opacity or epiretinal membrane. Comparable to the increased CD4/CD8 ratio in bronchoalveolar lavage fluid in pulmonary sarcoidosis, it has been reported that vitreous analysis producing an elevated CD4/CD8 ratio is highly suggestive of ocular sarcoidosis [34]. Blind conjunctival biopsies (i.e., in the absence of a conjunctival nodule) are not recommended due to low diagnostic yield [35]. However, if a conjunctival granuloma is identified on clinical examination, then this may provide a potential biopsy site [36].

While histopathologic confirmation of the diagnosis is desirable, there are times when no feasible biopsy site is identified. In these situations, ancillary testing may help to support the level of suspicion for sarcoidosis. Although serum angiotensin converting enzyme (ACE) is suggestive of sarcoidosis when elevated, this test is not sensitive for the diagnosis; therefore, its use is limited [3, 6, 7, 23, 35, 37–39]. Serum lysozyme lacks sensitivity and specificity and is not recommended for diagnosis [28]. While CSF analysis cannot provide pathologic confirmation of sarcoidosis, it is useful to exclude infectious and neoplastic processes and can be helpful in confirming intrathecal inflammation when neurosarcoidosis is suspected [28]. Predominantly mononuclear pleocytosis, high protein, elevated IgG index, oligoclonal bands, and elevated ACE are common findings in neurosarcoidosis, although normal CSF parameters do not exclude a diagnosis of neurosarcoidosis [3, 28]. Viral titers, mycobacterial polymerase chain reaction (PCR), bacterial and fungal cultures, Lyme disease and syphilis testing, flow cytometry, and cytology can be performed on the CSF to exclude infectious and neoplastic mimickers of inflammatory disease [28]. Additionally, suspicious cases without a reasonable biopsy site may be amenable to a trial of steroid as a surrogate "diagnostic" procedure after infectious processes have been excluded adequately. The suspicion for sarcoidosis increases when prompt improvement of symptoms and MRI findings occurs upon the initiation of steroid therapy.

Neurosarcoidosis involving the visual pathways requires treatment with steroid, and often, additional immunosuppressive agents, to minimize visual morbidity [6]. Options for steroid therapy include oral prednisone or IV methylprednisolone, and initial treatment should be followed by a slow taper [6]. Response typically is rapid, occurring within days to weeks [40]. Observation of this steroid response in suspicious but unconfirmed cases is suggestive of sarcoidosis. Long-term immunosuppressive or immunomodulatory therapy may be used in conjunction with or instead of steroid in patients who cannot tolerate steroid side effects or in those patients prone to relapse. First-line steroid-sparing treatment options include mycophenolate mofetil, azathioprine, methotrexate, and leflunomide, and use of cyclophosphamide, rituximab, or the monoclonal antibodies to tumor necrosis factor (TNF)-alpha, infliximab and adalimumab, may be considered in refractory disease [18, 41–45]. However, despite treatment, risk of relapse may remain high [46]. While the optimal

treatment regimen for neurosarcoidosis remains unknown, infliximab has shown the most promise in refractory cases [47, 48].

Case Resolution

The patient in the case underwent CT chest, which demonstrated bilateral hilar lymph node enlargement and perichondrovascular pulmonary nodules. Additionally, he developed a skin lesion on his forehead. The skin lesion was biopsied and demonstrated noncaseating granulomatous inflammation with multinucleated giant cells, consistent with cutaneous sarcoidosis. He was treated with prednisone and mycophenolate mofetil and has had a relapsing disease course.

Conclusion

As the clinical presentation of neuro-ophthalmic sarcoidosis is variable and can mimic many other infectious, inflammatory, and neoplastic processes, awareness of the patterns of neurologic, ocular, pulmonary, cutaneous, and other system involvement, as well as the appropriate diagnostic tests to identify these manifestations, often is crucial for accurate diagnosis and appropriate treatment. With appropriate treatment, reversal of neuro-ophthalmic symptoms, even including visual improvement from no light perception, may be possible.

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