Neuro-Ophthalmology 2021

Common Concerns, Uncommon Problems: Clues to Finding the Hidden Dangers!

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Peter A Quiros MD and Prem S Subramanian MD PhD

In conjunction with the North American Neuro-Ophthalmology Society

Ernest N Morial Convention Center
New Orleans, Louisiana
Friday, Nov. 12, 2021

Presented by:
The American Academy of Ophthalmology

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2021 Neuro-Ophthalmology Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the North American Neuro-Ophthalmology Society (NANOS), it is our pleasure to welcome you to New Orleans and **Neuro-Ophthalmology 2021: Common Concerns, Uncommon Problems—Clues to Finding the Hidden Dangers!**

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Neuro-Ophthalmology 2021 Contents

CME Credit

The Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance, or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

2021 Neuro-Ophthalmology Subspecialty Day Meeting Learning Objectives

Upon completion of this activity, participants should be able to:

- Direct the initial workup of a patient with visual loss from optic neuropathy
- Recognize urgent signs and symptoms in the evaluation of adults with diplopia
- Distinguish the key manifestations of vision-threatening and life-threatening systemic disorders
- Differentiate causes of eye pain and headache and outline a focused approach

2021 Neuro-Ophthalmology Subspecialty Day Meeting Target Audience

The intended audience for this program is comprehensive ophthalmologists.

Teaching at a Live Activity

Teaching instruction courses or delivering a scientific paper or poster is not an *AMA PRA Category 1 Credit*™ activity and should not be included when calculating your total *AMA PRA Category 1 Credits*™. Presenters may claim *AMA PRA Category 1 Credits*™ through the American Medical Association. To obtain an application form, please contact the AMA at www.ama-assn.org.

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2021 Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

Friday Subspecialty Day Activity: Glaucoma, Neuro-Ophthalmology, Pediatric Ophthalmology, Refractive Surgery, and Retina (Day 1)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Saturday Subspecialty Day Activity: Cornea, Oculofacial Plastic Surgery, and Retina (Day 2)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physicians registered as In Person and Virtual are eligible to claim the above CME credit.

How to Claim CME

Attendees can claim credits online.

For AAO 2021, you can claim CME credit multiple times, up to the 50-credit maximum, through Aug. 1, 2022. You can claim some in 2021 and some in 2022, or all in the same year.

For 2021 Subspecialty Day, you can claim CME credit multiple times, up to the 12-credit maximum per day, through Aug. 1, 2022. You can claim some in 2021 and some in 2022, or all in the same year.

You do not need to track which sessions you attend, just the total number of hours you spend in sessions for each claim.

Academy Members

CME transcripts that include AAOE Half-Day Coding Sessions, Subspecialty Day and/or AAO 2021 credits will be available to Academy members through the Academy's CME Central web page.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational

activities at AAOE Half-Day Coding Sessions, Subspecialty Day and/or AAO 2021.

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The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity.

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Academy Members

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Nonmembers

When you claim CME credits and complete the evaluation, a new browser window will open with a PDF of your certificate. Please disable your pop-up blocker. Your certificate will also be emailed to you.

CME Questions

Send your questions about CME credit reporting to cme@aao.org.

For Continuing Certification questions, contact the American Board of Ophthalmology at MOC@abpo.org.

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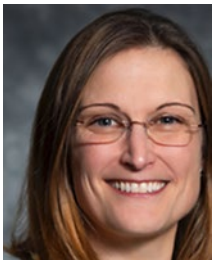

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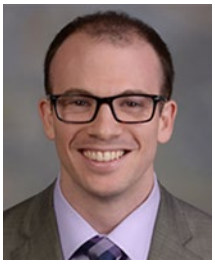

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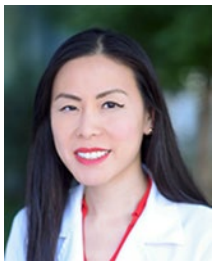

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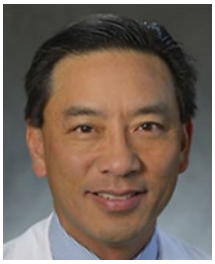

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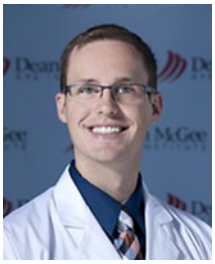

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- Access at www.aao.org/mobile
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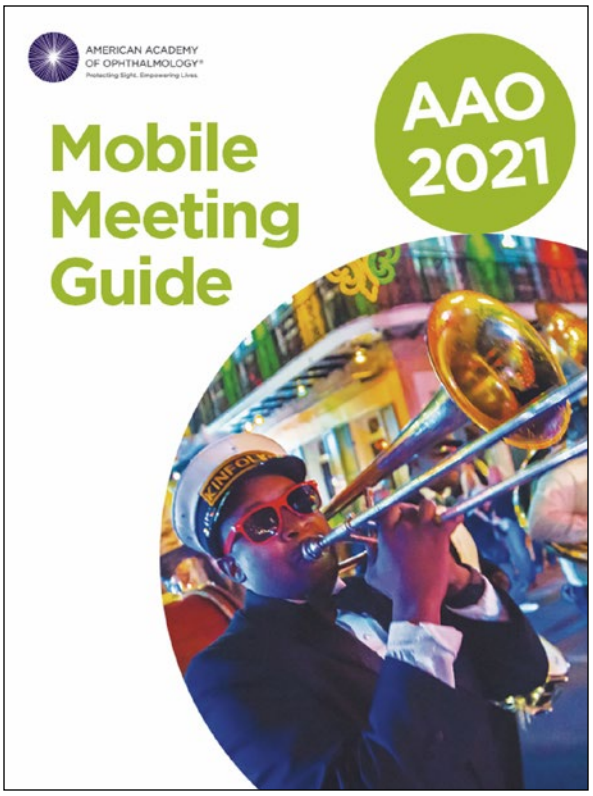
- Filter by meeting: Neuro-Ophthalmology Meeting
- Select "Current Session"
- Select "Interact with this session (live)" link to open a new window
- Choose "Answer Poll" or "Ask a Question"



Neuro-Ophthalmology 2021: Common Concerns, Uncommon Problems: Clues to Finding the Hidden Dangers!

In conjunction with the North American Neuro-Ophthalmology Society (NANOS)

DATE: FRIDAY, NOV. 12, 2021

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Welcome and Introductions	Peter A Quiros MD Prem S Subramanian MD PhD*	
Section I:	**I Can't See Straight—Diplopia** Moderators: Jason H Peragallo MD* and Madhura A Tamhankar MD* Virtual Moderator: Eric L Berman MD Panelists: Sophia Mihe Chung MD*, Karl C Golnik MD, Paul H Phillips MD, and R Michael Siatkowski MD*		
8:02 AM	Audience Interaction	Peter A Quiros MD	
8:03 AM	"It's Double When I Drive" 1	Jane A Bailey MD	2, 24
8:18 AM	"It's Double When I Drive" 2	Alberto G Distefano MD	2, 24
8:33 AM	"It's Double When I Drive" 3	Ahmara G Ross MD*	3, 25
8:48 AM	"It's Double When I Read" 1	Andrew Melson MD	3, 26
9:03 AM	"It's Double When I Read" 2	Sivashakthi Kanagalingam MD	4,27
9:18 AM	"It's Double When I Read" 3	Rod Foroozan MD	5, 27
9:33 AM	Summary	Peter A Quiros MD	
9:35 AM	REFRESHMENT BREAK		
Section II:	**Is This Nerve Okay? Optic Nerve Disease** Moderators: Anne S Abel MD and John J Chen MD PhD* Virtual Moderator: Courtney E Francis MD* Panelists: Anthony C Arnold MD*, Sophia Mihe Chung MD*, Mark L Moster MD*, and Joseph F Rizzo III MD		
10:05 AM	"My Nerve Looks Normal, but I Can't See" 1	Laura Bonelli MD	6, 29
10:20 AM	"My Nerve Looks Normal, but I Can't See" 2	Crandall E Peeler MD	6, 29
10:35 AM	"My Nerve Looks Normal, but I Can't See" 3	Sangeeta Khanna MD	7, 30
10:50 AM	Debate: What Should the Workup Be for Optic Atrophy?		
11:00 AM	"My Nerve Is Swollen, but My Vision Is Fine" 3	Melinda Y Chang MD	7, 31
11:15 AM	"My Nerve Is Swollen, but My Vision Is Fine" 2	Stacy L Pineles MD	8, 32
11:30 AM	"My Nerve Is Swollen, but My Vision Is Fine" 1	Mays A El-Dairi MD	9, 33
11:45 AM	In These Unprecedented Times . . .	Prem S Subramanian MD PhD*	11

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

11:50 AM	Summary	Prem S Subramanian MD PhD*	
11:52 AM	LUNCH		

Section III: More Than Meets The Eye—Systemic Disease Manifestations

Moderators: Chantal Boisvert MD and Guy V Jirawuthiworavong MD

Virtual Moderator: Larry P Frohman MD*

Panelists: Valerie Biousse MD*, Mark J Kupersmith MD*, Andrew G Lee MD, and Judith E Warner MD

1:18 PM	"I'm Blinded by the Light" 1	M Tariq Bhatti MD*	13, 34
1:33 PM	"I'm Blinded by the Light" 2	Melissa W Ko MD	13, 35
1:48 PM	"My Vision Fades Out" 1	Sachin Kedar MD*	14, 35
2:03 PM	"My Vision Fades Out" 2	Cristiano Oliveira MD	14, 36
2:18 PM	Debate: What to Do With Amaurosis and a "Normal" Workup		
2:28 PM	"I Need More Light to See" 1	Heather E Moss MD PhD*	15, 37
2:43 PM	"I Need More Light to See" 2	Courtney E Francis, MD*	15, 38
2:58 PM	Summary	Prem S Subramanian MD PhD*	
3:00 PM	REFRESHMENT BREAK		

Section IV: What a Pain? Headache and Eye Pain

Moderators: Valerie I Elmalem MD* and Raghu Mudumbai MD

Virtual Moderator: Barbara S Yates MD

Panelists: Kathleen B Digre MD*, Grant T Liu MD, and Nancy J Newman MD*

3:30 PM	"My Eye Hurts" 1	Julie Falardeau MD	17, 40
3:45 PM	"My Eye Hurts" 2	Andrew R Carey MD	17, 40
4:00 PM	"The Light Hurts My Eye"	Michael S Lee MD*	18, 41
4:15 PM	Mini-Talk: Taking a Headache History	Lynn K Gordon MD PhD	19
4:25 PM	"It Hurts When I Look Around" 1	Kimberly K Gokoffski MD	21, 42
4:40 PM	"It Hurts When I Look Around" 2	Amanda D Henderson MD	21, 43
4:55 PM	Closing Remarks	Peter A Quiros MD	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Case Presentations

Section I: I Can't See Straight—Diplopia

"It's Double When I Drive" 1

Jane A Bailey MD

CASE PRESENTATION

History and Exam

A 54-year-old man presented with a 2-week history of intermittent binocular vertical double vision. He said it had been staying about the same since it started, and he found that keeping his chin up helped him to drive without double vision. He also noted that his right eye felt strained and scratchy at times, and he had been using over-the-counter allergy eye drops for that. He was initially seen in urgent care and then sent to the ER, where he underwent MRI brain and MRA of the head and neck to rule out stroke or tumor; these were reported as normal.

His past medical history was positive for glucose intolerance, asthma, eosinophilic esophagitis, allergic rhinitis, erectile dysfunction, and benign prostatic hyperplasia, for which he was taking albuterol, beclomethasone inhaler, fluticasone nasal solution, loratadine, and sildenafil. He denied use of alcohol, tobacco, or other drugs. Review of systems was negative for eye pain, blurry vision, droopy eyelids, facial weakness, or numbness. He also denied any symptoms of giant cell arteritis or other neurologic symptoms.

On examination, his BCVA was 20/15 in each eye; pupils were round, equal, and briskly reactive to light; and visual fields were full to counting fingers. His external exam was normal, with symmetric lid fissures and no facial weakness or numbness. Strabismus examination showed –1 supraduction deficit of the right eye, with 1 PD esophoria and 2 PD right hypotropia in primary as well as right and left gazes and right and left head tilts, 10 PD right hypotropia in upgaze, and orthophoria in downgaze. He manifested a chin-up head position.

Intraocular pressures were normal in each eye. Slit lamp exam showed mild injection and conjunctivochalasis of the right eye, and fundus exam was unremarkable.

Clinical Course and Outcome

Review of the brain MRI with contrast that was previously performed in the emergency department showed enlargement of the inferior rectus muscles bilaterally, right more than left, with sparing of the tendon sheaths. The differential diagnosis included thyroid eye disease, as well as nonspecific orbital inflammation, metastatic disease, lymphoma, IgG4-related disease, sarcoidosis, and granulomatosis with polyangiitis.

Laboratory testing showed low TSH, < 0.02 (normal: 0.3-4.50) and elevated free T4, at 1.9 (normal: 0.7-1.5). Thyroperoxidase antibody and TSH receptor antibody were normal. Thyroid ultrasound showed a dominant nodule on the left, and subsequent fine needle aspiration for cytologic evaluation was benign. He was diagnosed with thyroiditis. After treatment with methimazole and prednisone, his lab values normalized.

Unfortunately, his double vision worsened, and he was unable to tolerate prisms, so he used a foil over the right lens. After his strabismus measurements had been stable for 8 months and his eyes had been quiet for that duration, he underwent successful inferior rectus recession on adjustable suture with resolution of his diplopia.

"It's Double When I Drive" 2

Alberto Distefano MD

CASE PRESENTATION

History and Exam

A 22-year-old man presented with sudden-onset vertical double vision in downgaze when looking at his phone and looking at his car dashboard. The double vision was not present when covering either eye. He denied eye pain or irritation, redness, facial weakness or numbness, and headache or other neurological symptoms. He did not have any significant medical history, was not on any medications, and denied smoking. He admitted to drinking 2-3 glasses of alcohol a week. Examination showed BCVA of 20/20 in each eye. Pupils were equal, round, and reactive to light without relative afferent defect. Visual fields were full to finger counting in all fields. External examination was normal, with no ptosis or eyelid retraction. Extraocular movements showed a mild depression deficit in the right eye only and were otherwise full. A small right hypertropia of 3 PD was present in primary gaze. It increased in right gaze to 6 PD and decreased in left gaze to 2 PD. It also increased in downgaze to 10 PD and decreased in upgaze to 1 PD. The right hypertropia increased in left head tilt to 5 PD and decreased in right head tilt to 1 PD. Findings isolated to the right inferior rectus muscle. Forced ductions were performed in the right eye and found to be full without restriction. IOP, slit lamp, and fundus examination were normal.

Clinical Course and Outcome

Laboratory workup revealed normal serum TSH, T3, and T4 levels. Acetylcholine receptor antibodies (binding, blocking, modulating) were negative. MRI of the brain and orbits with and without contrast was normal.

The patient re-presented urgently 4 months later with ptosis and worsening double vision. Exam now showed ptosis on right side in primary gaze. He was found to have a new elevation deficit in the right eye, in addition to stable depression deficit. Cover testing showed an intermittent left hypertropia of 3 PD in primary and left gaze that increased to 6 PD in right gaze.

In upgaze, there was a left hypertropia of 30 PD. In downgaze, there was a right hypertropia of 12 PD. Given the new symptoms, an ice pack test was performed. The ptosis on the right improved after 2 minutes of ice application and revealed a relative ptosis on the left. The patient was clinically diagnosed with ocular myasthenia gravis and referred to neurology for further evaluation. He was prescribed oral prednisone with improvement in symptoms.

"It's Double When I Drive" 3

Ahmara Gibbons Ross MD

CASE PRESENTATION

History and Exam

A 77-year-old woman presented for evaluation of intermittent double vision for 6 months that occurred at a distance and when looking from side gaze. She reported that while driving she would occasionally notice double vision while staring at the lines on the road; the images were side by side and disappeared with monocular occlusion. She attributed her symptoms to fatigue and would often take "short breaks" before driving home from work. She denied any other neurological symptoms such as headache, generalized weakness, difficulty breathing or swallowing, or changes to her vision when looking through each eye individually. She denied transient visual obscurations and pulsatile tinnitus.

Her past medical history was significant only for osteoporosis treated with vitamins and supplemental calcium. She had no significant ocular, surgical, or family history.

On examination, BCVA was 20/20 in both eyes with normal color. External examination revealed mild bilateral ptosis and higher lid creases and normal levator function. No variability, curtaining, or Cogan lid twitch was noted. Extraocular motility revealed mild bilateral abduction deficits. Orbicularis function was normal, and visual fields to confrontation were full bilaterally. Alignment testing showed 4 PD of esotropia in primary, upgaze, and downgaze. In lateral gaze, the esotropia measured 14 PD. Pupils were equal, round, and reactive to light without afferent pupillary defect. IOP was normal in each eye. Posterior segment examination was normal bilaterally.

Clinical Course and Outcome

Given the presence of bilateral ptosis, subtle bilateral abduction deficits, and incomitant esodeviation, the patient underwent laboratory workup that revealed normal acetylcholine receptor antibody testing. MRI of the orbits revealed no evidence of intracranial mass lesion or enlargement of extraocular muscles. Displacement of the lateral recti muscles inferiorly was noted on coronal MRI scan.

The patient was prescribed prisms in her glasses to help treat double vision in the primary position with satisfactory outcome.

"It's Double When I Read" 1

Andrew Melson MD

CASE PRESENTATION

History and Exam

A 61-year-old man presented for evaluation of difficulty reading for the past few months. He stated that "letters and words run together" when using his bifocals to read books and small print. Over this time frame, he had found himself closing one eye to read more comfortably. He now favored watching television and other distance activities that did not require him to occlude either eye. These symptoms had become constant over time and did not vary with time of day.

Sixth months prior to presentation, the patient underwent cataract surgery with mild improvement in vision and contrast. He reported 2 subsequent falls where he "lost balance." He was on artificial tears intermittently for dry eyes.

Review of systems was positive for sleep disturbances, recent increase in depression, and constipation. He had no significant past medical or social history and was on a baby aspirin and multivitamin. He recently retired early from his position as an oil-field executive. His wife states that he "lost his joy in the job and it affected his performance."

On examination, BCVA was 20/20 and J1+ in each eye with his habitual glasses prescription. Pupils were equal, round, and reactive to light. Intraocular pressures were 16 mmHg in each eye, and visual fields were full by confrontation technique. Ocular ductions were full bilaterally. Ocular alignment was orthophoric at distance and revealed 20 PD of exotropia at near. The near point of convergence was measured at 20 cm. Cranial nerve examination was unremarkable. External exam was notable for decreased blink rate without ptosis or orbicularis dysfunction. Slit-lamp examination was notable for mild blepharitis, decreased tear film breakup time, and posterior chamber IOL bilaterally. Fundus examination was within normal limits in each eye.

Clinical Course and Outcome

The patient was placed in trial frames with +2.50 added over their distance correction to simulate single-vision reading glasses. Increasing amounts of base-in prism were introduced until the patient achieved comfortable binocular single vision to an accommodative target at his preferred reading distance of 40 cm. Based on these measurements, the patient was given a prescription for single-vision readers with 5 PD of base-in prism bilaterally. Given the ocular findings of convergence insufficiency exotropia and decreased blink rate, and the combination of other symptoms (constipation, depression/apathy, falls and sleep disturbance), the patient was referred to a neurologist for further evaluation. The patient reported marked improvement in reading ability with the base-in reading glasses and has started treatment for his underlying disorder with good effect.

"It's Double When I Read" 2

"Here's my bag of prism glasses—none of them work!"

Shakthi Kanagalingam MD

CASE PRESENTATION

History and Exam

A 76-year-old right-handed white male was referred for persisting double vision. He reported a 5-year history of binocular diplopia. The diplopia was mostly oblique and sometimes vertical in nature. He underwent cataract surgery in both eyes 2 years prior. On average, he had been wearing prism glasses for 5 years but has been updating the prism prescription 2 to 3 times a year. His numerous pairs of glasses measure small amounts of either horizontal, vertical, or combinations of both prisms ground in.

He denied any ptosis or difficulty swallowing or breathing. He reported the diplopia was present most of the day, not particularly worse in the evening. Review of systems was otherwise negative. His past medical history was significant for psoriasis, testicular cancer (age 47) status post surgery, and atypical Parkinson disease with bradykinesia, drooling, and gait disturbance. His current medications include donepezil 5 mg, vitamin D2, and calcium carbonate supplement.

On examination, he had evidence of dermatochalasis, but no ptosis. There was no evidence of Cogan lid twitch, lid fatigability, or orbicularis oculi weakness. His BCVA was 20/30 in the right eye, and 20/20 in the left eye. Color vision was normal, and IOPs by applanation were normal in each eye. The pupils were round and equally reactive, with no evidence of a relative afferent pupillary defect. Visual fields were full bilaterally. Amsler grid testing demonstrated a central area of metamorphopsia in the right eye.

Sensorimotor examination revealed full motility in each eye. He measured an intermittent right hypertropia of 2-3 PD in all directions of gaze, including tilts. Also noted on examination was a small comitant intermittent esotropia of 2 PD. No significant torsion was measured. He had no notable head tilt. A 2-PD base-down and base-in prism placed over his right eye improved his symptoms only for a few seconds before he reported recurring diplopia.

Examination of the optic nerves revealed titled myopic discs bilaterally. The macula in each eye demonstrated fine central drusen. Additionally, there was a sheen and retinal striae were noted in the right macula. The peripheral retinae were intact bilaterally.

Macular OCT testing revealed an epiretinal membrane (ERM), causing distortion of the normal foveal contour of the right macula. Small elevations in the retinal pigment epithelial layer of the macula in each eye were consistent with macular drusen (Figure 1).

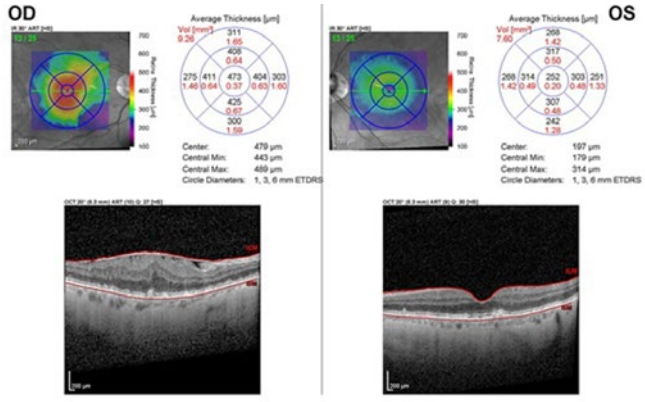


Figure 1

Clinical Course and Outcome

His prior testing included an MRI of the brain with gadolinium. This revealed nonspecific supratentorial white matter changes consistent with age-related findings. Myasthenia antibodies were negative. Single fiber electromyogram was unremarkable, with no evidence of increased jitter.

Differential diagnosis of vertical diplopia can include myasthenia gravis, decompensated congenital CN IV palsy, acquired CN IV palsy, thyroid eye disease, skew deviation, decompensated phoria, and retinal diplopia.

In our case, examination of the patient's retina revealed traction and distortion of the normal foveal contour of the right eye. His history of multiple failed prism glasses over the years, coupled with metamorphopsia of the right eye, favored dragged-fovea diplopia syndrome as the most likely diagnosis. He was evaluated by our retina surgeon, who discussed the risks and benefits of ERM peeling surgery. However, given that his BCVA in the right eye was 20/30, retinal surgery was discouraged. Eventually we prescribed a MIN occlusion lens for his right eye. He continues to enjoy his active lifestyle of hiking and biking with his new MIN lens.

"It's Double When I Read" 3

Rod Foroozan MD

CASE PRESENTATION

History and Exam

A 38-year-old woman noted difficulty reading for 7 months. She noted "jumping" and blurring of vision of the right eye. The symptoms were intermittent and lasted several seconds. While the problem seemed to be precipitated by reading, some episodes occurred while she was watching television. She confirmed that the symptoms persisted in the right eye with occlusion of the left eye, and were not present in the left eye. Three years prior she had similar symptoms, which resolved spontaneously after 3 months. She felt that caffeinated drinks may have aggravated the visual symptoms; however, her difficulty reading persisted after she stopped drinking caffeinated coffee.

She denied prior ocular problems or ocular surgery. She had taken lisinopril for borderline elevated blood pressure years before. She had worked as a nurse in an intensive care unit and had not used tobacco or alcohol.

Visual acuity was 20/20 in each eye. The pupils were briskly reactive with no relative afferent pupillary defect. Ocular ductions and versions were full, and she was orthophoric at distance in all cardinal gazes, as well as at near. Ocular saccades and pursuits were normal. Slit-lamp and fundus examinations were normal. Intermittently during the examination the patient became symptomatic with what she described as "jumping" of the vision of the right eye. Examination during the symptomatic episode revealed abnormal ocular oscillations (video).

Clinical Course and Outcome

Given the intermittent, repetitive incyclotorsion of the right eye, an MRI and MRA of brain were performed, which were unremarkable. Oral carbamazepine 200 mg 3 times per day was prescribed. The patient became lightheaded within 3 days of starting the medication and discontinued it.

The visual symptoms persisted for an additional 3 months and then resolved.

Section II: Is This Nerve Okay? Optic Nerve Disease

"My Nerve Looks Normal, but I Can't See" 1

Laura Bonelli MD

CASE PRESENTATION

History and Exam

A 42-year-old Latina woman noted the onset of visual loss in the right eye 5 days prior to presentation, becoming severe over the previous 2-3 days. Moving the eye produced vague aching, and the eye was mildly tender to touch, although there was no redness or swelling. She had no other systemic or neurologic symptoms. She had no prior episodes of visual loss.

Past medical history was positive for hypertension and hyperlipidemia, treated with lisinopril and atorvastatin. Family history was negative for eye disease.

On examination, she was mildly overweight, with VA right eye HM @ 3', left eye 20/20 without correction. Pupil diameters were 4 mm, with sluggish reactivity to light and a relative afferent pupillary defect right eye, normal reactivity left eye. The anterior segment exam was normal, and there was no proptosis. The eye movements were normal. Dilated funduscopy revealed clear media with bilaterally normal optic disc appearance, cup/disc ratio of 0.35, normal macular reflexes, and minor hypertensive vessel changes.

Humphrey perimetry showed minimal responses right eye, normal left eye. OCT retinal nerve fiber layer and ganglion cell–inner plexiform layer testing were normal bilaterally.

Clinical Course and Outcome

MRI of the brain showed nonspecific nonenhancing white matter lesions; thin sections of the orbits revealed enhancement of the right intraorbital optic nerve from globe to apex; the left nerve was normal. MRI of the spine was unremarkable.

The patient was admitted and underwent the following blood testing: CBC, ESR, CRP, ANCA, ANA, VDRL, FTA-ABS, ACE, Bartonella, Lyme, aquaporin-4 (AQP-4), and myelin oligodendrocyte glycoprotein (MOG) antibodies. Lumbar puncture was performed. She was treated with intravenous methylprednisolone 1 gm/day for 5 days. Examination on hospital day 5 revealed VA CF 3' right eye, 20/20 left eye, with no other changes in the examination. All blood and CSF testing were normal except that AQP-4 and MOG antibody test results were not yet available. She received plasmapheresis therapy over 4 days, with improvement of vision right eye to 20/400. AQP-4 antibody testing returned positive at a titer of 1:1000. Immunosuppression with rituximab was scheduled.

"My Nerve Looks Normal, but I Can't See" 2

Crandall E Peeler MD

CASE PRESENTATION

History and Exam

A 20-year-old man presented for evaluation of blurry vision and light sensitivity in the left eye that had been gradually worsening over the last year. He previously saw an optometrist annually for high myopia, and his BCVA had historically been 20/20 in both eyes until his most recent exam 1 week prior. His first visual symptom was discomfort in bright light settings. He then began to notice gradually worsening vision in the left eye. He did not recall any previous ocular injury and had never been treated for any infectious or inflammatory conditions in either eye.

His past medical history was significant for IgA nephropathy (diagnosed via biopsy). His only medication was lisinopril 5 mg daily. He had no family history of vision problems. He did not smoke or consume alcohol. He worked as a professional cellist.

On examination, BCVA was 20/20 in the right eye and 20/30-2 in the left eye. Pupils were equal, round, and reactive to light without a relative afferent pupillary defect. Color perception was full in the right eye and mildly decreased (8/11 plates) in the left eye by Ishihara testing. IOP was 17 on the right and 16 on the left. Slit-lamp examination was unremarkable in both eyes. Dilated posterior segment evaluation demonstrated slightly tilted optic nerves with sharp margins, 0.2 cup-to-disc ratios, and healthy rim color in both eyes. The maculae and vessels were normal. The temporal retinal periphery in both eyes was noted to have a subtle yellow sheen but was otherwise normal. Humphrey 24-2 SITA Fast visual field testing was full on the right and demonstrated a subtle pericentral defect on the left. OCT of the maculae showed very subtle decreased hyporeflectivity and continuity of the foveal ellipsoid zone, more apparent in the left eye.

Clinical Course and Outcome

An MRI of the orbits with and without contrast was normal. Fundus autofluorescence showed possible loss of the central physiologic hypoautofluorescence but was otherwise normal. Kinetic Goldmann perimetry was full to I2e, I4e, and V4e isopters in both eyes. Full-field electroretinography (ERG) showed normal amplitudes and implicit times bilaterally. Multifocal ERG showed mildly decreased amplitudes centrally, in the left eye more than the right, with normal implicit times.

Given suspicion for occult macular dystrophy, genetic testing was obtained and identified a pathogenic heterozygous mutation in the retinitis pigmentosa 1-like 1 (RP1L1) gene (c.133C>T, p.Arg45Trp). Over the course of the next year, the patient began to report mild visual acuity loss in the right eye as well.

"My Nerve Looks Normal, but I Can't See" 3

Sangeeta Khanna MD

CASE PRESENTATION

History and Exam

A 56-year-old man with past medical history of hypertension was referred for evaluation for 2 weeks of painless decreased vision in the left eye, which he described as washed-out colors and haziness temporally. This was stable since onset, and he denied any pain on eye movements. Review of systems was unremarkable. He takes hydrochlorothiazide for BP control. He consumes a glass of wine 2 or 3 times a week and quit smoking tobacco 20 years previously. Ten days after vision loss, he was seen by an ophthalmologist, who documented a visual acuity of 20/20 OD, 20/50 OS, noted normal disc appearance without disc edema, and referred the patient with a diagnosis of nonarteritic ischemic optic neuropathy OS.

On our examination, BCVA was 20/20 OD and 20/40 OS with mildly reduced color vision OS. Confrontation visual fields were full. Pupils were equal, round, and reactive to light with a mild 0.6 log unit relative afferent pupillary defect (RAPD) OS. IOP was 14 OU. Slit-lamp examination was remarkable only for rapid tear film breakup and 1+ nuclear sclerosis OU. Dilated posterior segment evaluation was normal, with sharp optic nerve margins, slightly large cup-to-disc ratio of 0.6, and healthy rim color OU. The maculae, vessels, and periphery were normal. Cranial nerve examination was unremarkable. Humphrey 30-2 SITA Fast visual field was normal OD; OS had mild inferior nonspecific depression. OCTs of the optic nerves showed normal retinal nerve fiber layer OU (84 OD and 78 OS); OCT of the macula showed binasal thinning of the ganglion cell–inner plexiform layer (GC-IPL) OS>OD, with an average GC-IPL of 72 OD and 68 OS.

Clinical Course and Outcome

The patient was sent for an outpatient MRI brain, which showed a large sellar mass with suprasellar extension causing chiasmal compression. The mass demonstrated uniform enhancement and was most consistent with a pituitary adenoma. He had lab testing for pituitary hormones. Prolactin was only mildly elevated at 32.2 (upper limit being 18.9 ng/mL), and the rest of the labs were normal. The patient was referred to neurosurgery and underwent trans-sphenoidal resection a few weeks later. At 2-month follow up, he reported improved vision in his left eye. His vision had improved to 20/20 OU, with full color vision OU; however, trace RAPD OS was again noted. Humphrey 30-2 SITA Fast visual field was normal in both eyes, and OCT was stable to prior. Follow-up MRI brain showed a partially empty sella without residual tumor and normal chiasmal anatomy.

"My Nerve Is Swollen, but My Vision Is Fine" 3

Melinda Y Chang MD

CASE PRESENTATION

History and Exam

A 17-year-old female presented to the emergency department with 2 weeks of headaches and blurry vision, in addition to emesis starting the day prior to presentation. She reported that the pain was located behind her eyes and was worse while laying down, frequently waking her from sleep. The headache had been constant since onset, although it fluctuated in intensity. She also had pulsatile tinnitus, as well as photophobia without phonophobia. She had gained approximately 40 pounds in the past 6 months. She was not on any medications.

On further questioning during her ophthalmologic examination, she stated that her vision was only blurry without glasses. Her visual acuity without correction was 20/150 in each eye, but she was refracted to 20/20 in each eye (right eye: –5.25 +1.00 x 90, left eye –5.00 + 1.00 x 90). Pupils, IOP, and ocular motility examinations were unremarkable; she had full abduction and was orthotropic. Anterior segment exam was also unremarkable. On dilated fundus examination, she was found to have tilted optic nerves that appeared elevated nasally. No spontaneous venous pulsations were seen. HVF 24-2 demonstrated a superior defect in the right eye and mildly enlarged blind spot in the left eye. On OCT, the average retinal nerve fiber layer (RNFL) thickness was 146 µm in the right eye and 133 µm in the left eye. Fluorescein angiography showed mild hyperfluorescence of the optic discs increasing in area over time, suggestive of leakage.

Clinical Course and Outcome

Although the optic nerves appeared consistent with myopic tilted optic discs, her symptoms, exam findings, and ancillary test results were suggestive of increased intracranial pressure. She underwent brain MRI and MRV, which were unremarkable with the exception of mild narrowing at the junction of the transverse and sigmoid sinuses bilaterally. Subsequently, a lumbar puncture revealed normal CSF constituents and an opening pressure of 35 cm H_2O.

She was advised to lose weight and start acetazolamide 250 mg, 4 times daily. Over 2 months, her symptoms improved and her OCT RNFL average thickness decreased to 93 µm in the right eye and 85 µm in the left eye. Her visual field normalized. The optic nerves still appeared to be tilted and elevated nasally. She had persistent headaches and was tapered off of acetazolamide and transitioned to topiramate.

"My Nerve Is Swollen, but My Vision Is Fine" 2

Stacy L Pineles MD

CASE PRESENTATION

History and Exam

A 13-year-old healthy male presented because he was referred by his endocrinologist. Due to a low growth velocity and short stature, he had been started on growth hormone approximately 7 weeks prior to his referral. He had recently developed a bothersome sound in his ears that sounded like he could hear his own heartbeat. He was unable to characterize whether this symptom was unilateral or bilateral. Due to this new symptom, his endocrinologist felt that an eye examination should be performed.

The child also endorsed chronic daily headaches that were alleviated by ibuprofen or acetaminophen. The headaches had been present for over 1 year and were not associated with any other symptoms such as positional changes, photophobia, phonophobia, nausea, or vomiting. He denied diplopia and transient visual obscurations. The pulsatile sound in his ears had become constant over the past month and was especially bothersome. Past medical history was otherwise normal. Aside from growth hormone, he was not taking any other medications, supplements, or topical creams. He had a family history of congenital color blindness in all males on his mother's side of the family.

On examination, his visual acuity was 20/20 OU. Color vision was 4/16 Ishihara plate OU. Pupils were round and reactive to light, without a relative afferent pupillary defect. Slit lamp examination was unremarkable. Dilated fundus examination revealed elevated optic nerves with hyperemia nasally and minimal obscuration of blood vessels. There were no hemorrhages or exudates. The remainder of the retina examination and cranial nerve examination was normal. Ancillary testing performed included the following:

- Fundus autofluorescence: normal
- OCT retinal nerve fiber layer (RNFL): slightly elevated (G117 OD and G136 OS)
- Enhanced depth imaging OCT: presence of peripapillary hyper-reflective ovoid mass-like structures (PHOMS) bilaterally and no visible optic disk drusen
- Humphrey visual field: nonspecific central depression bilaterally

Clinical Course and Outcome

The patient was referred for further testing, including an MRI brain/orbits with contrast and an MRV, and asked to temporarily discontinue his growth hormone. These tests were normal. Therefore, a lumbar puncture was performed. The opening pressure was 25 cm H_2O with normal constituents. There was discussion among the medical team regarding whether he truly had papilledema or whether it was pseudopapilledema, given the borderline opening pressure. However, given the presence of pulsatile tinnitus, the decision was made to start treatment with acetazolamide. After 4 weeks on acetazolamide, the patient had no improvement in his pulsatile tinnitus, and his examination was largely unchanged. At this point, he was referred to an ear, nose, and throat specialist, who ordered a CT temporal bone. The CT revealed a high riding jugular bulb, which is a rare cause of pulsatile tinnitus.

Given the cogent explanation for his pulsatile tinnitus and the unchanged eye examination, the patient was taken off acetazolamide. His eye examination was unchanged after an additional 6 weeks, and he was therefore restarted on growth hormone.

"My Nerve Is Swollen, but My Vision Is Fine" 1

Mays A El-Dairi MD

CASE PRESENTATION

A 10-year-old girl, adopted from China 2 months prior to presentation (2015), initially presented to the pediatric ophthalmology clinic for in-turning of the left eye. She was previously evaluated by her pediatrician and was felt to be healthy otherwise, but there was a remote history of lumbar laminectomy and tethered cord release. She denied any headaches, pulsatile tinnitus, or transient vision loss. She reported that her left eye had been turning in for as long as she could remember and that she turned her head to see on the left.

On examination, visual acuity corrected to 20/40 and 20/30 with a moderate with-the-rule astigmatic correction bilaterally. Pupils were equal in the light and dark with no relative afferent pupillary defect. She saw 10/10 Ishihara color plates. Confrontational visual fields were full bilaterally. Intraocular pressures were 19 mmHg in both eyes. On sensorimotor examination, she had 400 seconds of arc on stereopsis. She had –4 limitation of abduction of the left eye, with 10 PD intermittent esotropia in primary gaze, which increased to >30 PD on left gaze and 2 PD of exophoria on right gaze. There was narrowing of the palpebral fissure on adduction consistent with a left-sided Duane syndrome type 1.

Fundus examination showed bilaterally elevated crowded optic nerves with pearly deposits over the left nerve consistent with optic nerve head drusen. The vessels were slightly tortuous but not dilated. Initial visual fields had too many false positives to be interpretable.

OCT showed mild relative thickening of the retinal nerve fiber layer (RNFL) for age (OD: 124 µm and OS: 164 µm). Macular ganglion cell layer (GCL) map showed a mild asymmetric thinning (OS thinner than OD) but was within normal limits for age. Visual fields were normal.

She was followed with repeat photos and OCT at 3 months, 6 months, and 1 year, with stable examination, at which point she was discharged to be followed locally with instructions to follow back if a change occurred (2017).

She was referred to neuro-ophthalmology in 2021 (age 15) when a change in the shape of her optic nerves was detected on routine eye examination. She had started a minocycline a few weeks prior for acne management. She remained asymptomatic, with no headaches, changes in vision, or pulsatile tinnitus. She is athletic and practices cross fit.

On examination, she weighed 53.5 kg (118 lb) and was 155.6 cm (5' 1.25") tall (BMI 22.1). Visual acuity was 20/30 and 20/25. Extraocular movements were consistent with left Duane type I and unchanged from prior examination. Color vision 10/10 OU. The optic nerves showed more elevation and blurring of the disc margins in the right more than the left eye compared to the photos from 2015 (see Figure 1).

Visual fields were normal on the right and showed an enlarged blind spot with some nonspecific defects on the left (see Figure 2).

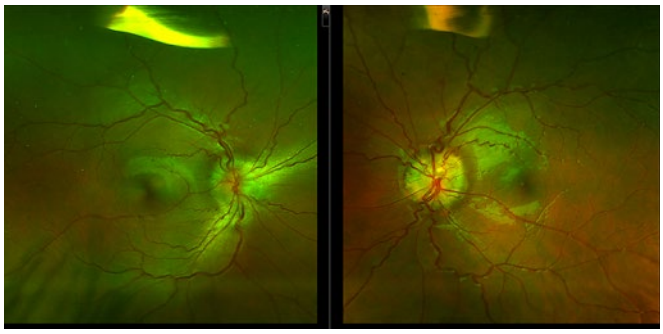


Figure 1

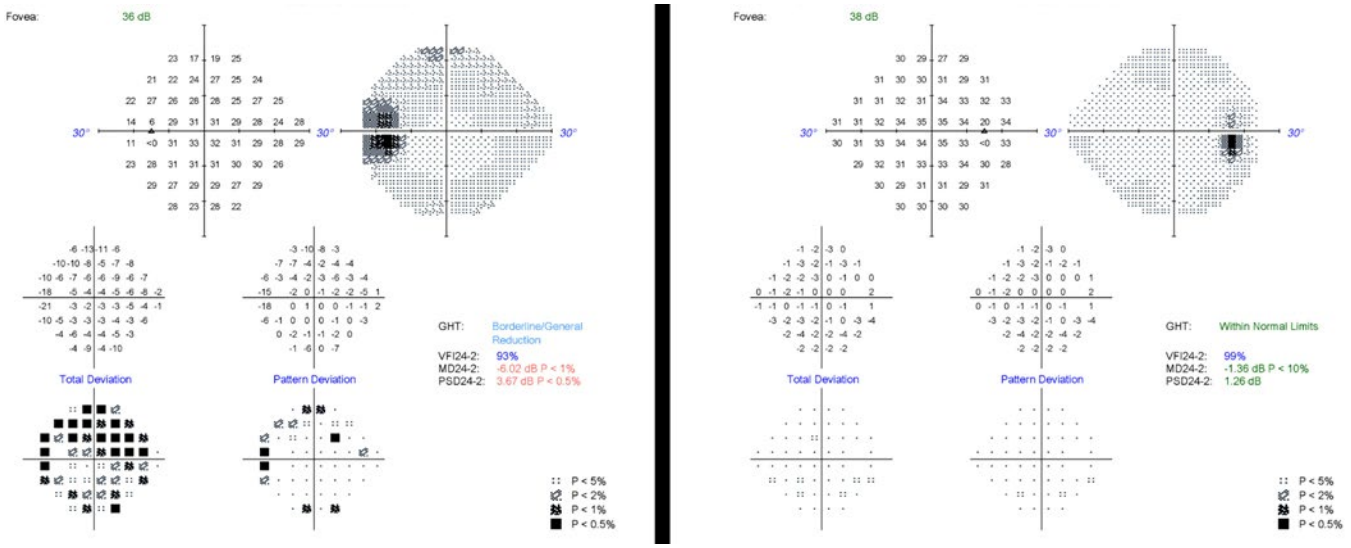


Figure 2

OCT RNFL showed an interval increase in the RNFL OD, with a rather stable RNFL OS; however, there was an interval thinning of the GCL OS. Enhanced depth imaging (EDI) OCT scan of the optic nerves showed no upward bowing of the Bruch membrane. The right eye had peripapillary hyperreflective ovoid mass-like structure (PHOMS), with possible deep drusen (see Figure 3). The left eye had obvious drusen on EDI OCT (see Figure 4).

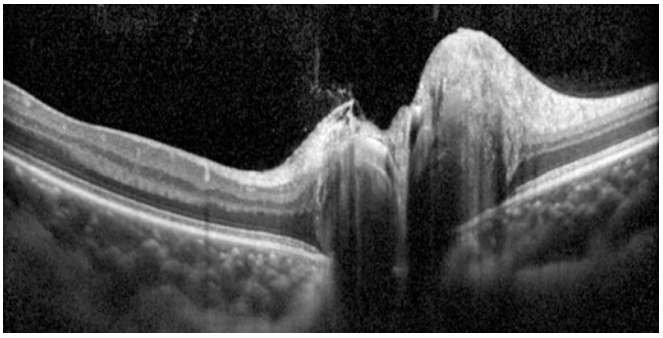


Figure 3

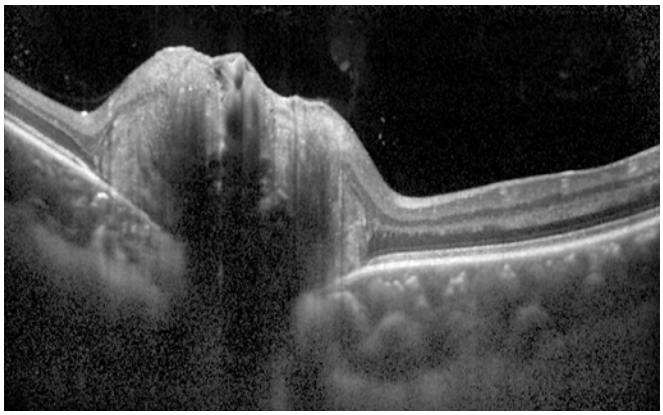


Figure 4

MRI brain and orbits with contrast, along with magnetic resonance venography (MRV), showed no abnormalities or indirect signs of elevated intracranial pressure. On follow-up 3 days after MRI/MRV, the visual acuity and visual fields were stable/normal. She was still asymptomatic. Fundus exam looked unchanged, but OCT showed a further increase in the RNFL in both eyes, with stable GCL thickness.

The parents agreed to stop minocycline with a plan for lumbar puncture and further evaluation/treatment if there was no improvement in the papilledema. On 4 weeks follow-up, there was interval improvement in the RNFL thickness, with stable vision, visual fields, and GCL map.

In These Unprecedented Times . . .

2021 Neuro-Ophthalmology Subspecialty Day

Prem S Subramanian MD PhD

The COVID-19 pandemic has impacted us in many ways, including our ability to effectively raise critical funds used to protect sight and empower lives. This objective requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC®
- Surgical Scope Fund (SSF)
- State Eye PAC

During AAO 2021 in New Orleans, invest in OPHTHPAC and Surgical Scope Fund at one of our two booths in the convention center or online. You may also invest via phone by texting MDEYE to 41444 for OPHTHPAC and SCOPE to 51555 for the Surgical Scope Fund.

We also encourage you to stop by our booth in the Hall B Lobby to learn more about OPHTHPAC Direct, a unique program that lets you decide who receives your political support.

Please help us in these unprecedented times to continue to protect quality patient eye care for everybody. Two Academy committees made up of your ophthalmology colleagues are working hard on your behalf to ensure this outcome. The OPHTHPAC Committee continues to identify Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. The Surgical Scope Fund Committee is raising funds to be used to protect Surgery by Surgeons during scope battles at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both OPHTHPAC and the Surgical Scope Fund. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology continues to strive, especially in these unprecedented times.

OPHTHPAC®

OPHTHPAC represents the profession of ophthalmology to the U.S. Congress. OPHTHPAC's most recent victories include the following:

Physician Relief

- ✓ Securing access to COVID-19 relief, including Provider Relief Funds and forgivable small business loans
- ✓ Pushing Congress to enact a provider-friendly "surprise" medical billing law

Medicare Payment

- ✓ Mitigating drastic Medicare cuts
- ✓ Obtaining a one-year moratorium extension on the 2% Medicare budget sequestration cut

Research & Relationships

- ✓ Increasing vision research funding by $11.6 million
- ✓ Helping get three new physicians elected to Congress, including an ophthalmologist

However, facing ophthalmology's federal issues is a continuous battle, and OPHTHPAC is always under pressure to ensure we have strong political connections in place to help protect ophthalmology, its members, and their patients.

The support OPHTHPAC receives from invested U.S. Academy members helps build the federal relationships that advance ophthalmology's agenda on Capitol Hill. These relationships allow us to have a seat at the table with legislators willing to work on issues important to us and our patients. We also use these congressional relationships to help shape the rules and regulations being developed by federal health agencies.

Get engaged with OPHTHPAC and help strengthen ophthalmology's voice on Capitol Hill as we address the following legislative and regulatory issues this year:

- Improving Medicare physician payments
- Fighting optometric scope expansion in the Veterans' Health Administration
- Obtaining relief from prior authorization and step therapy requirements that delay patient care
- Seeking solutions for rising drug prices and access to drugs in shortage
- Ensuring fair reimbursements for Part B drugs

At the Academy's annual Congressional Advocacy Day, the Academy and the **North American Neuro-Ophthalmology Society (NANOS)** ensure a strong presence of neuro-ophthalmologists to support ophthalmology's priorities. NANOS also supports participation of young ophthalmologists via the Academy's Advocacy Ambassador Program. Ophthalmologists visit members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. NANOS remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund (SSF)

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their efforts to protect patient safety from dangerous optometric surgery proposals. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 41 state/territorial ophthalmology societies reject optometric scope-of-practice expansions into surgery.

If you already have made a SSF contribution, please go to safesurgerycoalition.org to see the impact of your gift.

Dollars from the SSF are critical to building complete, cutting-edge political campaigns, including media efforts (TV, radio, and social media), educating and building relationships with legislators, and educating the voting public to contact their legislators. These political campaigns help the SSF to protect patient safety by defeating optometry's surgical initiatives.

Each of these endeavors is very expensive, and no one state has the critical resources to battle big optometry on their own. Ophthalmologists must join together and donate to the SSF and to fight for patient safety.

The Secretariat for State Affairs thanks the North American Neuro-Ophthalmology Society, who has joined state ophthalmology societies in the past in contributing to the SSF, and looks forward to its 2021 contribution. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the Surgical Scope Fund. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope-of-practice battles and many regulatory issues are all fought on the state level.

ACTION REQUESTED: Support ophthalmology's advocacy efforts

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative/regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal level, respectively, to help elect officials who will support the interests of our patients. Contributions to each of these three funds are necessary and help us protect sight and empower lives. Surgical Scope Fund contributions are completely confidential and may be made with corporate checks or credit cards. PAC contributions may be subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the Surgical Scope Fund, and your State Eye PAC. Please be part of the community that ensures ophthalmology has a strong voice in advocating for patients.

OPHTHPAC Committee

Jeffrey S Maltzman, MD (AZ)—Chair
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Surgical Scope Fund	OPHTHPAC®	State EyePAC
To protect patient safety by defeating optometric surgical scope-of-practice initiatives that threaten quality surgical care	Working across the political spectrum to advance ophthalmology and protect its members and patients at the federal level. Support for candidates for U.S. Congress.	Support for candidates for state House, Senate, and governor
Political grassroots activities, government relations, PR and media campaigns	Campaign contributions, legislative education	Campaign contributions, legislative education
No funds may be used for campaign contributions or PACs.		
Contributions: Unlimited.	Contributions: Limited to $5,000	Contribution limits vary based on state regulations.
Individual, practice, corporate, and organization	Personal and corporate contributions are accepted.	
Contributions are 100% confidential.	Contributions $200 and above are on the public record.	Contributions are on the public record depending upon state statutes.

Section III: More Than Meets The Eye—Systemic Disease Manifestations

"I'm Blinded by the Light" 1

M Tariq Bhatti MD

CASE PRESENTATION

History and Exam

A 58-year-old man experienced intermittent episodes of the left eye vision becoming "washed out" in bright sunlight, lasting 2-3 minutes. However, the visual symptom did not occur every time he was in the sunlight. His medical history was notable for type 2 diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease (status post coronary artery bypass artery surgery), and a recent left middle cerebral artery territory stroke. He was taking aspirin in combination with dipyridamole, atorvastatin, atenolol, and nitroglycerin as needed. He denied headaches, jaw claudication, scalp tenderness, eye pain, or photosensitivity.

Blood pressure was 115/65. Visual acuity was 20/20 OU with 11/11 color plates identified OU and no relative afferent pupillary defect. Slit lamp examination was normal OU. Intraocular pressures were 15 mmHg OD and 16 mmHg OS. Funduscopic examination was normal OU. There was no scalp tenderness, and the superficial temporal artery pulses were intact bilaterally. Automated perimetry demonstrated nonspecific peripheral changes OU.

Clinical Course and Outcome

Photostress recovery test was abnormal in the left eye, with visual recovery of 10 seconds OD and 98 seconds OS. Ophthalmodynamometry (ODM) documented a diastolic pressure of 50 mmHg OD and 20 mmHg OS. Computed tomography angiography demonstrated complete occlusion of the left internal carotid artery. The patient was not considered a candidate for carotid artery endarterectomy, and it was recommended he continue with medical therapy.

"I'm Blinded by the Light" 2

Melissa W Ko MD

CASE PRESENTATION

History and Exam

A 65-year-old woman presents with an acute onset of vertigo and bilateral loss of vision. Three days prior, while standing at the kitchen sink, she noted acute symptoms of dizziness and headache along with feeling like a veil over her vision. She also reports rare intermittent episodes of vertigo and binocular double vision that occurred a handful of times in the last year. She was provided meclizine by her PCP last year for these vertiginous episodes. During this current episode, she had general imbalance and incoordination, with fatigue, and spent the next 2 days lying in bed taking meclizine every 6 hours without relief. She denied any speech or swallowing difficulties or extremity weakness. On the third day of persisting symptoms, her son brought her to the PCP, who sent her to the ophthalmologist. She was told "her eye problem might be related to the brain" and was referred to neuro-ophthalmology for a routine consultation.

She has a past medical history of diabetes, hypertension, and hyperlipidemia. She does not drink and has a remote history of smoking. Her father died of a myocardial infarction.

Blood pressure was 134/70. Vision was 20/20 OU with 11/11 color plates, equal pupils and no relative afferent pupillary defect. Slit-lamp examination was unremarkable OU, and IOPs were 17 mmHg OU. The visual field examination demonstrated a left homonymous hemianopsia. Neurologic examination revealed gait unsteadiness on ambulation.

Clinical Course and Outcome

Patient was sent directly to the ER. She underwent a noncontrast head CT that revealed areas of hypoattenuation in the right frontal white matter, subcortical left frontal lobe, and medial right occipital lobe along the calcarine fissure.

- CT angiography of the head and neck revealed a right vertebral artery stenosis (75%).
- MRI brain: positive diffusion weighted imaging showing early to subacute infarcts in the right frontal, left frontal, and medial right occipital lobe.
- EKG monitor: mainly sinus rhythm with 5 runs of tachycardia
- Cardiac ECHO (TEE) revealed a normal study with no thrombus or atheroma.
- Follow-up Holter monitor revealed paroxysmal atrial fibrillation.

She was started on apixaban, a statin, metformin, and levothyroxine.

Discussion

Where there is inadequate blood flow through the posterior circulation of the brain, which is supplied by the 2 vertebral arteries and basilar artery, vertebrobasilar insufficiency (VBI) occurs.[1-4] This posterior circulation supplies the "high-end real estate" of the brain, including the brainstem, thalamus, hippocampus, cerebellum, occipital, medial temporal lobes, and cervical spinal cord.[1-4] A stroke to these regions can have devastating neurologic and ophthalmic consequences, and thus early recognition of the signs of VBI is critical. Specific to ophthalmology, VBI can impact regions that supply posterior visual pathways and ocular motility. VBI's presenting features

can overlap with more benign etiologies, mimicking vestibular neuritis, labyrinthitis, or benign paroxysmal positional vertigo (BPPV).[1-2] Key ophthalmic symptoms in VBI can include diplopia, transient blurred vision, oscillopsia, and homonymous visual field loss.[1-6]

Who is at risk? The patient with atherosclerotic risk factors including smoking, hypertension, diabetes mellitus, hyperlipidemia, pre-existing coronary artery disease, older age, men, and family history. Approximately 25% of the TIAs and strokes affect the vertebrobasilar distribution.[3]

VBI mainly results from hemodynamic insufficiency and decreased perfusion. Emboli in the vertebral artery distribution are less common compared to the carotid arteries, but can occur secondary to atrial fibrillation, endocarditis, or vertebral artery dissection.[1-2] In younger patients, etiologies to consider include demyelination, dissection, vasculitis, and hypercoagulable states.[1-2] In the appropriate clinical setting, neoplasm and migraine should also be considered.

Treatment is tailored to the underlying etiology of VBI. In patients due to hemodynamic insufficiency, reducing vascular risk factors is critical and patients should be on an antiplatelet agent. In instances of atrial fibrillation and concern for an embolic etiology, cardiology consultation for additional evaluation and discussion regarding anti coagulation.[1-4]

"My Vision Fades Out" 1

Elizabeth Fortin MD

Presented by Sachin Kedar MD

CASE PRESENTATION

History and Exam

A 29-year-old woman reported intermittent episodes of "dark vision in my left eye" for the past 2 years. She did not notice any specific triggers to the vision changes, but they seemed to occur during stressful periods at work. She reported moderate headaches after most of the episodes, but 1 episode affected only the vision, without associated headaches. Her medical history was notable for occasional migraine headaches and asthma, for which she was taking inhalers as needed. She denied any persistent vision changes outside the episodes or any focal neurological symptom.

Visual acuity was 20/20 OU with 8/8 color plates tested with Ishihara and no evidence of a relative afferent pupillary defect. Slit-lamp examination was unremarkable, and IOPs were 14 in the right eye and 13 in the left eye. Funduscopic examination was normal OU.

Clinical Course and Outcome

Automated visual fields were full in both eyes. Upon further history, she reported that the vision loss was preceded by an impression of unusual "brightness" in both eyes that lasted about 5 minutes. She then noticed a "zone of darkness in her left eye" and stated that when she tried covering her left eye during the most recent episode, she noticed a "small shadow in my right eye," although it was "not as bad as in my left eye." This "darkness" lasted about 15 minutes and completely resolved. She was seen in an outside ED after the most recent episode, and a CT head and CTA head and neck were unremarkable.

"My Vision Fades Out" 2

Cristiano Oliveira MD

CASE PRESENTATION

History and Exam

A 70-year-old woman presented for evaluation reporting episode of transient vision loss in the left eye that occurred earlier that same day (in the morning). She described multiple gray spots in the left eye that expanded, evolving to complete loss of vision in that eye (completely black). There was no eye pain, headache, or other symptoms associated. She believed the vision loss lasted for about 45 minutes and that her vision had returned to baseline. The right eye was not affected.

Past medical history was notable for polycystic kidney disease with incidental unruptured right posterior communicating (Pcom) artery and left supraclinoid internal carotid artery (ICA) aneurysm, found during the workup for episode of painless, transient vision loss in the right eye that occurred 8 months prior to presentation. The cardioembolic workup, which also included MRI brain/orbits, transthoracic echocardiogram, Holter monitoring, and laboratory testing for ESR/CRP, was otherwise unrevealing. She underwent stent-assisted coil embolization of the right Pcom aneurysm and stent flow diversion embolization of the left ICA aneurysm 6 months prior to presentation. She was on dual antiplatelet therapy following the procedures up until 1 week prior to presentation, when therapy was switched to low-dose aspirin alone after follow-up catheter angiogram that showed patent stents and successfully treated aneurysms.

On examination, her BCVA was stable at 20/25 in each eye, full Humphrey 24-2 SITA Fast in both eyes, with no dyschromatopsia or relative afferent pupillary defect in either eye. The anterior segment slit-lamp examination was unrevealing in both eyes. The dilated funduscopy showed arterial embolus in a superior distal branch, temporal to the macula in the left eye, with confirmed occlusion on fluorescein angiography.

Clinical Course and Outcome

The patient had contrast-enhanced MRI brain on the same day, with no acute infarcts, and MRA head/neck that the same findings cerebral catheter angiogram done 1 week before with patent stents and no other intracranial or extracranial vascular abnormality. She was advised to resume dual antiplatelet therapy that same day (ticagrelor twice daily plus low-dose aspirin daily). She had follow-up with endovascular neurosurgeon, and the dual antiplatelet regimen was switched to clopidogrel and low-dose aspirin with the plan to keep her on it indefinitely. There was no recurrence of the vision loss, and in her follow-up examination 1 week later, no embolus was observed and the visual function was stable.

"I Need More Light to See" 1

Aubrey L Gilbert MD PhD

Presented by Heather E Moss MD PhD

CASE PRESENTATION

History and Exam

A 65-year-old woman presented for evaluation of a 2-week history of worsening "smoky" vision with new floaters in the left eye and left peri- and retroorbital pain. Additionally, she reported paresthesias in her arms and both sides of her face. She had been in her normal state of health in the months leading up to the onset of these symptoms.

Her past medical history was notable for hyperlipidemia, prediabetes, paroxysmal atrial fibrillation, osteoporosis, and chronic obstructive pulmonary disease. She did not consume alcohol but did have a 50 pack/year cigarette smoking history. There was no known family history of ophthalmologic, neurologic, or autoimmune disease. Her medications at the time included simvastatin, dabigatran, and an albuterol inhaler.

On ophthalmologic exam, BCVA measured 20/30 in the right eye and 20/40 in the left. Pupils were equal, round, and reactive to light without relative afferent pupillary defect appreciated. Intraocular pressure measured 17 in each eye. Slit lamp and dilated fundus examinations were notable for mild left optic disc edema. Visual fields were full to confrontation testing. The remainder of the cranial nerve exam was unremarkable.

Clinical Course and Outcome

MRI demonstrated mildly increased T2 signal and caliber, along with enhancement of the left optic nerve and scattered nonspecific white matter hyperintensities elsewhere in the brain. MRI of the spine showed mild degenerative changes. She was initially diagnosed with optic neuritis and treated with intravenous steroid, with some improvement in her symptoms.

Over the next couple of months, however, she went on to develop recurrent symptoms in the left eye as well as progressively worsening vision and new floaters in the right eye. She also had a number of other new neurologic symptoms develop, including ataxia, dysarthria, leg weakness, difficulty with urination, saddle numbness, worsening pain in her face, arms, and legs, and confusion. Ophthalmologic exam became notable for bilateral disc edema and vitritis in both eyes. Repeat neuroimaging of the brain and spine demonstrated mild bilateral optic nerve enhancement but no other changes. Metabolic, rheumatologic, and infectious studies were normal. Lumbar puncture revealed elevated protein, lymphocytic pleocytosis, and abnormal oligoclonal bands.

She was initially suspected to have multiple sclerosis, then seronegative neuromyelitis optica. She continued to worsen despite treatment with rituximab, going on to develop significant cognitive impairment and seizures. Additional testing was performed for paraneoplastic disease, and she was found to have high titers of collapsin response mediator family-5 (CRMP-5/CV-2) antibody as well as antibodies to gamma-amino-butyric acid type B receptor ($GABA_BR$). A search for cancer revealed small cell carcinoma of the lung with spread that appeared limited to paratracheal and hilar lymph nodes.

She underwent chemotherapy and was also treated with additional high-dose steroid, mycophenolate mofetil, and plasmapheresis. Her vision stabilized and she experienced some improvement in her neurologic symptoms but remained quite impaired despite treatment.

"I Need More Light to See" 2

Kimberly M Winges MD

Presented by Courtney E Francis MD

CASE PRESENTATION

History and Exam

A 54-year-old man was referred by optometry because he was having more trouble seeing in dim lighting. He is an executive at a large advertising company and also noted changes to the color saturation on a presentation at work involving the red hue on a slide that his colleague felt was too bright and off-putting. He also complained of general difficulty discriminating small text on his smartphone when composing emails, despite adequate reading glasses prescription. He denied history of acute vision loss, diplopia, headache, or prior neurologic conditions apart from the occasional migraine, for which he took caffeine and NSAIDs with relief. Systemic review of systems was positive for easy fatiguability, which he attributed to his "workaholic" lifestyle. When prodded further, he admitted to working about 12 hours a day and frequently skipping meals. His job involved entertaining potential clients multiple times a week and traveling frequently to international destinations. He was vegetarian, ran for exercise, and considered himself athletic. He lived alone, smoked 1 pack per day, consumed 3-4 beers a night, and drank 5-6 cocktails in addition when entertaining. Family history did not reveal any relevant ocular or neurologic history.

Eye exam revealed BCVA of 20/30 OD and 20/40 OS, manifest refraction of –1.50 D sphere OU, and IOP of 15 mmHg OU. He had full confrontation visual fields to finger counting, no relative afferent pupillary defect, and 3/6 Hardy-Rand and Rittler color plates OU. Slit lamp biomicroscopy was normal OU, without clinically significant cataract. Dilated fundus exam showed optic nerves with a normal cup-to-disc and temporal pallor OU. No disc hemorrhages, edema, or gliosis were appreciated. Peripheral retinal exam was normal OU.

Humphrey visual fields (HVF) showed 1 abnormal test location centrally in both eyes on 24-2 SITA Standard testing strategy. Therefore, a HVF 10-2 OU was performed, revealing central depression in each eye with a normal foveal threshold. OCT testing showed thinning of the temporal retinal nerve fiber layer quadrant and diffuse thinning of the macular ganglion cell layer OU.

Clinical Course and Outcome

In summary, this is a case of a high functioning 54-year-old male patient with mild decrease in visual acuity, decreased color vision, and central field loss in both eyes on visual field testing.

OCT corroborated the evidence for damage to the papillomacular bundle and ganglion cells, consistent with a mitochondrial optic neuropathy. His risk factors for a nutritional optic neuropathy included vegetarian diet, overconsumption/abuse of alcohol, and smoking. He had no known family history of genetic mitochondrial disease such as dominant optic atrophy, and his history was inconsistent with Leber hereditary optic neuropathy. He had no other history of toxic or heavy metal exposures, use of high-risk medication such as ethambutol, or radiation exposure. He did not have a history of gastric bypass or GI symptoms of malabsorption.

MRI of the orbits with and without contrast was performed to exclude a compressive optic neuropathy and was normal. Labs were sent for CBC, B12, folate, syphilis screening, QuantiFERON Gold, and HBA1c. A mild macrocytic anemia was detected, as well as B12 level of 146 pg/mL (normal: 200-600 pg/mL). Red blood cell folate levels were normal. Subsequent testing for methylmalonic acid (MMA) was high, at 440 nmol/L (normal for his age[1]: 50-440 nmol/L), but total homocysteine level (tHcy) and heavy metals were normal. He was treated with intramuscular injections of B12, and his vision improved to 20/25 OU, but OCT showed persistence of papillomacular bundle atrophy. Visual fields improved and were stable over time. He was given nutritional and addiction counseling. He continues in the same profession and takes vitamin supplements with his vegetarian diet. He reported less fatigue at work and mild macrocytic anemia resolved.

Section IV: What a Pain? Headache and Eye Pain

"My Eye Hurts" 1

Julie Falardeau MD

CASE PRESENTATION

History and Exam

A 50-year-old woman developed the new onset of left-sided eye pain shortly after 2 root canals 1 year previously. The pain was centered on the eye but over time had extended to the cheek. She also reported a recent onset of mild ocular injection with intermittent epiphora in left eye, improved with artificial tears. There was no associated vision loss or diplopia. Review of systems was positive for a 7-year history of numbness affecting a small area of her left cheek, which was the result of a Mohs surgery for resection of a left upper lip basal cell carcinoma. She felt that the area of numbness had somewhat progressed toward the eye.

Her past medical history was otherwise unremarkable. She was a nonsmoker and consumed a glass of wine twice a week. She was taking daily multivitamins but no prescription drug.

On examination, BCVA was 20/20 with each eye. She counted fingers in all fields with each eye. Pupils were equal, round, and reactive to light without relative afferent pupillary defect. IOP was 12 in each eye. Slit-lamp examination was remarkable only for trace of ocular injection in left eye, with mild superficial keratitis. Dilated posterior segment evaluation was entirely normal with healthy optic discs (0.4 cup-to-disc ratio).

Clinical Course and Outcome

She was instructed to use artificial tears and was referred to neurology for further evaluation. MRI of the brain was obtained and was interpreted as normal. Her left-sided facial numbness progressed over time and the periocular pain became more intense. She developed left-sided facial hyperesthesia with crawling sensation. After being diagnosed with trigeminal neuralgia superimposed with idiopathic facial pain, she failed treatment with carbamazepine, lamotrigine, gabapentin, pregabalin, and duloxetine.

Six months later, she was referred to neuro-ophthalmology for new onset of binocular diplopia. Examination demonstrated a left sixth nerve palsy. Her exam was also remarkable for left-sided sensation deficit involving V1, V2, and V3, along with poor corneal reflex in her left eye. A review of the enhanced brain MRI done 6 months prior revealed a left-sided enhancing lesion involving the cavernous sinus and Meckel cave. A control MRI was obtained, which showed slight enlargement of the pre-existing lesion. She was referred to neurosurgery and radiation oncology. A craniotomy with biopsy was performed, and the pathology showed extensive perineural spread from aggressive basal cell carcinoma. PET scan showed no other lesion. After undergoing focal radiation therapy, her sixth nerve palsy slowly improved but did not resolve, requiring correction with prisms. She developed a left-sided neurotrophic keratopathy, closely monitored by a cornea specialist. The eye pain subsided, but the facial paresthesia and hyperesthesia did not improve.

"My Eye Hurts" 2

Andrew R Carey MD

CASE PRESENTATION

History and Exam

A 30-year-old female came in for second opinion of painful left eye. Past medical history was significant for obesity and motor vehicle collision 8 years prior. Her family history was significant for rheumatoid arthritis in her mother, paternal uncle, and both paternal grandparents.

Symptoms began 3 months prior, consisting of constant pressure-like pain, with baseline pain of 4 out of 10 going up to 7 out of 10 nightly. Eye exam at that time was reportedly normal, but symptoms worsened. CT scan was ordered, which showed thickening of left extraocular muscles involving the tendons, felt to be consistent with orbital inflammation. She was put on prednisone 60 mg by outside ophthalmology, pain and swelling improved but did not resolve after 2 months and having significant side effects from prednisone.

Exam with me showed visual acuity OU 20/20; IOP OD 12 mmHg and OS 21 mmHg by applanation; pupils were equal, round, and reactive with OS 0.6-0.9 LU relative afferent pupillary defect; and to confrontation visual fields in the OS showed a relative inferior scotoma while OD was normal. Color was full OU. Extraocular motility was full and orthotropic in primary but with an esotropia of 12^ in left gaze. Hertel measurements showed relative 5-mm proptosis on the left, and palpebral fissure was 2 mm wider on the left. Funduscopy was normal OD, and OS showed tiny flame hemorrhage on the left disc with scattered dot-blot hemorrhages but no disc edema or cystoid macular edema.

Clinical Course and Outcome

The prior CT scan images were reviewed and showed a dilated superior ophthalmic vein on the left. Gonioscopy showed a pink tinge to the Schlemm canal OS and was normal OD. A conventional cerebral angiogram was performed which demonstrated rapid retrograde filling of the left superior ophthalmic vein with pulsatile drainage. However, this could not be accessed via intra-arterial approach. The patient underwent orbital approach for cannulation of the superior ophthalmic vein and embolization of the fistula. Postoperatively her IOP reduced by 7 mmHg with resolution of conjunctival dilated vessels and venous stasis retinopathy as well as resolution of pain.

"The Light Hurts My Eye"

Kathleen B Digre MD

Presented by Michael S Lee MD

CASE PRESENTATION

History and Exam

A 35-year-old woman is referred to you because "Light hurts my eyes." She has a history of migraine in the past, but it was never severe. She could use an ibuprofen, and it didn't interfere with her life. She had a minor motor vehicle accident about 6 months earlier, and she is now not leaving her house; she has the windows blackened, and she is wearing sunglasses all of the time.

Your examination shows the following: visual acuity 20/20 without relative afferent pupillary defect. Her visual fields are normal and her fundus is normal, and for all you can tell, her neurological examination is normal.

What do you diagnose? What do you suggest as treatment?

Mini-Talk: Taking a Headache History

Lynn K Gordon MD PhD

Outline

A 61-year-old male is referred to ophthalmology to rule out papilledema. He has a 3-day history of new-onset headache, without any prior history of headache. His past medical history is significant for hypertension, hyperlipidemia, gastroesophogeal reflux disease, and obesity.

You are running an hour late in the clinic, and although he was referred solely for the ophthalmoscopic evaluation, you realize that the real question is whether this is a primary or secondary headache and what and when other diagnostic testing is required. Primary headaches are very prevalent, the most common of which are tension and migraine.[1] However, you do not want to miss the less common primary cluster or trigeminal autonomic cephalgia (TAC) headaches or secondary headaches that require a different diagnostic and therapeutic plan. A detailed headache history is taken based on the descriptors in Table 1.

Table 1. Primary Headaches

Headache Type	Common Symptoms/Signs	History: Top Questions
Migraine[2]	1. Moderate to severe pain 2. Unilateral pain in ~60%; often described as pulsating 3. Duration is 4-72 hours. 4. Associated symptoms include photophobia and phonophobia, nausea and/or vomiting. 5. Worsened by routine activities 6. Associated with disability—lost workdays or social events 7. Headache pain may be preceded or occur along with transient neurologic symptoms known as "aura" or other prodromal symptoms.	1. Ask about frequency, duration, laterality, character of the pain, severity, and associated symptoms. Headache diaries are helpful in making the diagnosis as well as understanding therapeutic responses to interventions. 2. Ask about photophobia, phonophobia, nausea, vomiting. One of the diagnostic criteria is the presence of photophobia and phonophobia or nausea and/or vomiting. 3. Understand how activity impacts the headache; migraines are typically worsened by movement and physical activity. 4. Ask the patient about disability. Migraines are likely to cause lost days at work or at important social events.
Tension[3] (TTH)	1. Mild to moderate pain 2. Pain is bilateral in >80%. 3. Duration is hours to days. 4. No associated symptoms 5. Headache not typically worsened by routine activities 6. Recurrent headaches, ranging from 1 day/month up to 15 days/month 7. Often described as a band of pain, like a "hatband," but may occur in forehead, occiput, neck	1. Headache diaries reveal frequency, laterality, and severity of headache as well as location. 2. Ask about photophobia, phonophobia, nausea, and vomiting, all of which are uncommon in TTH. 3. Inquire about autonomic features, such as lacrimation, conjunctival injection. These should not be present in TTH. 4. Identify if activity worsens the headache. 5. Ask about comorbidities: depression, migraine, fibromyalgia, sleep disturbance, all of which require additional therapy.
Trigeminal Autonomic Cephalgia (TAC)[4]	1. Unilateral pain in V1 along with ipsilateral autonomic symptoms/signs: conjunctival injection, lacrimation, nasal congestion, miosis, eyelid edema, facial swelling 2. Categories of TAC (cluster, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua) are differentiated by duration and frequency of attacks as well as response to therapy.	1. Ask about headache frequency, periodicity, laterality, and duration. 2. Inquire about associated autonomic symptoms and signs.
Cluster (Most common headache in the TAC category)[5]	1. Severe or very severe pain 2. Unilateral pain, orbital, supraorbital, temporal 3. Duration 15-180 minutes 4. Associated ipsilateral autonomic symptoms: conjunctival injection, lacrimation, nasal congestion, miosis, eyelid edema, facial swelling 5. Restless or agitated during the event 6. Cluster periods: Headaches occur in series of events that occur at least every other day or up to 8 times per day, typically at the same time each day during a cluster period.	1. Ask about headache frequency and events: Do the headaches typically occur at the same time each day? 2. Understand the severity and laterality. 3. Ask if others could tell that they have a headache just by looking at them. 4. Ask about eye redness or facial swelling. 5. Inquire about what they do during the headache: Are they agitated (common in cluster), or do they want to be in a quiet, dark room?

Secondary headaches result from activation of pain-sensitive nerves and can be benign conditions, such as the common but challenging medication overuse headache or the ice cream headache. However, secondary headaches can result from sight- or life-threatening conditions such as vasculitis, infections (meningitis or encephalitis), vascular abnormalities (brain aneurysms or arteriovenous malformations), and brain tumors, among others. To best care for the patient you need a straightforward and easy approach to the history and examination.

An initial general approach to diagnosing new headaches includes the following questions:

1. Are there any red flags present in the history or physical examination?
2. Is the medical and neurological exam unchanged from baseline?
3. To help in diagnosing migraine, the 3 most important screening questions are:
   i. Has a headache limited your activities for at least 1 day in the past 3 months?
   ii. When you have a headache are you nauseated?
   iii. Are you bothered by light when you have a headache, do you prefer to be in a darker or quieter room?
4. Are there any unusual or autonomic features to the headache?

More extensive items can be used to quickly evaluate the patient for specific red flags or to help refine the differential diagnosis. In the past we have used the pneumonic SNOOP4,[6] but a larger list, SNNOOP10,[7] was recently published and is very helpful as a screening tool. A SNNOOP questionnaire can be developed to ascertain the following items:

1. **S**ystemic symptoms, including fever. When positive, you should consider infections or specific noninfectious intracranial lesions such as pheochromocytoma or carcinoid.
2. **N**eoplasm. In patients with a prior history of neoplasm, consider intracranial metastases.
3. **N**eurologic deficits. When the patient has associated neurologic deficits, one must consider a large differential diagnosis including vasculitis, infections, or mass lesions.
4. **O**nset is sudden or abrupt. The concern with an abrupt onset is whether the patient has a vascular cause, for example an aneurysm with hemorrhage.
5. **O**lder age (defined in this publication as over 65, but by prior authors as over 50). One always needs to think about vasculitis in the proper setting as well as other vascular abnormalities or intracranial masses.
6. **P10**
   i. **P**attern change or recent onset of new headache. Consider intracranial mass or vascular lesion.
   ii. **P**ositional headache. Think about the possibility of altered intracranial pressure: either low or high.
   iii. **P**recipitated by sneezing, coughing, or exercise. Evaluate for possible Chiari malformation or posterior fossa lesion.
   iv. **P**apilledema. Concern for mass lesion or intracranial hypertension.
   v. **P**rogressive or atypical. Consider intracranial mass or vascular lesion.
   vi. **Pregnancy**. Evaluate the patient for vascular diseases or hypertension-related causes such as preeclampsia.
   vii. **P**ain in or around the eye with autonomic features. Differential diagnosis will include posterior fossa lesions, cavernous sinus abnormalities, trigeminal autonomic cephalgia (a primary headache syndrome), and ophthalmic causes.
   viii. **P**osttraumatic onset. Concern for subdural hematoma or vascular causes.
   ix. **P**athology of the immune system: immunosuppression or HIV. Evaluate for potential infectious cause.
   x. **P**ainkiller overuse. A very common cause of headache is overuse of over-the-counter analgesics.

The following are red flags in this case: (1) he had no prior headache history, (2) he was older than 50 years of age, and (1) he described new neurologic symptoms of dizziness and double vision. He required urgent neuroimaging to evaluate for a space-occupying lesion.

The key to taking a headache history is to develop a simple but comprehensive screening tool to help differentiate the primary from the secondary headaches and to determine what additional testing is needed. The ultimate goal is to provide appropriate and timely diagnostic testing followed by therapeutic interventions to minimize morbidity or mortality.

References

1. McNeil M. Headaches in adults in primary care. evaluation, diagnosis, and treatment. *Med Clin N Am*. 2021; 105(2021):39.
2. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol*. Epub ahead of print 2021 Jun 18. doi: 10.1038/s41582-021-00509-5.
3. Ashina S, Mitsikostas DD, Lee MJ, et al. Tension-type headache. *Nat Rev Dis Primers*. 2021; 7(1):24.
4. Giani L, Ceccini AP, Leone M. Cluster headache and TACS: state of the art. *Neurolog Sci*. 2020; 41:367.
5. Duri H, Ailani J. Cluster headache: a review and update in treatment. *Curr Neurol Neurosci Rep*. 2021; 21:31.
6. Dodick DW. Pearls: headache. *Semin Neurol*. 2010; 30(1):74.
7. Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice: SNOOP10 list. *Neurology* 2019; 92:134.

"It Hurts When I Look Around" 1

Kimberly K Gokoffski MD and Lilangi Ediriwickrema MD

CASE PRESENTATION

History & Exam

A 33-year-old otherwise healthy male patient presents to the clinic complaining of progressive blurry vision of his left eye. He reports that he accidentally poked his eye when putting away supplies 6 months prior to presentation, after which he began slowly losing vision in that eye. He subsequently developed pain that was more notable with eye movements, prompting him to seek care.

On external examination, there was marked left ocular proptosis, left upper eyelid ptosis, and mild left cheek hypesthesia. His BCVA was 20/20 in the right eye and hand motion in the left eye. There was a left relative afferent pupillary defect and left mydriasis, and slit-lamp examination was notable for left optic nerve pallor with edema. Hemorrhages were not noted along the disc margin. Extraocular movements were full in the right eye and restricted in all fields of gaze in the left eye. Humphrey 24-2 SITA Fast visual field was normal in the right eye (stim III) but exhibited a diffuse dense scotoma in the left eye (stim V). OCT of the left eye revealed mild retinal nerve fiber layer (RNFL) thinning and diffuse patchy ganglion cell layer (GCL) loss.

Clinical Course and Outcome

Patient obtained urgent neuroimaging in the setting of a left orbital apex syndrome. MRI of the brain and orbits revealed a prominent T1 hyperintense and contrast-enhancing mass lesion that involved the intraconal and extraconal space, compression, and displacement of the optic nerve, as well as contiguous extension into the cavernous sinus. Serological analysis was negative or within normal limits for HLAB27, SSA-SSB, ANCA, ACE, RPR, QuantiFERON, and IGG subclasses. He underwent an urgent left orbitotomy with mass lesion biopsy and was begun on oral prednisone, which led to prompt amelioration of the pain with eye movements. Immunohistochemical analysis revealed reactive lymphoid follicles and polyclonal plasma cells, with a high Ki-67 proliferative index in the germinal centers. IgG4 immunohistochemical staining revealed more than 15 positive cells per high power field, with some areas demonstrating the ratio of IgG4:IgG to be more than 0.4.

Given the diagnosis of IgG4-related orbitopathy, the patient was referred to rheumatology and underwent systemic imaging and workup. The inflammation was found to be localized to the left orbit and cavernous sinus, and the patient was maintained on a chronic steroid course with a slow taper. At 4 months in his postoperative course, the patient was noted to have clinical improvement but persistent enhancement on neuroimaging. At approximately 1 year following surgery, the patient's vision improved to 20/30 and his extraocular movements greatly improved. He exhibited a small paracentral scotoma on Humphrey visual field testing and had notable RNFL and GCL loss on OCT in the setting of a persistent left afferent pupillary defect. The patient was transitioned to steroid-sparing disease-modifying therapy.

"It Hurts When I Look Around" 2

Amanda D Henderson MD

CASE PRESENTATION

History and Exam

A 49-year-old woman with no past medical history presented with 1 week of bilateral eye pain, worse with eye movements, and bilateral blurred vision for 2 days, associated with nausea. She had no headaches, transient visual obscurations, pulsatile tinnitus, or diplopia. On examination, visual acuity was 20/70 in the right eye and 20/50 in the left eye. There was no relative afferent pupillary defect. Extraocular motility was full. IOP was 15 mmHg in both eyes. Anterior segment examination was unremarkable, and fundus examination demonstrated bilateral optic disc swelling. Humphrey visual field 24-2 showed a cecocentral scotoma in the right eye and superior and inferior arcuate defects in the left eye.

Clinical Course and Outcome

MRI brain and orbits with and without contrast demonstrated bilateral, longitudinally extensive retrobulbar optic nerve enhancement. There were no T2/FLAIR hyperintensities in the brain. MRI spinal cord was normal, with no evidence of active or chronic demyelination. Serum testing, including ESR, CRP, T-spot, ANA, ANCA, aquaporin-4-IgG, and serologies for syphilis, Lyme, bartonella, and HIV, was negative. Cerebrospinal fluid (CSF) glucose, cell count, and cultures were unremarkable. CSF protein was mildly elevated at 62 (normal $\leq$ 45), and identical oligoclonal bands were detected in the serum and CSF (suggestive of a systemic immune reaction and not suggestive of multiple sclerosis). Serum myelin oligodendrocyte glycoprotein-IgG (MOG-IgG) was positive.

She was treated with methylprednisolone 1 gm daily for 5 days, followed by a slow prednisone taper. Acuity initially declined to 20/400 in the right eye and light perception in the left eye 2 days after presentation, but acuity recovered to 20/20 in the right and left eyes over 3 weeks thereafter. Five months after initial presentation, she had tapered prednisone to 10 mg daily without recurrence. Her MOG-IgG remained positive at that time. She was started on chronic immunosuppression with mycophenolate mofetil.

Diagnosis and Teaching Points

Section I: I Can't See Straight—Diplopia

"It's Double When I Drive" 1

Jane A Bailey MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Thyroid eye disease with asymmetric extraocular muscle restriction causing diplopia, without proptosis or lid retraction

Teaching Points

Thyroid eye disease (TED) is an important cause of restrictive strabismus in adults. Although commonly associated with hyperthyroidism, TED can occur in patients who are euthyroid or hypothyroid.[1] Endocrine abnormalities can occur before, during, or after orbit disease. Enlargement of extraocular muscles is caused by autoantibodies directed against thyroid receptors that activate orbital fibroblasts, which then express extracellular matrix molecules. TED is more common in women than in men and may be exacerbated by smoking. Patients diagnosed over the age of 50, such as in this case, have a worse prognosis overall.

When a patient presents with lid retraction, chemosis, and proptosis, the diagnosis is straightforward; however, TED can be asymmetric with subtle diplopia without overt proptosis and eyelid changes. The inferior rectus is most commonly affected, followed by the medial, superior, and lateral recti, in that order. Oblique muscles are rarely involved, as indicated by the mnemonic "IMSLO." The diagnosis of TED is clinical; however, presence of thyroid hormone abnormalities or circulating antibodies such as anti-thyroglobulin or anti-thyrotropin receptor can support the diagnosis. CT or MRI orbital imaging of TED patients shows enlargement of the extraocular muscles with sparing of the tendons, sometimes crowding the optic nerve at the orbital apex. The most concerning potential abnormalities in patients with TED are compressive optic neuropathy and corneal decompensation from exposure.

The differential diagnosis of TED includes orbital pseudotumor, IgG4 disease, granulomatosis with polyangiitis, and carotid-cavernous fistula. Neoplasms are important to consider as well, particularly if the muscle involvement violates the "IMSLO" rule. Orbital pseudotumor was unlikely given lack of pain and proptosis, and sparing of the muscle tendons on MRI. Fistulas typically cause more diffuse orbital engorgement and prominent conjunctival vessels. This patient's relatively symmetric fusiform inferior rectus muscle enlargement would be atypical for metastasis to the orbit. Myasthenia gravis should always be considered in TED patients with diplopia, particularly if there is ptosis instead of lid retraction. Myasthenia gravis is more commonly seen in patients with TED, and the clinical picture can be confusing when the two diseases overlap. Any patient over 50 who presents with new diplopia should have a careful history taken for possible giant cell arteritis causing ischemia of the extraocular muscles.

The aim of treatment for TED is to avoid permanent optic nerve and corneal damage, and to relieve diplopia and pain. Smoking cessation and achieving euthyroid status are key. It is important to note that radioactive iodine thyroid ablation can exacerbate preexisting TED. Oral selenium is a safe, inexpensive supplement that has shown benefit in patients with mild disease.[2] Management options for diplopia in the acute phase of TED include elevating the head of the bed if there is edema, temporary press-on prisms or ground-in prisms, or occlusion. Once the disease is inactive and stable, strabismus surgery can be considered. Adjustable sutures are an important tool because the extraocular muscles affected by TED are abnormal and have varying elasticity. Teprotumumab, an insulin growth receptor 1R blocker, has been shown in clinical studies to reduce signs and symptoms of active TED.[3]

References

1. Munoz-Ortiz J, Sierra-Cote M, Zapata-Bravo E, et al. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. *Syst Rev*. 2020; 9(1):201.
2. Drutel A, Archambeaud F, Caron P. Selenium and the thyroid gland: more good news for clinicians. *Clin Endocrinol*. 2013; 78(2):155-164.
3. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *New Engl J Med*. 2020; 382(4):341-352.

"It's Double When I Drive" 2

Alberto Distefano MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Ocular myasthenia gravis

Teaching Points

Sudden onset of diplopia in a young adult raises the possibility of conditions such as myasthenia gravis (MG), thyroid eye disease (TED), and intracranial space–occupying lesions. Presence of concomitant ptosis along with diplopia is seen in over 90% of patients with MG. In our patient, however, there was no ptosis at presentation. Moreover, acetylcholine receptor antibody tests were negative. TED seemed unlikely given the lack

of extraocular muscle enlargement seen on MRI scan. While inferior division third nerve palsy is also a diagnostic consideration, MRI failed to reveal any structural intracranial lesion along the course of the third cranial nerve. Given his age, demyelinating disease is also a consideration, although diplopia as a presentation of MS is rare. Typically, in those with longstanding MS, one can see presence of internuclear ophthalmoplegia with skew deviation. In older individuals, brain stem infarction causing skew deviation is a possibility. While MG can mimic any type of ocular misalignment, vertical strabismus alone is an uncommon presentation of MG. In particular, there are only 2 cases reporting ocular MG that presented as an isolated inferior rectus palsy.[1] However, other atypical presentations have been described, including convergence insufficiency, CN VI palsy, and decompensating esophoria.[2-4] More typically, patients present with variable ptosis and/or diplopia. Lid fatigability and Cogan lid twitch are also cardinal signs of ocular MG, both of which this patient also demonstrated on exam after the onset of ptosis.

In MG, antibodies against acetylcholine receptor sites on the postsynaptic membrane of the neuromuscular junction prevent the nerve impulse from initiating muscle contraction, resulting in progressive weakness with sustained activity. Blood tests for the antibodies are available; however, 20% of patients with generalized MG and 50% of those with ocular MG will be seronegative, as in our patient. Single-fiber electromyography can also be performed; it has a sensitivity of 91%-100% in generalized vs. 80%-88% in ocular MG.[2,3] The ice pack test has a sensitivity and specificity of over 90% for ocular myasthenia with ptosis. The ice pack test can also be performed in those with diplopia alone, although the results are less obvious. [4]

Treatment of MG includes the use of oral therapies such as cholinesterase inhibitors, corticosteroids, and other immunosuppressive therapies. Other treatments include plasmapheresis, intravenous human immune globulin, and thymectomy, when indicated per individualized treatment plans.

Ocular MG should always be on the differential for painless double vision and/or ptosis in any age group. Seronegative MG is common. Single fiber EMG can be pursued if clinical suspicion is high.

References

1. Spoor TC, Shippman S. Myasthenic gravis presenting as an isolated inferior rectus paresis. *Ophthalmology* 1979; 86:2158-2160.
2. Arblaster GE, Shipman TL, Pepper IM. Decompensating esophoria as the presenting feature of myasthenia gravis. *J AAPOS*. 2009; 13:310-311.
3. Feuer H, Jagoda A. Myasthenia gravis presenting as a unilateral abducens nerve palsy. *Am J Emerg Med*. 2001; 19:410-412.
4. Colavito J, Cooper J, Ciuffreda KJ. Non-ptotic ocular myasthenia gravis: a common presentation of an uncommon disease. *Optometry* 2005; 76:363-365.

"It's Double When I Drive" 3

Ahmara Gibbons Ross MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

The patient had intermittent horizontal diplopia at a distance, worse with lateral gaze due to sagging eye syndrome (SES).

Teaching Points

Sagging eye syndrome (SES) has been described as a leading cause of strabismus in older adults presenting with a combination of (1) horizontal and vertical strabismus, (2) ptosis with high lid creases, and (3) deepening of the upper eyelid sulcus.[1] In one study, a third of female patients between the ages of 60 and 80 years presenting with diplopia were diagnosed with SES.[2]

The etiology of SES originates from the dense ligament that connects the superior rectus (SR) to the lateral rectus (LR) pulley system.[3] This band supports the LR muscle from the downward and oppositional force of the inferior oblique, which supports the muscle's vertical position along the globe. Age-related degeneration of this ligament results in inferior sagging of the LR muscle and associated pulley system, causing esotropia and cyclovertial strabismus.[4]

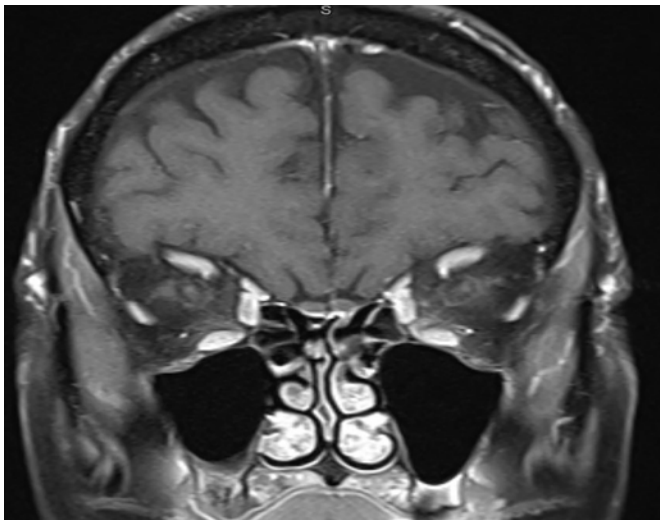

Figure 1. T1-weighted coronal MRI of sagging eye syndrome. Note inferior displacement of the lateral rectus muscles consistent with the sagging eye syndrome diagnosis.

Typically, coronal sections of orbital MRI scans demonstrate supero-temporal bowing of the LR-SR band in mild cases of SES and abrupt termination of a remnant band in the superolateral orbit in more severe cases.[4]

In our case, a differential diagnosis of sixth nerve palsy, thyroid eye disease, myasthenia gravis, skew deviation, or heavy eye syndrome could certainly be entertained and should be ruled out with history, examination testing, and if necessary, imaging prior to making the diagnosis of SES. Management of the disease can range from observation (if the patient is not very symptomatic) to prism prescription and strabismus surgery.[5]

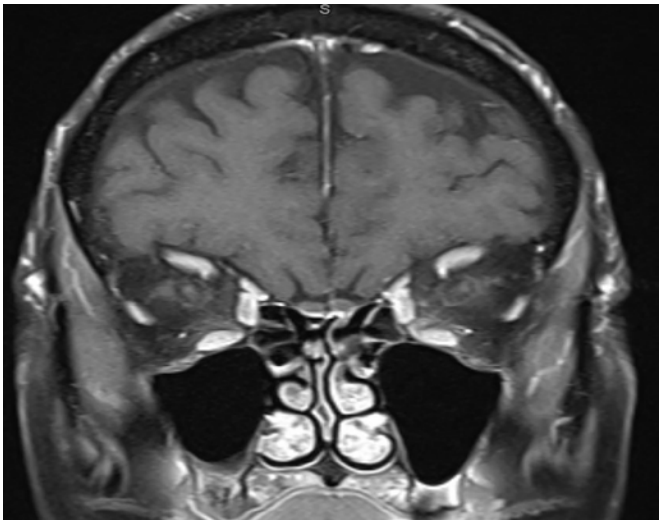

Figure 2

References

1. Chaudhuri Z, Demer JL. Sagging eye syndrome: connective tissue involution as a cause of horizontal and vertical strabismus in older patients. *JAMA Ophthalmol*. 2013; 131(5):619-662.
2. Goseki T, Suh SY, Robbins L, Pineles SL, Velez FG, Demer JL. Prevalence of sagging eye syndrome in adults with binocular diplopia. *Am J Ophthalmol*. 2020; 209:55-61.
3. Demer JL. More respect for connective tissues. *J AAPOS*. 2008; 12(1):5-6.
4. Repka MX, Eric Downing E. Characteristics and surgical results in patients with age-related divergence insufficiency esotropia. *J AAPOS*. 2014; 18:370-373.
5. Chaudhuri Z, Demer JL. Long-term surgical outcomes in the sagging eye syndrome. *Strabismus* 2018; 3:1-5.

"It's Double When I Read" 1

Andrew Melson MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Convergence insufficiency (CI) as a comorbidity of Parkinson disease (PD)

Teaching Points

Our patient presented with complaints suggestive of ocular misalignment though he lacked overt recognition of diplopia. This is a common presentation among patients with CI, who often describe nebulous "blurry vision," "drifting," or "running together" of letters and words while reading, and these symptoms are often, sometimes subconsciously, alleviated by squinting one eye closed. This prompted careful measurement of ocular motility and alignment, both at distance and near. Our patient demonstrated the quintessential manifestations of CI, including exotropia worse at near, decreased convergence amplitudes, and a remote near point of convergence.

Difficulty with reading is a common complaint in patients with PD. There are a variety of ocular manifestations of the disease that can affect both afferent and efferent function. In this case, one clue to the diagnosis was self-occlusion of either eye during near tasks, indicating the presence of binocular diplopia at near. Occult visual manifestations of PD include saccadic and pursuit dysmetria, impaired spatial orientation, and decreased contrast sensitivity.[1]

In this patient, CI was the primary ocular manifestation of previously unidentified PD. Though CI is not exclusive to PD, it occurs with markedly increased frequency in those with PD vs. those without.[2] In fact, the presence of CI may be a marker for simultaneous cognitive impairment.[3] While typical PD motor symptoms such as tremor, bradykinesia, gait disturbance, and rigidity are fairly specific to the disease, they are often preceded by autonomic dysfunction, visual impairment, or other nonmotor symptoms such as sleep, mood, or sexual dysfunction.

Ocular surface disease is a common visual comorbidity in patients with PD and results from decreased blink rate, blepharitis, and dopaminergic medications. Severe dry eye can lead to unilateral or bilateral monocular diplopia, which can occur concomitantly with binocular diplopia from CI. Ocular surface lubrication with artificial tears should be encouraged, and punctual occlusion may be necessary in severe cases. The tremor of PD may limit the feasibility of artificial tear use, and punctal occlusion can be helpful in these scenarios as well. Medications that may exacerbate dry eye or further impair accommodation such as antihistamines should also be avoided. Other important ocular manifestations of PD include blepharospasm and apraxia of eyelid opening. Botulinum toxin treatments for blepharospasm and apraxia of eyelid opening can be effective but need to be balanced against the risk for exacerbation of ocular surface disease and reduced blink rate.

Careful consideration of spectacle features and assistive devices is warranted for patients with PD. Due to difficulty with head and eye movement, bifocal or progressive additions are poorly tolerated in some PD patients and large frame glasses may be preferred. When large base-in prisms are necessary, they are best tolerated in single-vision reading glasses and typically require correcting only 40%-50% of the measured near deviation.[4] When prism is not tolerated, patients may benefit from increasing viewing distance by projecting reading material onto a computer screen or television. While convergence exercises may benefit younger patients with CI, it is rarely effective in patients with PD. Medial rectus resections may be considered in those with a component of exodeviation at distance as well. Patients with associated tremor often find it difficult to read while holding material and may benefit from standing or tabletop book holders.

References

1. Biousse V, Skibell B, Watts R, et al. Ophthalmologic features of Parkinson's disease. *Neurology* 2004; 62(2):177-180.
2. Irving EL, Chriqui E, Law C, et al. Prevalence of convergence insufficiency in Parkinson's disease. *Mov Disord Clin Pract*. 2016; 4(3):424-429.

3. Holden SK, Van Dok E, Pelak VS. Co-occurrence of convergence insufficiency and cognitive impairment in Parkinsonian disorders: a pilot study. *Front Neurol*. 2019; 10:864.
4. Tamhankar MA, Luo S, Kwong B, et al. Benefits and side effects of prisms in the management of diplopia in adults: a prospective study. *J AAPOS*. 2021; S1091-8531(21)00086-0.

"It's Double When I Read" 2

"Here's my bag of prism glasses—none of them work!"

Shakthi Kanagalingam MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Dragged-fovea diplopia syndrome (DFDS)

Teaching Points

1. DFDS can occur in patients with any significant macular pathology, including choroidal neovascular membrane, ERMs, or other maculopathies. These patients experience central binocular diplopia secondary to displacement of 1 or both foveas. The dragged fovea can lose correspondence with the other fovea, resulting in a conflict between the central and peripheral fusion. The momentary alignment of both foveas by prism placement is quickly lost as peripheral fusion mechanism overcomes the central fusion.
2. Patients often present with a long-standing history of failed ground-in prism glasses. Sensorimotor examination commonly reveals a small-angle, relatively comitant vertical deviation. Amsler testing and careful retinal examination, including OCT evaluation to assess the macular contour, can be useful in identifying these patients. A lights on–lights off test with the use of a central single white optotype size 20/70-20/100 against a black background can be helpful in establishing this diagnosis. A patient with DFDS would report 2 distinct letters with the room lights on but would be able to fuse the images into a single letter when the lights are turned completely off. In the dark environment, peripheral retinal stimuli are absent and central fusion can be achieved. However, with the lights on, binocular vision is dominated by the stronger peripheral fusion mechanisms.
3. Most DFDS patients are refractory to prism correction. Undergoing ERM peeling surgery does not usually result in resolution of the diplopia symptoms. Monocular occlusion by means of Scotch tape, Bangerter foils, or MIN lens is used to eliminate diplopic symptoms.

Suggested Readings

1. De Pool E, Campbell JP, Broome S, Guyton DL. The dragged-fovea diplopia syndrome: clinical characteristics, diagnosis, and treatment. *Ophthalmology* 2005; 112(8):1455-1462.
2. Burgess D, Roper-Hall G, Burde RM. Binocular diplopia associated with subretinal neovascular membranes. *Arch Ophthalmol*. 1980; 98:311-317.
3. Veverka KK, Hatt SR, Leske DA, et al. Causes of diplopia in patients with epiretinal membranes. *Am J Ophthalmol*. 2017; 179:39-45.

"It's Double When I Read" 3

Rod Foroozan MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Superior oblique myokymia of the right eye

Teaching Points

Superior oblique myokymia is a condition that causes paroxysmal bursts of small amplitude, torsional, and vertical oscillations of the involved eye. It affects 1 eye and has been reported in patients 20-50 years of age. The abnormal oscillations last seconds, and the frequency of the episodes may vary widely, from multiple times per day to remissions that may last months to years. Magnetic search coils have shown that the frequency of the oscillations may vary widely from 1-50 Hz, and the amplitude is small (less than 1 degree). The abnormal oscillations result in symptoms that have been described as "tilting," "quivering," "jumping," "vibrating," "jiggling," and "shaking," or "like an earthquake." Because the episodes are intermittent and the oscillations may not be present at the time of examination, oftentimes the diagnosis of superior oblique myokymia must be suspected on the basis of the history alone. The repetitive incyclotorsion may often be provoked by having the patient look down and in, in the field of action of the superior oblique muscle. Slit-lamp biomicroscopy or direct funduscopy may be necessary to see the abnormal ocular oscillations. Outside of the office, patients may be able to video their own eye movements to document the episodes.

The underlying etiology of superior oblique myokymia is not clear. Ephaptic transmission (direct neural transmission occurring from adjacent neuronal cell membranes that does not rely on synaptic function) from neuronal irritation has been thought to play a role. A variety of compressive lesions of CN IV have been noted, and a history of prior CN IV palsy has been reported in some patients. Magnetic resonance angiography showing vascular compression (similar to that of hemifacial spasm) of the fourth nerve at the root exit zone of the brainstem has been reported in some patients.

No definitive treatment for superior oblique myokymia has emerged, and the relative infrequency of the condition makes a randomized trial unlikely. Because the condition often spontaneously resolves or remains intermittent, some patients decide

not to pursue treatment. Those with impairment in activities of daily living because of the persistent oscillations are frequently willing to try treatment. Medical options have included agents that have been thought to act as membrane stabilizers, thereby limiting ephaptic transmission. This has included topical therapy with beta-blockers such as timolol and oral antiseizure agents. In prior reports, the most commonly effective agent has been carbamazepine, although many medications (including gabapentin, phenytoin, propranolol) have been tried. A determination of efficacy has been difficult because of the spontaneously remitting nature of the condition.

For patients with persistent and refractory symptoms, injection of botulinum toxin into the superior oblique muscle has been reported as an effective treatment. Surgery on the extraocular muscles, including superior oblique myectomy (often with corresponding inferior oblique myectomy to avoid the effects of a superior oblique palsy) or other weakening procedure on the superior oblique tendon (particularly the anterior fibers), has been noted to improve symptoms while preserving some muscle function, thereby avoiding diplopia. Magnetic search coils have shown this type of surgery on the superior oblique may eliminate the bursts of abnormal oscillations. Neurosurgical vascular decompression of the trochlear nerve has also produced long-lasting improvement of symptoms in some patients with confirmed impingement on the fourth nerve.

The differential diagnosis of superior oblique myokymia includes other conditions that may cause monocular oscillations. A few patients with repeated excyclotorsion and elevation have been described as having inferior oblique myokymia. Eyelid myokymia can causes symptoms similar to those from the quivering described from superior oblique myokymia, as patients may have difficulty distinguishing movement of the eyelid from movement of the globe. The differential diagnosis of the abnormal ocular oscillations includes the Heimann-Bielschowksy phenomenon, which is a pendular dysconjugate eye movement that occurs in eyes with poor visual function (typically with visual acuity less than 20/200). The abnormal oscillation is typically more vertical or elliptical but may have a torsional component. The amplitude is larger and the frequency slower than that of superior oblique myokymia. Asymmetric or monocular nystagmus in childhood, associated with a glioma of the visual pathway, may cause torsional eye movement and is often associated with evidence of optic neuropathy. This type of nystagmus may be indistinguishable from spasmas nutans, which consists of a low-amplitude and high-frequency asymmetric ocular shimmering, torticollis, and head nodding and frequently resolves spontaneously. Monocular nystagmus has been reported to occur from seizure activity involving the brainstem. Symptomatic monocular oscillopsia has been noted in patients after craniotomy or with bony defects of the skull, such as an absent sphenoid wing, from intracranial pulsations of cerebrospinal fluid.

Other abnormal ocular oscillations that can cause an acquired abnormality of horizontal and torsional eye movements include the following:

- Square-wave jerks are intermittent, abnormal, back-to-back saccades that often occur in patients with dysfunction of the basal ganglia, such as in Parkinsonism. This may result in a complaint of jumping of vision; however, these movements are horizontal and bilateral.
- See-saw nystagmus, often with a lesion involving the interstitial nuclear of Cajal, where one eye rises an incyclotorts and the other eye depresses and excyclotorts
- Oculopalatal tremor, resulting from disruption of the dentato-rubro-thalamic tract, is characterized by pendular oscillations, often more vertical, of both eyes, which typically occur at 1-3 Hz. There is often synchronous involvement of the palate with the abnormal eye movement.

These conditions are not likely to be confused with superior oblique myokymia because they are bilateral.

Selected Readings

1. Foroozan R, Buono LM, Sergott RC, Kawasaki A. Jumping Jack Flash. *Surv Ophthalmol*. 2006; 51(1):63-67.
2. Williams PE, Purvin VA, Kawasaki A. Superior oblique myokymia: efficacy of medical treatment. *J AAPOS*. 2007; 11(3):254-257.
3. Kawasaki T, Fujitsu K, Ichikawa T, et al. Superior oblique myokymia: a case report of surgical treatment, review of the literature, and consideration of surgical approach. *World Neurosurg*. 2019; 131:197-199.
4. Hashimoto M, Ohtsuka K, Suzuki Y, Minamida Y, Houkin K. Superior oblique myokymia caused by vascular compression. *J Neuroophthalmol*. 2004; 24(3):237-239.
5. Zhang M, Gilbert A, Hunter DG. Superior oblique myokymia. *Surv Ophthalmol*. 2018; 63(4):507-517.

Section II: Is This Nerve Okay? Optic Nerve Disease

"My Nerve Looks Normal, but I Can't See" 1

Laura Bonelli MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Neuromyelitis optica spectrum disorder (NMOSD)-associated optic neuritis

Teaching Points

Compared with MS-related optic neuritis, NMOSD occurs more frequently in an older, nonwhite population and is more commonly bilateral at onset or rapidly sequential over days to weeks. It may present with either normal or edematous disc appearance. The vision loss is typically more severe than MS-related optic neuritis. Pain with eye movement may or may not be present. The MRI appearance of the optic nerve may aid in differentiating it from MS-related forms. Involvement that is posterior, long (> ½ orbital length) segment, or bilateral suggests NMOSD or MOG-antibody associated disorder (MOGAD); chiasmal involvement is more suggestive of NMOSD, and the additional feature of prominent optic nerve sheath and perineural enhancement further suggests MOGAD. Although certain neurologic syndromes may overlap with MS-related disease, simultaneous spine (with cord sensory and motor dysfunction and longitudinal enhancement), area postrema (with intractable hiccups or vomiting), and hypothalamic (with sleep cycle, body temperature, and other systemic regulatory dysfunction) involvement are more suggestive of NMOSD.

The paradigm for management of acute optic neuritis has changed. Following the results of the Optic Neuritis Treatment Trial (ONTT), Longitudinal Optic Neuritis Study (LONS), and CHAMPS studies, for cases that appeared to be MS-related, ancillary blood testing was not recommended. MRI of the brain was indicated to assess the risk of developing MS, based on the white matter lesion load, but orbital MRI was not usually required for diagnosis. Corticosteroid therapy was administered in cases where faster visual recovery was desired, but it was not required in all cases, as it did not alter the final visual outcome. With the improved recognition of non-MS forms of optic neuritis, management of the acute case has changed. Antibody testing for AQP-4 and MOG is performed in all severe cases, and an argument could be made for doing so in every case unless the patient has classic features of MS. Because the MRI appearance of the optic nerve may aid in differentiating MS-related optic neuritis from NMOSD and MOGAD categories, orbital images are now recommended in every case; spine images are now commonly performed as well.

Because NMOSD-related and MOGAD-related optic neuritis outcomes may be better with immediate corticosteroid therapy, most if not all cases of severe acute optic neuritis are now treated immediately (before antibody testing has returned) with high-dose intravenous corticosteroids. This aggressive approach, along with plasmapheresis in nonresponding cases, likely improves the usually poor visual prognosis in NMOSD optic neuritis. Following stabilization of the acute event, immunosuppression therapy is required to reduce the frequency and severity of disease flares in NMOSD. While azathioprine and mycophenolate have been used successfully, rituximab is the most common immunosuppressive therapy. More recently, there were 3 separate successful randomized clinical trials leading to the FDA approval of eculizumab, satralizumab, and inebilizumab for the treatment of NMOSD.

References

1. Chen JJ, Pittock SJ, Flanagan P, Lennon VA, Bhatti MT. Optic neuritis in the era of biomarkers. *Surv Ophthalmol*. 2020; 65(1):12-17.
2. Prassad S, Chen J. What you need to know about AQP4, MOG and NMOSD. *Sem Neurol*. 2019; 39(6):718-731.
3. Fujihara K. Neuromyelitis optic spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. 2019; 32(3):385-394.
4. Weinshenker BG, Wingerchuck DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc*. 2017; 92(4):663-679.

"My Nerve Looks Normal, but I Can't See" 2

Crandall E Peeler MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Occult macular dystrophy (OMD) due to a mutation in RP1L1

Teaching Points

Typically, patients with macular disease (ie, AMD or cystoid macular edema) have findings that are readily apparent on careful ophthalmoscopy, making the diagnosis straightforward. Occasionally, however, an occult retinal cause of vision loss may have no or only subtle structural findings—even on high-quality OCT—and may manifest with symptoms similar to an optic neuropathy. When a "retina vs. optic nerve" debate arises, a combination of careful history-taking, detailed examination,

and ancillary testing can help determine the primary cause of vision loss.

Historical features such as metamorphopsia, photopsia, and light sensitivity are strongly suggestive of a retinal etiology. Patients commonly describe bending or crowding of normally straight lines, such as a door or window frame, in the setting of macular disease that distorts the photoreceptor architecture. This symptom may also be elicited in clinic with Amsler grid testing. Centrally appearing photopsias, as opposed to those occurring in the far periphery commonly encountered with vitreoretinal traction, are often described with autoimmune dysfunction of the outer retina (ie, paraneoplastic retinopathy, acute idiopathic blindspot enlargement, multiple evanescent white dot syndrome, and acute zonal occult outer retinopathy).[1] "Day blindness" or severe glare sensitivity (hemeralopia) coupled with central acuity loss is a common feature of photoreceptor—specifically cone—dysfunction seen in various hereditary retinal dystrophies.[2] Additionally, certain toxic retinopathies such as those caused by hydroxychloroquine and vigabatrin may initially present with a normal fundus appearance, necessitating a careful review of medication use.[3]

On examination, color vision testing can be useful in distinguishing optic nerve causes from retinal causes of vision loss. Though both etiologies may cause dyschromatopsia, relatively intact visual acuity with a significant reduction in color perception is much more common with optic nerve dysfunction. The presence of an afferent pupillary defect also suggests optic nerve disease. Though extensive, asymmetric retinal lesions can cause an APD, these are typically associated with clear structural abnormalities. On visual field testing, both retinal and optic nerve dysfunction can cause central scotomas, but associated cecocentral and nerve fiber bundle patterns point more toward optic nerve disease, while ring-type defects are a defining feature of maculopathies. A prolonged photostress recovery time following bright light exposure is also relatively specific to retinal disease. On dilated ophthalmoscopy, careful attention to subtle macular pigment changes or early optic atrophy can provide clues to the source of vision loss.[3]

Even with a detailed history and exam, ancillary testing is often required to definitively identify the cause of vision loss. OCT can be useful for detecting early thinning of the peripapillary retinal nerve fiber layer or macular ganglion cell layer suggestive of optic neuropathy, or it may show subtle structural changes in the macula to support a retinal cause of vision loss. Fundus autofluorescence can highlight pigmentary changes in the central macula, and fluorescein angiography can identify capillary nonperfusion and central macular ischemia as can occur in diabetes. ERG often proves to be the most useful tool in identifying retinal dystrophies, with the hallmark of OMD being a normal full-field ERG and subnormal multifocal ERG centrally, as seen in the patient presented here.[4]

OMD is a retinal dystrophy inherited in an autosomal dominant fashion with variable penetrance and a wide range of age at symptom onset. Patients often present with an essentially normal-appearing fundus and a gradual decline in central acuity, photophobia, and color vision disturbances. As is typical of hereditary retinal dystrophies, visual acuity loss is often bilateral and symmetric, although reports exist of unilateral or asymmetric involvement at initial presentation ("pseudo-unilateral" OMD).[5] The RP1L1 gene encodes a component of photoreceptor cilium and is crucial for the development and maintenance of photoreceptor outer segments. RP1L1 mutations cause either a cone dystrophy (the OMG phenotype) or rod dystrophy (retinitis pigmentosa phenotype). If ERG testing suggests OMD, genetic testing for known disease-causing variants of RP1L1 can confirm the diagnosis. Visual acuity loss gradually worsens, and ellipsoid zone changes become more prominent over time, to the point that a clear maculopathy may appear on funduscopy (termed RP1L1 maculopathy).[4,6]

References

1. Volpe NJ, Rizzo JF. Retinal disease in neuro-ophthalmology: paraneoplastic retinopathy and the big blindspot syndrome. *Semin Ophthalmol*. 1995; 10:234-241.
2. Simunovic MP, Moore AT. The cone dystrophies. *Eye* 1998; 12:553-565.
3. Padungkiatsagul T, Leung LS, Moss HE. Retinal disease that can masquerade as neurological causes of vision loss. *Curr Neurol Neurosci Rep*. 2020; 20:1-14.
4. Noel NCL, MacDonald IM. RP1L1 and inherited photoreceptor disease: a review. *Surv Ophthalmol*. 2020; 65:725-739.
5. Okuno T, Hayashi T, Sugasaw J, et al. Elderly case of pseudo-unilateral occult macular dystrophy with Arg45Trp mutation in RP1L1 gene. *Doc Ophthalmol*. 2013; 127:141-146.
6. Nakamura N, Tsunoda K, Mizuno Y, et al. Clinical stages of occult macular dystrophy based on optical coherence tomography findings. *Invest Ophthalmol Vis Sci*. 2019; 60:4691-4700.

"My Nerve Looks Normal, but I Can't See" 3

Sangeeta Khanna MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Chiasmal compression due to pituitary adenoma. This patient had symptoms of compressive optic neuropathy left side due to a sellar mass.

Teaching Points

Patients with chiasmal compression often present with the primary symptom of decreased vision. Vision loss is generally gradual, insidious, and painless; rarely, it can be rapidly progressive because of rapid expansion of the pituitary tumor (pituitary apoplexy). Initially, the fundus examination is normal: as the compression progresses, the optic nerves develop pallor but can also sometimes show increased cupping, which can be confused and treated as normal-tension glaucoma for years before imaging is done for continued loss of vision. Formal visual field testing is often helpful in demonstrating bitemporal field loss respecting the vertical meridian as a clue to chiasmal compression. Additionally, these patients show preferential ganglion cell loss in the nasal hemiretina and characteristic vertical midline-respecting binasal macular GC-IPL thinning on OCT, corresponding to the visual field defects.[1]

Treatment decisions in compressive optic neuropathy are weighted upon field loss and status of the corresponding retinal ganglion cell loss. Monitoring the thickness of the ganglion cell layer complex in the macula is a sensitive method to pick up significant axon loss in cases of compressive optic neuropathy.[2] Binasal ganglion cell complex loss is typical of chiasmal compression and can be seen with minimal or no detectable visual field loss,[3] as demonstrated by this case. Other authors also suggest that OCT GC-IPL analysis can be more sensitive than visual field testing with standard automated perimetry in the detection of compressive chiasmopathy or optic neuropathy,[4] but both visual field and OCT testing should be done when evaluating for chiasmal compression.[5]

Another teaching point from this case is that the diagnosis of anterior ischemic optic neuropathy (which was the referring doctor's diagnosis) should not be made in absence of optic disc edema concurrent with onset of symptoms.

References

1. Jeong AR, Kim EY, Kim NR. Preferential ganglion cell loss in the nasal hemiretina in patients with pituitary tumor. *J Neuroophthalmol*. 2016; 36(2):152-155.
2. Kardon RH. Role of the macular optical coherence tomography scan in neuro-ophthalmology. *J Neuroophthalmol*. 2011; 31(4):353-361.
3. Tieger MG, Hedges TR 3rd, Ho J, et al. Ganglion cell complex loss in chiasmal compression by brain tumors. *J Neuroophthalmol*. 2017; 37(1):7-12.
4. Blanch RJ, Micieli JA, Oyesiku NM, Newman NJ, Biousse V. Optical coherence tomography retinal ganglion cell complex analysis for the detection of early chiasmal compression. *Pituitary* 2018; 21(5):515-523.
5. Lukewich MK, Micieli JA. Chronic chiasmal compression and persistent visual field defect without detectable changes in optical coherence tomography of the macular ganglion cell complex. *Am J Ophthalmol Case Rep*. 2019; 16:100533.

"My Nerve Is Swollen, but My Vision Is Fine" 3

Melinda Y Chang MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Pseudotumor cerebri syndrome in a patient with both papilledema and pseudopapilledema due to myopic tilted optic discs

Teaching Points

Myopia may be associated with pseudopapilledema due to tilted optic discs in up to 37% of children with myopia.[1] Tilted optic discs are associated with greater myopia and longer axial length; the tilting is progressive over time as myopia and peripapillary atrophy increase.[2] The pathophysiology of the progressive temporal tilting of the optic nerve in myopia is unknown, but biomechanical factors such as scleral thinning and repetitive strain from normal eye movements have been suggested.[2, 3]

Tilted discs may also occur in patients with congenital tilted disc syndrome (CTDS). In contrast to myopic discs, the optic disc in CTDS is tilted nasally—ie, the nasal aspect of the disc is shifted posteriorly, while the temporal aspect is tilted anteriorly and may appear elevated or swollen. Other clinical features associated with CTDS include situs inversus of the retinal vessels (as they emerge from the disc, the vessels are directed nasally before sweeping temporally), inferonasal thinning of the retinal pigment epithelium with depigmentation, localized (typically inferonasal) ectasia, and myopic astigmatism.[4]

Both myopic tilted discs and CTDS may cause pseudopapilledema. As with other types of pseudopapilledema, ancillary tests such as fluorescein angiography (FA), optical coherence tomography (OCT), and ultrasonography (US) may assist in differentiating from true papilledema.[5] Superimposed papilledema in eyes with tilted optic discs may be difficult to diagnose. Special considerations in evaluating for papilledema in patients with tilted discs include (1) the baseline OCT RNFL thickness is frequently thinner than normal in myopic eyes,[6] so a "normal" RNFL may actually indicate superimposed mild optic disc edema, (2) peripapillary atrophy may lead to hyperfluorescence on the FA due to a window defect, which must be differentiated from leakage due to optic disc edema, and (3) CTDS may be associated with a superotemporal visual field defect that is refractive (improves or disappears with myopic correction), which can sometimes be confused with a bitemporal hemianopia (which would be concerning for an intracranial abnormality affecting the optic chiasm).[7] In general, FA may be the most useful ancillary test to identify coexistent papilledema and pseudopapilledema, since papilledema with or without pseudopapilledema demonstrates leakage of dye at the optic disc, except in very mild cases.[8]

Because there is no single test that accurately identifies papilledema superimposed on pseudopapilledema from tilted optic discs in all situations, thorough history and clinical examination are paramount. Ancillary testing must be interpreted in the clinical context. In this case, the patient's symptoms of positional headaches and pulsatile tinnitus, history of recent weight gain, absence of spontaneous venous pulsations, and leakage on FA were concerning for papilledema secondary to pseudotumor cerebri syndrome, which led to the workup that confirmed the diagnosis.

References

1. Samarawickrama C, Mitchell P, Tong L, et al. Myopia-related optic disc and retinal changes in adolescent children from Singapore. *Ophthalmology* 2011; 118(10):2050-2057.
2. Kim TW, Kim M, Weinreb RN, Woo SJ, Park KH, Hwang JM. Optic disc change with incipient myopia of childhood. *Ophthalmology* 2012; 119(1):21-6 e1-3.
3. Chang MY, Shin A, Park J, et al. Deformation of optic nerve head and peripapillary tissues by horizontal duction. *Am J Ophthalmol*. 2017; 174:85-94.
4. Witmer MT, Margo CE, Drucker M. Tilted optic disks. *Surv Ophthalmol*. 2010; 55(5):403-428.
5. Chang MY, Velez FG, Demer JL, et al. Accuracy of diagnostic imaging modalities for classifying pediatric eyes as papilledema versus pseudopapilledema. *Ophthalmology* 2017; 124(12):1839-1848.

6. Rauscher FM, Sekhon N, Feuer WJ, Budenz DL. Myopia affects retinal nerve fiber layer measurements as determined by optical coherence tomography. *J Glaucoma*. 2009; 18(7):501-505.
7. Giuffre G. The spectrum of the visual field defects in the tilted disc syndrome: clinical study and review. *Neuroophthalmology* 1986; 6(4):239-246.
8. Pineles SL, Arnold AC. Fluorescein angiographic identification of optic disc drusen with and without optic disc edema. *J Neuroophthalmol*. 2012; 32(1):17-22.

"My Nerve Is Swollen, but My Vision Is Fine" 2

Stacy L Pineles MD

DIAGNOSIS AND TEACHING POINTS

Final Diagnosis

Pseudopapilledema with pulsatile tinnitus due to a high riding jugular bulb

Teaching Points

Distinguishing low grade papilledema (Frisen grade <2, no vessel obscuration) from pseudopapilledema can be challenging in children, especially the younger ones. Multiple imaging modalities have been used over the past few decades, and most recently, OCT has become a more popular method due to the ease of obtaining it in the younger population.

Table 1 outlines the common signs for distinguishing pseudopapilledema from papilledema in children.

Signs of Papilledema vs. Pseudopapilledema on OCT

- Thickening of the peripapillary RNFL: Segmentation errors are common and sometimes harder to correct. It is also dependent on the axial length/refractive error (short eyes have thicker RNFL).
- Enhanced depth imaging OCT of the optic nerve
  - Upward bowing of Bruch membrane.[2,3] Sensitivity low, specificity for retrobulbar pathology is high.
  - PHOMS can be present in both. The presence of signal-poor core with a hyperreflective cap is more suggestive of calcified optic nerve head drusen.[4]
  - Bruch membrane opening (BMO). Nerves with papilledema have large BMO that reverses as the swelling resolves.[5] Nerves with pseudopapilledema have a smaller BMO.[6]
- Macular map: Ganglion cell layer (GCL) map correlates with visual fields when visual fields can't be obtained. GCL might appear thin in previous high-grade papilledema with vision loss or in pseudopapilledema whereby partial optic atrophy has already happened.

The most important use of OCT in elevated optic nerves is that it provides a baseline to determine response to treatment. In true papilledema, the RNFL can be observed to decrease after lumbar puncture and initiating intracranial pressure–lowering medications; whereas pseudopapilledema will be stable after treatment.

Table 1: Common Findings of Papilledema and Pseudopapilledema on Various Imaging Modalities

Modality	Papilledema	Pseudopapilledema
OCT	RNFL thickening	Can see RNFL thickening
	Upward bowing of BM	Flat or v-shaped opening of BM
	Enlargement of BMO	Smaller BMO
	Sometimes GCL thinning	Sometimes GCL thinning
	PHOMS	PHOMS
	Baseline changes after LP and with treatment	No changes after LP and ICP-lowering medications
		Minimal change over time, unless new event
	Might show peripapillary CNV	Might show peripapillary CNV
	En face OCT may reveal wrinkles, folds, and creases	En face OCT unlikely to reveal wrinkles, folds, and creases
	Drusen may be seen if coexistent	Drusen may be seen
FA	Leakage possibly seen especially if previously high grade, diffuse	Might leak if there is a CNV focally
Autofluorescence	Negative	Positive when drusen are visible
Ultrasound	Dilation of nerve sheath, positive 30 deg test (expertise lost with time)	Hyper-reflectivity on US; does not rule out coexistent true edema
Fundus photography	May look the same but serves as a good baseline	

Abbreviations: RNFL, retinal nerve fiber layer; BM, Bruch membrane; BMO, Bruch membrane opening; GCL, ganglion cell layer; PHOMS, peripapillary hyper-reflective ovoid mass-like structures; LP, lumbar puncture; ICP, intracranial pressure; FA, fluorescein angiography.

Signs of Papilledema vs. Pseudopapilledema on Fluorescein Angiography (FA)

- Preinjection autofluorescence is not commonly seen in children, as it requires drusen to be visible or calcified.
- On FA, optic disc drusen exhibit early and late nodular staining of the optic nerve head. In contrast, leakage of dye tends to occur with optic disc edema when it is at least Frisen stage 2.
  - In adults, early nodular staining or late nodular staining is present in more than 50% of patients with buried drusen.[8]
  - In very mild optic disc edema, there may be a lack of dye leakage.
- Both papilledema and pseudopapilledema may be associated with choroidal neovascular membranes on FA.

In the largest study of children with pseudopapilledema, FA had the highest accuracy (97%) for classifying an eye as pseudo- vs. true papilledema. Other modalities had substantial likelihood (30%-70%) of misinterpretation. Other imaging modalities, if used in isolation, are more likely to lead to misinterpretation of pseudopapilledema as papilledema,[9] which could potentially result in failure to identify a life-threatening disorder causing elevated intracranial pressure and papilledema. Typically, a combination of the history, clinical examination, and fundus photos (followed longitudinally) is the most reliable approach by which to judge pseudo- vs. true papilledema, in combination with any of the imaging modalities discussed above.

In conclusion, there is no one modality to distinguish papilledema from pseudopapilledema in a child, although many of the tests described above can be additive. No single imaging modality should replace a clinical examination and judgement.

References

1. Kovarik JJ, Doshi PN, Collinge JE, Plager DA. Outcome of pediatric patients referred for papilledema. *J AAPOS*. 2015; 19(4):344-348.
2. Gampa A, Vangipuram G, Shirazi Z, Moss HE. Quantitative association between peripapillary Bruch's membrane shape and intracranial pressure. *Invest Ophthalmol Vis Sci*. 2017; 58(5):2739-2745.
3. Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. *Invest Ophthalmol Vis Sci*. 2011; 52(9):6558-6564.
4. Chen JJ, Kardon RH. Avoiding clinical misinterpretation and artifacts of optical coherence tomography analysis of the optic nerve, retinal nerve fiber layer, and ganglion cell layer. *J Neuroophthalmol*. 2016; 36(4):417-438.
5. Thompson AC, Bhatti MT, El-Dairi MA. Bruch's membrane opening on optical coherence tomography in pediatric papilledema and pseudopapilledema. *J AAPOS*. 2018; 22(1):38-43 e3.
6. Malmqvist L, Li XQ, Eckmann CL, et al. Optic disc drusen in children: the Copenhagen Child Cohort 2000 Eye Study. *J Neuroophthalmol*. 2018; 38(2):140-146.
7. Gospe SM 3rd, Bhatti MT, El-Dairi MA. Anatomic and visual function outcomes in paediatric idiopathic intracranial hypertension. *Br J Ophthalmol*. 2016; 100(4):505-509.
8. Pineles SL, Arnold AC. Fluorescein angiographic identification of optic disc drusen with and without optic disc edema. *J Neuroophthalmol*. 2012; 32:17-22.
9. Chang MY, Velez FG, Demer JL, et al. Accuracy of diagnostic imaging modalities for classifying pediatric eyes as papilledema versus pseudopapilledema. *Ophthalmology* 2017; 124(12):1839-1848.

"My Nerve Is Swollen, but My Vision Is Fine" 1

Mays A El-Dairi MD

DIAGNOSIS & TEACHING POINTS

Teaching Points

1. In asymptomatic elevated optic nerves, pseudopapilledema can be difficult to distinguish from papilledema, especially in children. (See Pineles/El-Dairi outline on distinguishing papilledema from pseudopapilledema.)
2. True papilledema can be caused by dangerous etiologies and carries a risk of vision loss, and therefore needs a workup and treatment.
3. Per the Idiopathic Intracranial Hypertension Treatment Trial, headache was the most common symptom in increased intracranial pressure, but 16% of participants didn't have a headache.
4. The absence of headache does not protect from the risk of vision loss.
5. Medications to consider in iatrogenic papilledema include tetracyclines, growth hormone, vitamin A, lithium, and exogenous hormonal treatments.

Selected Readings

1. Baheti NN, Nair M, Thomas SV. Long-term visual outcome in idiopathic intracranial hypertension. *Ann Indian Acad Neurol*. 2011; 14(1):19-22.
2. Friedman DI, Quiros PA, Subramanian PS, et al; the NORDIC IIHTT Study Group. Headache in idiopathic intracranial hypertension: findings from the Idiopathic Intracranial Hypertension Treatment Trial. *Headache* 2017; 57(8):1195-1205.

Section III: More Than Meets The Eye—Systemic Disease Manifestations

"I'm Blinded by the Light" 1

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DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Light-induced amaurosis (LIA) or Whisnant phenomenon due to complete internal carotid artery occlusion

Teaching Points

In 1979 Drs. Furlan, Whisnant, and Kearns described 5 patients with visual loss precipitated by bright light due to high-grade stenosis or occlusion of the ipsilateral internal carotid artery.[1] The retinal findings were normal in 2 patients, visible emboli in 2 patients, and venous stasis retinopathy in 1 patient. The retinal artery pressure was noted to be decreased in all the patients. The authors pointed out that the visual loss did not occur every time after exposure to light. This condition of LIA has also been referred to as the Whisnant phenomenon, named after Dr. Jack P. Whisnant, chair of the Department of Neurology at the Mayo Clinic in Rochester, Minnesota.[2]

LIA is on the spectrum of the ocular ischemic syndrome.[3] From a pathophysiological perspective, exposure of the retina to a source of bright light results in an increase in the metabolic demand of the photoreceptor cells. However, due to internal carotid artery insufficiency, a compensatory increase in blood supply cannot be met, resulting in a blood flow supply–metabolic demand mismatch or, more precisely, phototransduction dysfunction from a lack of photopigment protein turnover.[4]

Clinical symptomology is the foundation upon which the diagnosis of LIA is established. Other entities included in the differential diagnosis of LIA include giant cell arteritis, macular degeneration, macular dystrophy, and chorioretinitis. The clinical examination can be normal, but there may be visible emboli or signs of retinal ischemia, such as midperipheral retinal hemorrhages or venous dilation. Typically, LIA is unilateral, but in some cases, the transient visual loss can occur in both eyes simultaneously due to bilateral internal carotid artery disease that can mimic occipital ischemia due to vertebrobasilar insufficiency.[5]

Photostress recovery test can be a useful clinical test to support LIA.[6,7] In addition, the use of the ODM can provide evidence of decreased retinal artery pressure. ODM allows assessment of the diastolic and systolic pressure of the central retinal artery. However, it should be noted that the measurements do not represent the actual intravascular pressure because of multiple contributing variables.[8] Mechanistically, external compression of the eye by the device results in elevation of the IOP with subsequent pulsation of the central retinal artery, indicating the diastolic pressure, and complete collapse of the central retinal artery, indicating the systolic pressure.[9] Antin and Karlin established ODM criteria for abnormal values:[10]

- Diastolic pressure
  - <50 units: >10 units difference in the measurements between the 2 eyes
  - >50 units: >20% difference in the measurements between the 2 eyes
- Systolic pressure
  - >50 units: >20% difference in the measurements between the 2 eyes

Wiebers et al found that ODM had a 5% detection rate of recognizing <75% carotid artery stenosis compared to a 97% detection rate in patients with >75% carotid artery stenosis.[11] Samples et al performed ODM in combination with carotid angiogram and found that retinal artery perfusion decreased in 3 of 10 patients (30%) with 50%-89% carotid artery stenosis and 30 of 42 patients (71%) with >90% carotid artery stenosis.[12] Intravenous fluorescein angiography can often demonstrate retinal ischemic changes, such as microaneurysms, slow arteriovenous transit time, and arteriolar leakage.[13] OCT angiography may have a role in assessing carotid artery disease. Pierro and colleagues found that choroidal thickness was decreased in ipsilesional eyes compared to contralesional and control eyes.[14] Ultimately, however, to confirm the clinical suspicion of carotid artery disease requires ultrasonography, magnetic resonance angiography, or computed tomography angiography.[15]

References

1. Furlan AJ, Whisnant JP, Kearns TP. Unilateral visual loss in bright light: an unusual symptom of carotid artery occlusive disease. *Arch Neurol*. 1979; 36(11):675-676.
2. Brown RD Jr, Rocca WA. Jack P. Whisnant, MD, FAAN (1924–2015). *Neurology*. 2015; 85(21):1832-1833.
3. Terelak-Borys B, Skonieczna K, Grabska-Liberek I. Ocular ischemic syndrome—a systematic review. *Med Sci Monit*. 2012; 18(8):RA138-144.
4. Donnan GA, Sharbrough FW, Whisnant JP. Carotid occlusive disease: effect of bright light on visual evoked response. *Arch Neurol*. 1982; 39(11):687-689.
5. Wiebers DO, Swanson JW, Cascino TL, Whisnant JP. Bilateral loss of vision in bright light. *Stroke* 1989; 20(4):554-558.
6. Glaser JS, Savino PJ, Sumers KD, McDonald SA, Knighton RW. The photostress recovery test in the clinical assessment of visual function. *Am J Ophthalmol*. 1977; 83(2):255-260.
7. Kaiboriboon K, Piriyawat P, Selhorst JB. Light-induced amaurosis fugax. *Am J Ophthalmol*. 2001; 131(5):674-676.
8. Smith VH. The clinical value of ophthalmodynamometry. *Proc R Soc Med*. 1961; 54(10):859-862.
9. Pence NA. Ophthalmodynamometry: the technique and its use in the detection of carotid artery occlusive disease. *J Am Optom Assoc*. 1980; 51(1):49-55.

10. Antin S, Karlan R. Ophthalmodynamometry: criteria for normal and abnormal readings and another technic. *Neurology* 1962; 12:153-156.

11. Wiebers DO, Folger WN, Forbes GS, Younge BR, O'Fallon WM. Ophthalmodynamometry and ocular pneumoplethysmography for detection of carotid occlusive disease. *Arch Neurol*. 1982; 39(11):690-691.

12. Samples JR, Trautmann JC, Sundt TM Jr. Interpretation of results of compression ophthalmodynamometry. *Stroke* 1982; 13(5):655-659.

13. Sarkies NJ, Shilling JS, Russell RW. Fluorescein angiography in carotid disease. *Trans Ophthalmol Soc U K*. 1986; 105(pt 4):489-493.

14. Pierro L, Arrigo A, De Crescenzo M, et al. Quantitative optical coherence tomography angiography detects retinal perfusion changes in carotid artery stenosis. *Front Neurosci*. 2021; 15:640666.

15. Saxena A, Ng EYK, Lim ST. Imaging modalities to diagnose carotid artery stenosis: progress and prospect. *Biomed Eng Online*. 2019; 18(1):66.

"I'm Blinded by the Light" 2

Melissa W Ko MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Vertebrobasilar insufficiency (VBI) with prodromal symptoms of diplopia and vertigo, compounded by atrial fibrillation led to completed right occipital stroke

Teaching Points

When you hear hoofbeats of ataxia, vertigo, and visual symptoms—think VBI. The classical papers by Hoyt describe "transient bilateral visual blurring as a frequent symptom of VBI with flashing points of light having a streaming effect resembling snowflakes rushing through headlight beams of a moving automobile."[5-6] Total vision loss is rare, and "attacks of longer duration may be accompanied by flickering, flashing points of silvery light in a homonymous field of vision."[5-6] But one must place these symptoms within the context of the company that it often keeps. Classical symptoms of VBI include oscillopsia or episodic diplopia during attacks of vertigo or ataxia. Hoyt commented that patients often fail to mention these fleeting attacks and need to be questioned directly.[6] Remember, transient monocular blindness is not part of VBI. The bilateral nature of VBI vision loss can be differentiated from the monocular blackouts of vision associated with carotid insufficiency. This patient was having a "brain attack" with TIAs of the posterior circulation. Prompt recognition of the constellation of VBI symptoms aligned with the "time is brain *and* vision" mantra is critical for evaluation by multidisciplinary stroke teams and urgent deployment of time sensitive thrombolytic agents.

References

1. Costello F. Carotid artery dissection and vertebrobasilar insufficiency. *Int Ophthalmol Clinics*. 2009; 49(3):1-14.

2. Pirau L, Forshing L. Vertebrobasilar insufficiency. In: *Stat Pearls*. Treasure Island (FL): Stat Pearls Publishing; 2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482259/.

3. Sparaco M, Ciolli L, Zini A. Posterior circulation ischemic stroke—a review. Part I: Anatomy, aetiology and clinical presentations. *Neurol Sci*. 2019; 40(10): 1995-2006.

4. Sparaco M, Ciolli L, Zini A. Posterior circulation ischemic stroke—a review. Part II: Imaging and acute treatment. *Neurol Sci*. 2019; 40(10): 2007-2015.

5. Hoyt WF. Some neuro-ophthalmological considerations in cerebral vascular insufficiency. *AMA Arch Ophthalmol*. 1959; 62(2):260-272.

6. Hoyt WF. Transient bilateral blurring of vision: considerations of an episodic ischemic symptom of vertebral-basilar insufficiency. *Arch Ophthalmol*. 1963; 70(6): 746-751.

"My Vision Fades Out" 1

Elizabeth Fortin MD

Presented by Sachin Kedar MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Migraine aura

Teaching Points

Migraine is by far the most common cause of transient bilateral vision loss. It occurs with greater frequency in women and usually starts in the second or third decade of life.[1] About one-third of migraineurs will experience auras, of which 90% will be visual in nature.[2-3] There is some evidence to suggest that patients over 50 years old are more likely to experience auras without headaches than patients <50 years-old.[3]

Visual auras have a broad variety of presentations, including "positive" (such as bright dots, white flashes of light, and bright zigzags) and "negative" (eg, scotomata, blurry or "foggy" vision) visual phenomena.[4] Fortification spectrum, which is considered to be the most "classic" presentation of visual aura, is present in only 20% of cases.[5] According to the International Classification of Headache Disorders third edition (ICDH-3), migraine auras usually spread over 5 minutes and resolve over 5 to 60 minutes.[6]

The physiological mechanism to explain the "positive" visual phenomena associated with migraines is not fully understood, but the thought is that it is the result of neuronal excitation, in contrast to the "negative" visual phenomena, which are thought to be due to neuronal depression. This neurophysiological ensemble was described in 1943 by the Brazilian neurophysiologist Aristides Leao and later named after him as the "spreading depression of Leao."[7]

Most available therapies for migraines target the headache phase of the condition and have limited effect on migraine auras. The acute management includes simple analgesics, antiemetics, and migraine-specific treatments such as triptans.[8-9] Multiple medications such as antidepressants, anticonvulsants, and antihypertensive medicines are used for migraine prophylaxis when the frequency of headaches justifies their usage.[10] Lamotrigine, a glutamate antagonist, may have a superior effect on the prevention of migraine aura.[11-12]

References

1. Hupp S, Kline L, Corbett J. Visual disturbances of migraine. *Surv Ophthalmol*. 1989; 33:221.
2. Fraser C, Hepschke J, Jenkins B, Prasad S. Migraine aura: pathophysiology, mimics and treatment options. *Semin Neurol*. 2019; 39(6):739-748.
3. Quintana S, Genovese A, Rausa F, Manzoni GC, Torelli P. Migraine with typical aura: clinical features and their relationship with sex and age of onset—results from the analysis of a large case series. *Neurol Sci*. 2018; 39(suppl 1):135-136.
4. Quieroz L, Rapoport A, Weeks R, et al. Characteristics of migraine visual aura. *Headache* 1997; 37:137-141.
5. Vincent M, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. *Cephalgia* 2007; 27:1368-1377.
6. Headache Classification Committee of the International Headache Society (HIS). The international classification of headache disorders. 3rd edition (beta version). *Cephalalgia* 2013; 33(09):629-808.
7. Leao AA. Spreading depression of activity in the cerebral cortex. *J Neurophysiol*. 1944; 7:359-390.
8. Becker WJ. Acute migraine treatment. *Continuum (Minneap Minn)*. 2015; 21(4 Headache):953-972.
9. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review)—report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55(06):754-762.
10. Shapiro RE. Preventive treatment of migraine. *Headache* 2012; 52(suppl 2):65-69.
11. Pascual J, Caminero AB, Mateos V, et al. Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; 44(10):1024-1028.
12. Lampl C, Katsarava Z, Diener HC, Limmroth V. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry*. 2005; 76(12):1730-1732.

"My Vision Fades Out" 2

Cristiano Oliveira MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

The patient had transient vision loss in the left eye due to embolus related to ophthalmic artery covered by pipeline embolization device (PED) in the after change from dual antiplatelet therapy to monotherapy with low-dose aspirin.

Teaching Points

Transient monocular vision loss is an alarming symptom that requires prompt assessment, given that patients could eventually have permanent vision loss and potentially other devastating neurological deficits, depending on the underlying cause. Careful and thorough evaluation, including the review of the patient's past medical history, can guide the workup and final diagnosis.

In the present case, the patient underwent workup that included the contrast-enhanced MRI brain and MRA head/neck, the latter with no evidence of stenosis or atherosclerotic disease. The vision loss in her case was related to the prior history of stent flow diversion embolization of the left ICA aneurysm and the recent preceding change in antiplatelet regimen.

According to the neurosurgical literature, the main focus seems to be on making sure there is good collateral circulation with the external carotid in case of ophthalmic artery occlusion by PED placed in ICA segment spanning the ophthalmic artery, during or immediately after the procedure. Unfortunately, there is less consideration and discussion about the potential for embolic events from emboli generated by turbulent flow through and around the ophthalmic artery. The use of dual antiplatelet therapy is maintained typically for 6 months and then switched to monotherapy with low-dose aspirin. After that switch, some patients, as in the present case, may be more prone to thromboembolic events involving the ophthalmic artery.

Selected Readings

1. Rouchaud A, Leclerc O, Benayoun Y, et al. Visual outcomes with flow-diverter stents covering the ophthalmic artery for treatment of internal carotid artery aneurysms. *AJNR Am J Neuroradiol*. 2015; 36(2):330-336.
2. Heller RS, Lawlor CM, Hedges TR 3rd, Bababekov YJ, Safain MG, Malek AM. Neuro-ophthalmic effects of stenting across the ophthalmic artery origin in the treatment of intracranial aneurysms. *J Neurosurg*. 2014; 121(1):18-23.
3. Park H, Nakagawa I, Yokoyama S, et al. Central retinal artery thromboembolism without ophthalmic artery occlusion during stent-assisted coil embolization of ophthalmic artery aneurysm. *World Neurosurg*. 2019; 121:77-82.

4. Griessenauer CJ, Ogilvy CS, Foreman PM, et al. Pipeline embolization device for small paraophthalmic artery aneurysms with an emphasis on the anatomical relationship of ophthalmic artery origin and aneurysm. *J Neurosurg*. 2016; 125(6):1352-1359.

5. Becske T, Brinjikji W, Potts MB, et al. Long-term clinical and angiographic outcomes following pipeline embolization device treatment of complex internal carotid artery aneurysms: five-year results of the pipeline for uncoilable or failed aneurysms trial. *Neurosurgery* 2017; 80(1):40-48.

"I Need More Light to See" 1

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DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Paraneoplastic optic neuropathy with ataxia and other multifocal neurologic symptoms associated with antibodies to CRMP-5/CV-2 and $GABA_BR$

Teaching Points

A number of paraneoplastic syndromes involve neuro-ophthalmic manifestations, and they can present with variable afferent and/or efferent visual dysfunction as well as a host of other neurologic symptoms.[1] These disorders may manifest as a result of immune response to tumor-related antigens—cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), cancer-associated cone dysfunction (CACD), paraneoplastic vitelliform maculopathy (PVM), and paraneoplastic optic neuritis (PON)—or from effects of ectopic peptide production due to tumor-expressed growth factors—bilateral diffuse uveal melanocytic proliferation (BDUMP) and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome (POEMS).[2] Because paraneoplastic symptoms can be very heterogeneous, they can be challenging to diagnose, but given that they often precede recognition of underlying cancer, it is important to maintain them in the differential.[3]

Paraneoplastic optic neuropathy specifically has been described in the setting of a number of different cancers but is primarily associated with small cell carcinoma of the lung and thymoma.[4] Classically, it presents in a middle or older age patients with subacute simultaneous or sequential bilateral visual impairment that progresses over a number of weeks. Visual symptoms may range from decreased to no light perception with or without positive visual phenomena. The majority of patients demonstrate optic disc edema. Vitreous cells, retinal hemorrhages, and retinitis have also been commonly reported. Neuroimaging may or may not demonstrate abnormal findings, and abnormal findings may also be nonspecific.[5,6] In many cases paraneoplastic optic neuropathy is painless. However, the patient described above did have pain, and painful axonal asymmetric polyradiculoneuropathy is a recognized feature in many cases of anti-CRMP-5/CV-2 associated disease; this has been noted to help distinguish this entity from other paraneoplastic neuropathies.[7] The pain, however, is usually in a polyradicular distribution as it was for this patient (ie, it is not the classic pain with eye movements of typical optic neuritis).

The CRMP-5/CV-2 protein, described in a 2001 report from the Mayo Clinic, is found in both small-cell lung carcinomas and adult central and peripheral neurons, including synapses. Immunoglobulin G (IgG) antibodies to this protein were present in 0.018% of ~68,000 patients screened for paraneoplastic disease at Mayo over a 17-year period, making the frequency of its occurrence similar to that of the more widely recognized PCA-1 (anti-Yo) antibody. In their cohort of patients with anti-CRMP-5/CV-2 antibodies, the Mayo researchers noted high frequencies of cranial neuropathy (17%, including 7% optic neuropathy) and chorea (11%), but they also very commonly found patients to have neuromuscular junction disorders (12%), subacute dementia (25%), cerebellar ataxia (26%), autonomic neuropathy (31%), and peripheral neuropathy (47%). Nearly all of the patients with the IgG were smokers, and the vast majority had lung cancer (77%,) although 6% had thymoma. In addition to presence in serum, the CRMP-5/CV-2 antibody was also found in equal or higher titers in the cerebrospinal fluid of 37% of patients, and the CSF was inflammatory in 86% of patients, demonstrating a lymphocytic pleocytosis, elevated protein, or elevated IgG index or synthesis rate.[8]

While CRMP-5/CV-2 IgG is not present in healthy subjects, it is found in up to 10% of patients with small cell lung cancer in the absence of a paraneoplastic syndrome, albeit usually at a lower titer.[9,10] Interestingly, like the patient described above, most paraneoplastic optic neuropathy patients are found to have additional paraneoplastic autoantibodies, and this perhaps contributes to the variability and overlapping of presentations.[11] The additional antibody present in this patient, anti-$GABA_BR$, has been associated with limbic encephalitis with rapidly progressive dementia and seizures.

The mainstay of treatment for paraneoplastic optic neuropathy is to address the underlying cancer. Additional therapy, including immunosuppression and plasma exchange, may also be used.[12] Only half of CRMP-5/CV-2 IgG patients in a 2020 retrospective cases series demonstrated improvement in visual function following immunosuppressive treatment, however.[6] Patients with CRMP-5/CV-2 IgG have been reported to have a 5-year survival rate of approximately 67%.[7]

References

1. Ko MW, Dalmau J, Galetta SL. Neuro-ophthalmic manifestations of paraneoplastic syndromes. *J Neuro-Ophthalmol*. 2008; 28:58-68.

2. Przeździecka-Dołyk J, Brzecka A, Ejma M, et al. Ocular paraneoplastic syndromes. *Biomedicines* 2020; 8(11):490.

3. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc*. 2011; 86(4):364.

4. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP—5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol*. 2001; 49:146-154.

5. Gordon L, Dinkin, M. Paraneoplastic syndromes in neuro-ophthalmology. *Continuum (Minneap, Minn)*. 2019; 25(5):1401-1421.

6. Cohen DA, Bhatti MT, Pulido JS. Collapsin response-mediator protein 5e associated retinitis, vitritis, and optic disc edema. *Ophthalmology* 2020; 127:221-229.

7. Dubey D, Lennon VA, Gadoth A, et al. Autoimmune CRMP5 neuropathy phenotype and outcome defined from 105 cases. *Neurology* 2018; 90(2):e103-e110.

8. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol*. 2001; 49(2):146-154.

9. Galanis E, Frytak S, Rowland KM, et al. Neuronal autoantibody titers in the course of small cell lung carcinoma and platinum associated neuropathy. *Cancer Immunol*. 1999; 48:85-90.

10. Bataller L, Wade DF, Graus F, et al. Antibodies to Zic4 in paraneoplastic neurologic disorders and small-cell lung cancer. *Neurology* 2004; 62:778-782.

11. Cross SA, Salomao DR, Parisi JE, et al. Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. *Ann Neurol*. 2003; 54(1):38-50.

12. Durrani A, Shah RJ, Kim SJ. Successful long-term treatment of paraneoplastic optic neuropathy with mycophenolate mofetil, prednisone, and plasmapheresis. *Am J Ophthalmol Case Rep*. 2017; 8:31-34.

"I Need More Light to See" 2

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DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Vitamin B12 deficiency–induced mitochondrial optic neuropathy

Teaching Points

Toxic and/or nutritional optic neuropathy is an acquired optic neuropathy that causes a symmetric decrease in vision, color vision, and central or ceco-central visual field loss, often detected better on HVF 10-2 rather than 24-2 SITA Standard testing. Most patients with this condition do not have a relative afferent pupillary defect because of the symmetry of the optic neuropathy (hence, "relative" afferent pupillary defect). However, most do have some degree of red hue desaturation, which can be picked up in a clinical exam by an astute provider presenting a red target to the patient in each area of the field as well as centrally, and asking whether the target is "bright red or some other shade, such as pink, brown, or orange." After months of deficiency, OCT eventually shows retinal nerve fiber papillomacular bundle atrophy, as well as ganglion cell layer atrophy.

Pathophysiology is not entirely understood and likely varied, but the proposed common pathway of toxic and nutritional optic neuropathy is mitochondrial injury from intra- and extracellular free radical damage. Vitamin B12 (cobalamin) is the most common culprit, although folate and copper deficiencies also cause mitochondrial injury.[2] The term "tobacco-alcohol amblyopia" has been previously used but is largely a misnomer and no longer preferred. This disease is an acquired optic neuropathy, not amblyopia, and there is no proof that tobacco and alcohol together have a synergistic deleterious effect.[3] Alcohol overconsumption can lead to lack of nutrient intake as well as poor gut absorption of B12. Tobacco abuse, especially that involving pipe or cigar smoking, is an etiology that should be considered a diagnosis of exclusion.

Serum vitamin B12 levels directly measure circulating but not tissue concentrations. Low serum B12 is suggestive but not always adequate to monitor B12 status.[4] Lab workup for nutritional optic neuropathy also involves testing for the following components: serum methylmalonic acid, which increases in vitamin B12 deficiency; plasma total homocysteine levels, which increases in both vitamin B12 and folate deficiencies[5,6]; complete blood count (CBC) with smear analysis to rule out anemia, macrocytosis, and neutrophil hypersegmentation; levels of intrinsic factor and parietal cell antibodies to evaluate for pernicious anemia; and red blood cell folate level, which is a more reliable tissue storage indicator than serum folate level.[2] Serum and urinary copper levels may also be quantified, as well as that of other B vitamins (niacin, riboflavin, pyridoxine, and thiamine). MRI of the orbits/brain with/without contrast is recommended to evaluate for intracranial mass that can cause progressive bilateral optic nerve atrophy and vision loss. Genetic testing for dominant optic atrophy and even Leber hereditary optic neuropathy, which in rare cases can also present similarly, should be considered. An occult maculopathy might also be suspected in the presence of bilateral central vision loss, which may require high-resolution OCT of the macula, fundus autofluorescence, intravenous fluorescence angiography, and/or multifocal electroretinogram where appropriate. Finally, one should consider functional visual loss in the presence of a completely normal eye exam and testing.

Nutritional optic neuropathy is found more commonly in times of war or famine. It has been the subject of major public health crises such as the Cuban epidemic of optic neuropathy, which affected 51,000 people in Cuba in the 1990s and arose from a combination of nutritional deficiencies plus wide consumption of bootleg alcohol containing small amounts of methanol.[7,8] In the mainstream medical community, it can be difficult to detect and may lead to awkward conversations in clinic; in particular with patients who do not have a history of diagnosed alcoholism and who appear to be functioning above average versus their peers. Treatment involves smoking and alcohol cessation and intramuscular and oral vitamin B12 supplementation. After diagnosis, it is advantageous to involve the primary care doctor, nutritionist, and when appropriate, psychologist, as treatment of nutritional optic neuropathy can require major lifestyle changes. Therefore, it is crucial that the ophthalmologist takes care to give the patient time and space to process such a diagnosis, as well as involving other members of the care team in its treatment. Many patients regain some or all of their visual function with treatment, but the anatomic changes of optic nerve pallor and OCT atrophy persist.

References

1. Erdogan E, Nelson GJ, Rockwood AL, Frank EL. Evaluation of reference intervals for methylmalonic acid in plasma/serum and urine. *Clin Chim Acta*. 2010; 411:1827-1829.

2. Margolin E, Shemesh A. Toxic and nutritional optic neuropathy [updated 2020 Jul 5]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. Available from: https://www-ncbi-nlm-nih-gov.liboff.ohsu.edu/books/NBK499979/

3. Grzybowski A, Zülsdorff M, Wilhelm H, Tonagel F. Toxic optic neuropathies: an updated review. *Acta Ophthalmol*. 2015; 93(5):402-410.

4. Grzybowski A. Low serum vit. B12 level does not mean vit. B12 deficiency: problems related to the diagnosis of vitamin B12 deficiency. *Curr Eye Res*. 2014; 39(4):425-426.

5. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Diagnosis of cobalamin deficiency I: usefulness of serum methylmalonic acid and total homocysteine concentrations. *Am J Hematol*. 1990; 34(2):90-98.

6. Bailey RL, Carmel R, Green R, et al. Monitoring of vitamin B-12 nutritional status in the United States by using plasma methylmalonic acid and serum vitamin B-12. *Am J Clin Nutr*. 2011; 94(2):552-561.

7. Sadun A. Acquired mitochondrial impairment as a cause of optic nerve disease. *Trans Am Ophthalmol Soc*. 1998; 96:881-923.

8. González-Quevedo A, Santiesteban-Freixas R, Eells JT, Lima L, Sadun AA. Cuban epidemic neuropathy: insights into the toxic-nutritional hypothesis through international collaboration. *MEDICC Rev*. 2018; 20(2):27-31.

9. Jefferis JM, Hickman SJ. Treatment and outcomes in nutritional optic neuropathy. *Curr Treat Options Neurol*. 2019; 21(1):5.

10. Türkyılmaz K, Öner V, Türkyılmaz AK, Kırbaş A, Kırbaş S, Şekeryapan B. Evaluation of peripapillary retinal nerve fiber layer thickness in patients with vitamin B12 deficiency using spectral domain optical coherence tomography. *Curr Eye Res*. 2013; 38(6):680-684.

Section IV: What a Pain? Headache and Eye Pain

"My Eye Hurts" 1

Julie Falardeau MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Perineural tumor spread from aggressive basal cell carcinoma

Teaching Points

Head and neck cancer can spread by direct extension or by hematogenous or lymphatic routes. An additional means of spread is extension of tumor along nerves, a phenomenon called perineural tumor spread (PNTS). Cutaneous cancers such as squamous cell carcinoma , basal cell carcinoma, or melanoma are commonly associated with PNTS. Mucosal squamous cell carcinoma, salivary gland carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma can also lead to PNTS.

In general, perineural spread in skin cancer is through the fifth or seventh cranial nerve. The initial ophthalmic symptoms of PNTS typically involve pain and numbness in and around the eye and also affecting the face (focal area in the early stage). When this involves the first division of the trigeminal nerve, corneal sensation is disrupted. Complete loss of corneal sensation often leads to neurotrophic changes including surface problems, punctate keratopathy, and potentially corneal opacity resulting in loss of vision. Cavernous sinus involvement is common with PNTS and is often heralded by other cranial nerve palsies, including involvement of the third, fourth, or sixth cranial nerves. Pupillary involvement may occur secondary to third nerve palsy, producing mydriasis, or due to sympathetic nerve involvement in the cavernous sinus, producing miosis (Horner syndrome).

When the seventh nerve is affected by perineural spread, decreased blink frequency often leads to surface problems. The combination of a fifth and seventh nerve palsy is particularly severe, often resulting in corneal epithelial breakdown followed by possible infection or even corneal melt.

Much less commonly, decreased vision may be due to involvement in the orbital apex resulting in optic nerve pathology. This can be separated from surface abnormalities by the presence of an afferent pupillary defect and visual field defect (central scotomas or arcuate visual field changes).

MRI is the most sensitive imaging method for the detection of perineural tumor spread (PNTS), and contrast-enhanced orbit protocol should be included when cavernous sinus involvement is suspected. PNTS can be subtle on imaging, and it usually requires careful evaluation over multiple sequences. The findings are frequently missed, especially when the MRI is reviewed by radiologists with inadequate neuroradiology training. Consequently, the diagnosis of PNTS is often delayed until the patient develops additional manifestations.

Radiation therapy is typically recommended for PNTS.

Key Points

- Pain + numbness = Red flag
- MRI orbits with and without contrast is the study of choice when cavernous sinus pathology is suspected.
- If you suspect perineural spread and MRI is reported as normal, do not hesitate to call the radiologist and ask to take a closer look at the impaired cranial nerve(s).

Selected Readings

1. Ableman TB, Newman SA. Perineural spread of head and neck cancer: ophthalmic considerations. *J Neurol Surg B Skull Base*. 2016; 77(2):131-139.
2. Bakst RL, Glastonbury CM, Parvathaneni U, et al. Perineural invasion and perineural tumor spread in head and neck cancer. *Int J Radiation Oncol Biol Phys*. 2019; 103(5):1109-1124.
3. Panizza B, Warren T. Perineural invasion of head and neck skin cancer: diagnosis and therapeutic implications. *Curr Oncol Rep*. 2013; 15(2):128-133.

"My Eye Hurts" 2

Andrew R Carey MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Direct cavernous carotid fistula (CCF)

Teaching Points

The differential for pain and swelling of the postseptal orbital tissues includes infectious, inflammatory, neoplastic, and vascular etiologies.

Thyroid eye disease (TED), also called Graves ophthalmopathy, is the most common cause of orbital inflammation as well as the most common cause of both unilateral and bilateral proptosis. Thyroid-stimulating antibodies and thyroperoxidase antibodies have extremely high sensitivity for TED. However, TED should not cause thickening of the extraocular muscle tendons as seen in our patient.

Nonspecific orbital inflammation (NSOI) is less common than TED and can lead to thickening of the tendons. While typically idiopathic, NSOI this can be related to underlying

autoimmune conditions such as ANCA-associated vasculitides, sarcoid, and lupus. NSOI is typically rapidly responsive to steroids and should not cause engorgement of the superior ophthalmic vein as seen in our patient.

Infiltrative disease such as lymphoproliferative lesions and histiocytic disease can likewise cause enlargement of the extraocular muscle bellies and tendons and should also not result in engorgement of the superior ophthalmic vein as seen in our patient.

The presence of enlarged superior ophthalmic vein is a crucial finding on neuroimaging and may require review with neuro-ophthalmology and/or neuroradiology. Computed tomography (CT) and MRI scan as well as CT angiography and magnetic resonance angiography have similar sensitivity for CCF. Orbital ultrasound may also be helpful in identifying dilated superior ophthalmic vein, and color Doppler may show retrograde flow within the vein. Gold standard for diagnosis is conventional angiogram, sometimes referred to as "digital subtraction angiography."

There are 2 types of cavernous fistulas: low flow, which are often indirect from dural feeders, and high flow, which are often direct fistulas with the carotid artery. High-flow fistulas typically result from trauma and have rapid onset and progression with more severe presentations. While low-flow fistulas may resolve spontaneously, high-flow fistulas typically require embolization to prevent progressive vision loss, which typically results from glaucoma and less commonly central retinal vein occlusion or ischemic optic neuropathy, in addition to the morbidity from pain, proptosis, and diplopia.

Selected Readings

1. Henderson AD, Miller NR. Carotid-cavernous fistula: current concepts in aetiology, investigation, and management. *Eye (Lond)*. 2018; 32(2):164-172.
2. Guédon A, Saint-Maurice JP, Thépenier C, et al. Results of transvenous embolization of intracranial dural arteriovenous fistula: a consecutive series of 136 patients with 142 fistulas. *J Neurosurg*. Epub ahead of print 2021 May 28:1-9. doi: 10.3171/2020.10.JNS203604.
3. Jozef Č. Carotid-cavernous fistula from the perspective of an ophthalmologist: a review [English]. *Cesk Slov Oftalmol*. Epub ahead of print 2020; 1:1-8. doi: 10.31348/2020/8.
4. Tseng GW, Kuo TY, Yen PS, Tsai CH, Lu MK. Sonographic clue in non-traumatic carotid-cavernous fistula: report of a case and literature review. *Acta Neurol Taiwan*. 2020; 29(1):18-23.
5. Nishimuta Y, Awa R, Sugata S, et al. Long-term outcome after endovascular treatment of cavernous sinus dural arteriovenous fistula and a literature review. *Acta Neurochir (Wien)*. 2017; 159(11):2113-2122.

"The Light Hurts My Eye"

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Presented by Michael S Lee MD

DIAGNOSIS & TEACHING POINTS

Teaching Points

In this situation, photophobia is a *symptom*, not a diagnosis!! There is a protocol to follow to come up with the diagnosis. First, take a careful history. The head injury is an important clue, and even mild head trauma can set up chronic migraine. In the history, remember to be sure to "SNOOP" to identify a more sinister cause to the photophobia since there are so many possible causes!

The "SNOOP" pneumonic[1] can keep you out of hidden dangers:

S = Systemic symptoms (eg, fever, weight loss); systemic illness (cancer, immunocompromised)

N = Neurologic symptoms or signs

O = Onset fast (less than 1 minute)

O = Older (over 50)

P = Previous headache history/progressive headache; postural (worse upright); precipitated by exertion or Valsalva; pulsatile tinnitus, visual obscurations (pseudo-tumor symptoms); pregnancy

On examination, your job is to look for several contributors.

First, start with a complete eye examination. For some of the key areas on your examination, it's important to be careful that the examination is indeed normal. Pay attention to visual fields to be sure there is no bitemporal hemianopia—pituitary tumors may present with photophobia!

Next perform a careful slit-lamp examination. Here the ophthalmologist will feel at home to diagnose the common causes of photophobia like iritis, uveitis, blepharitis, dry eye, and so forth. Sometimes the examination is "normal"; however, if the symptom is photophobia, stain the cornea, and add a drop of anesthetic. If the pain goes away with the anesthetic, it could be related to corneal neuropathy or dry eye. But it could also be migraine (similar to doing an occipital nerve block to disrupt the trigeminal nerve arc). To rule out dry eye you really need to do a Schirmer's with the anesthetic—since we can at least treat this disorder!

The examination should exclude any retinal disorder since retinitis pigmentosa and cone dystrophies can have photophobia. Always look for frequent blinking since the majority of patients with blepharospasm have significant photophobia, and this also can be treated! Remember there is "reflexive" blepharospasm—some individuals have continuous blinking, but some have significant blinking *only* induced by light, and then they have trouble stopping the blinking. This distinction has confused and eluded many savvy ophthalmologists and can be missed.

Finally, if all of this is normal, then consider migraine causing the photophobia. There are many clues to migraine. If the patient has 2 of the following 3—photophobia, a disabling headache, and nausea—in the majority of cases, the patient has

migraine.[2] It is important for ophthalmologists to understand what could make migraine more chronic and thereby increase photophobia to near daily! There are nonmodifiable factors like female sex and low educational status. Having a mild or moderate head injury is also not modifiable and is likely to play a large role in this case. Other factors to consider are frequent headache, overuse of medication, acute therapy that doesn't work, obesity, snoring, depression, and stressful life events, any of which will increase the risk of chronic migraine. About 90% of individuals with traumatic brain images will have photophobia—and for some it may be chronic.

As for the diagnosis of our patient: she has a normal eye examination and normal neurological examination. She has progressed to chronic migraine due to mild head trauma. She can be treated for migraine. Most ophthalmologists may not wish to treat migraine, so partner with either a headache specialist or with a neurologist who understands migraine. There are things, though, that an ophthalmologist could suggest, including basics like the importance of regular diet, frequent exercise, and adequate sleep. The use of FL41-tinted lenses has been found to be helpful to many individuals with migraine- and blepharospasm-associated photophobia. The other thing all ophthalmologists need to know is that when individuals have chronic photophobia, depression and anxiety are often present as well.

References and Selected Readings

1. Dodick DW. Pearls: headache. *Semin Neurol*. 2010; 30(1):74-81.
2. Lipton RB, Dodick D, Sadovsky R, et al; ID Migraine validation study. A self-administered screener for migraine in primary care: The ID Migraine Validation Study. *Neurology* 2003; 61(3):375-382.
3. Albilali A, Dilli E. Photophobia: when light hurts, a review. *Curr Neurol Neurosci Rep*. 2018; 18(9):62.
4. Burstein R, Noseda R, Fulton AB. Neurobiology of photophobia. *J Neuroophthalmol*. 2019; 39(1):94-102.
5. Diel RJ, Mehra D, Kardon R, Buse DC, Moulton E, Galor A. Photophobia: shared pathophysiology underlying dry eye disease, migraine and traumatic brain injury leading to central neuroplasticity of the trigeminothalamic pathway. *Br J Ophthalmol*. 2021; 105(6):751-760.
6. Katz BJ, Digre KB. Diagnosis, pathophysiology, and treatment of photophobia. *Surv Ophthalmol*. 2016; 61(4):466-477.
7. Noseda R, Copenhagen D, Burstein R. Current understanding of photophobia, visual networks and headaches. *Cephalalgia* 2019; 39(13):1623-1634.

"It Hurts When I Look Around" 1

Kimberly K Gokoffski MD and Lilangi Ediriwickrema MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Probable IgG4-related ophthalmic disease (IgG4-ROD)

Teaching Points

- Involvement of cranial nerves 2-6 must always raise the suspicion for an orbital apex syndrome.
- Given the chronicity of the patient's presentation, the differential was more suspicious for an inflammatory or low-flow vascular condition over that of an infiltrative, metastatic, infectious, or hemorrhagic etiology.
- The differential for orbital inflammation includes a host of diseases, including sarcoidosis, Sjögren disease, lymphoma, thyroid eye disease, granulomatosis with polyangiitis, Erdheim Chester disease, idiopathic orbital inflammation, IgG4-related disease, and sclerosing orbital inflammation.
- Histopathologically, IgG4-related disease can reveal a dense lymphoplastic infiltrate, focally storiform fibrosis, and/or obliterative phlebitis. The pathologic diagnosis of IgG4-related disease is made when 2 of these 3 major pathological features are present. Supporting findings include nonobliterative phlebitis and eosinophilia. Immunohistochemical analysis typically reveals more than 10 IgG4-positive plasma cells per high power field, and the ratio of IgG4-positive plasma cells to IgG-positive plasma cells should be greater than 40%. Lacrimal disease requires a higher proportion of positive cells per high power field.
- The clinical diagnosis of definite IgG4-related disease is dependent on findings of diffuse or localized swelling or mass lesions, elevated serum IgG4 concentrations, and histopathologic findings. Probable IgG4-RD is present when clinical and pathological findings exist, whereas possible IgG4-RD is present with clinical and hematological findings exist.[1]
- Ophthalmic and orbital IgG4-ROD diagnostic criteria have been modified to include imaging findings (masses, enlargement, hypertrophic lesions), histopathologic findings (germinal center involvement, lymphocytic and plasmacytic infiltration, and ratio of IgG4+ cells to IgG+ cells > 40%, and more than 50 IgG4+ cells per HPF), and serological abnormalities (serum IgG4 > 134 mg/dl).[2] Definite IgG4-ROD requires all 3 findings, probable disease is dependent on radiographic and histopathologic findings, and possible disease is dependent on radiographic and serologic findings.
- Primary treatment consists of corticosteroids followed by disease-modifying therapies such as rituximab, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, mizoribine, and anti-TNFa inhibitors. Rituximab has been shown to have the highest response rate (93%) with low relapse rate (9%). Rarely, radiotherapy can be considered.

References and Selected Readings

1. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol*. 2012; 22:21-30.
2. Goto H, Takahira M, Azumi A; Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol*. 2015; 59(1):1-7.
3. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012; 366:539-551.
4. Toyoda K, Oba H, Kutomi K, et al. MR imaging of IgG4-related disease in the head and neck and brain. *AJNR Am J Neuroradiol*. 2012; 33(11):2136-2139.
5. McNab AA, McKelvie P. IgG4-related ophthalmic disease: Part I. Background and pathology. *Ophthalmic Plast Reconstr Surg*. 2015;31(2):83-88.
6. McNab A, McKelvie P. IgG4-related ophthalmic disease: Part II. Clinical aspects. *Ophthalmic Plast Reconstr Surg*. 2015; 31(3):167-178.
7. Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, Salomao DR. Orbital inflammation with IgG4-positive plasma cells, manifestation of IgG4 systemic disease. *Arch Ophthalmol*. 2011; 129:421-428.
8. Andrew N, Kearney D, Selva D. IgG4-related orbital disease: a meta-analysis and review. *Acta Ophthalmol*. 2013; 91(8):694-700.
9. Wu A, Andrew NH, McNab AA, et al. IgG4-related ophthalmic disease: pooling of published cases and literature review. *Curr Allergy Asthma Rep*. 2015; 15:530.
10. Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol*. 2011; 23(1):67-71.

"It Hurts When I Look Around" 2

Amanda D Henderson MD

DIAGNOSIS & TEACHING POINTS

Final Diagnosis

Myelin oligodendrocyte glycoprotein (MOG)-IgG associated bilateral optic neuritis (ON)

Teaching Points

Myelin oligodendrocyte glycoprotein antibody–associated disorder (MOGAD), which commonly presents with ON, is an entity distinct from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). Like MS-associated ON, MOGAD-associated ON usually presents with painful extraocular movements,[1] which may occur prior to the onset of vision loss. ON secondary to MOGAD may also be associated with a prodromal migraine-like headache (ie, unilateral, associated with photophobia, nausea).[2] MOGAD-associated ON often presents with optic disc swelling, and simultaneous, bilateral involvement is common.[1,3,4] In MOGAD, coexisting nerve and perineural enhancement is common, although perineural enhancement can be seen in isolation.[1,4,5] Nerve enhancement usually is longitudinally extensive, involving the retrobulbar segment of the optic nerve.[1,3] It is crucial to discriminate between MS, seropositive NMOSD, and MOGAD, as prognosis and treatment differ for these diseases.

MOGAD predicts a higher risk of relapse than seropositive NMOSD or MS, though some patients will never have a second episode.[6,7] Because some cases of MOGAD behave phenotypically like chronic relapsing inflammatory optic neuropathy (CRION), with relapse of the ON as steroids are withdrawn, a slow oral steroid taper following the acute high-dose treatment has been recommended.[8] Prophylactic long-term immunosuppressive treatment may be considered in MOGAD, specifically in the setting of poor visual recovery from an episode of ON.[8]

References

1. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin oligodendrocyte glycoprotein antibody-positive optic neuritis: clinical characteristics, radiologic clues, and outcome. *Am J Ophthalmol*. 2018; 195:8-15.
2. Asseyer S, Hamblin J, Messina S, et al. Prodromal headache in MOG-antibody positive optic neuritis. *Mult Scler Relat Disord*. 2020; 40:101965.
3. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler*. 2016; 22(4):470-482.
4. Akaishi T, Sato DK, Nakashima I, et al. MRI and retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: a comparative study. *J Neurol Neurosurg Psychiatry*. 2016; 87(4):446-448.
5. Lopez-Chiriboga AS, Van Stavern G, Flanagan EP, et al. Myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-positive optic perineuritis. *Neuroophthalmology* 2019; 1-4.
6. Jitprapaikulsan J, Chen JJ, Flanagan EP, et al. Aquaporin-4 and myelin oligodendrocyte glycoprotein autoantibody status predict outcome of recurrent optic neuritis. *Ophthalmology* 2018; 125(10):1628-1637.
7. Pache F, Zimmermann H, Mikolajczak J, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: Afferent visual system damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients. *J Neuroinflamm*. 2016; 13(1).
8. Chen JJ, Bhatti MT. Clinical phenotype, radiological features, and treatment of myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG) optic neuritis. *Curr Opin Neurol*. 2020; 33(1):47-54.

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