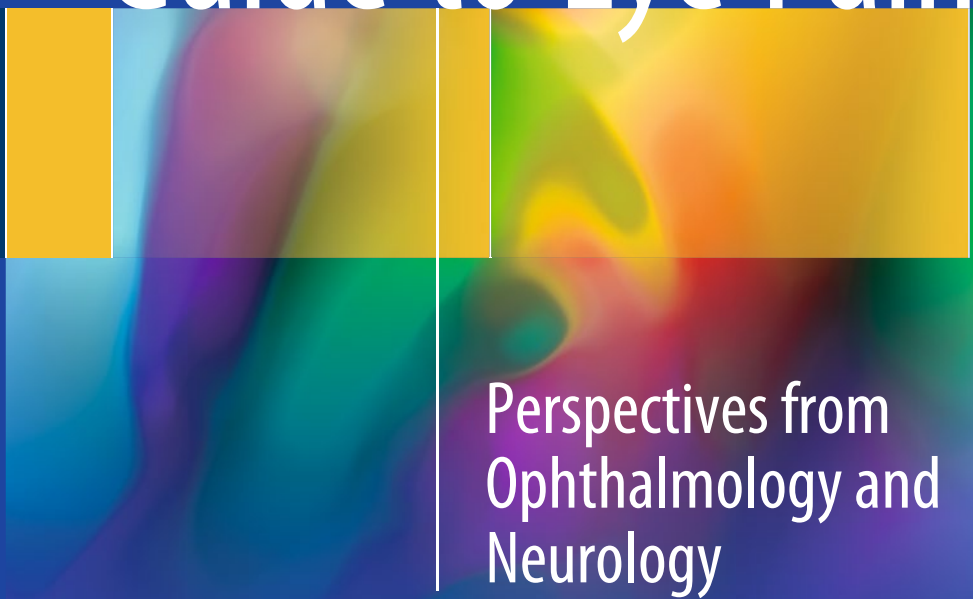
Michael S. Lee · Kathleen B. Digre

A Case-Based Guide to Eye Pain



Perspectives from Ophthalmology and Neurology

Springer

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Michael S. Lee
University of Minnesota
Minneapolis, Minnesota
USA

Kathleen B. Digre
University of Utah
Salt Lake City, Utah
USA

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Foreword

"I have pain in (or around or behind) my eye." This sentence is one that most physicians, be they ophthalmologists, optometrists, neurologists, or primary care providers, dread to hear. In large part, this is because pain is such a subjective complaint. Thus, the first assumption that most physicians make when they see a patient with the complaint of "eye pain" is that they will not find the cause of the pain. This, in turn, will make them believe that it is most likely that (1) there is nothing really wrong with the patient, (2) the patient will be unhappy with them, and (3) the patient will want some type of drug for the pain.

In reality, pain is a complex symptom with many etiologies. On the one hand, its cause may be something straightforward, like a dry eye, and its treatment may be as simple as ocular lubrication or punctal occlusion. On the other hand, patients with eye pain may have a potentially vision-threatening condition such as intermittent angle-closure glaucoma or even a life-threatening condition such as an intracranial aneurysm or tumor. The ophthalmologist who finds no ocular cause for the patient's complaints is sure to be perplexed as will the neurologist who finds no neurologic cause and who obtains neuroimaging that is unremarkable. The primary care provider may not even know to whom to refer the patient or what to do when the patient returns from the general ophthalmologist and/or neurologist with no diagnosis. Even neuro-ophthalmologists are not immune to the confusion that comes in dealing with patients who have eye pain. *A Case-Based Guide to Eye Pain—Perspectives from Ophthalmology and Neurology,* written by two neuro-ophthalmologists, Dr. Mike S. Lee, an ophthalmologist, and Dr. Kathleen B. Digre, a neurologist, thus is a welcome addition to everyone's practice, particularly as it is, as the title indicates, case based—like a conversation with a colleague.

The book begins with a chapter on key signs and symptoms, emphasizing their importance in diagnosis. There follows a list of the various abbreviations used in the book. The subsequent cases, all of which contain excellent figures and illustrations, are then grouped into two main sections. The first section contains 18 cases demonstrating ocular causes of pain, ten with relatively normal examination findings and eight in which there are abnormal but often subtle findings. The second section contains 25 cases demonstrating neurologic causes of eye pain, 15 in patients with

little or no neurologic or eye findings and ten with abnormal findings. All 43 cases begin with the history and examination, followed by commentary by both Dr. Lee and Dr. Digre. Thus, the reader gets the views of both an ophthalmologist and a neurologist. Each case ends with a summary, key points, and references for the reader who wishes to pursue the topic further. The book ends with four appendices. Appendix 1 lists the tables in the book. Appendix 2 lists the figures in the book. Appendix 3 discusses how to obtain a proper history and perform an appropriate examination in a patient with eye pain, and Appendix 4 discusses the pathophysiology of eye pain.

Although eye pain is frustrating for patients and can be frustrating for the physicians who care for such patients, the diagnosis and treatment of its cause can not only improve a patient's quality of life but also can prevent major ocular or neurologic morbidity. This book fills a void in the ophthalmic, neurologic, and general medical literature and should be on the shelf in every physician's office.

Neil R. Miller, M.D., F.A.C.S.

Preface

Most of us have a "Do not schedule this with me" diagnosis list, and many of our colleagues have told us that "eye pain" resides near the top of that list. Unfortunately, there is not a good department for these patients, and there are a lot of them showing up in our offices and clinics. In our neurology and ophthalmology residencies and fellowships, we never received formal teaching or training in eye pain and, honestly, had to learn a lot by trial and error (and by fire). So when a Springer editor approached us in the fall of 2015 about writing a book about the subject, it intrigued us.

She told us that no book on eye pain existed and that readers enjoy case-based books. So, we set out to demystify the topic and create a practical approach to the patient with eye pain. At first, we thought to target neurologists and ophthalmologists, but, as we inquired around, our colleagues in the emergency room and urgency room and primary care asked if they could read some of the chapters as well.

There are 43 cases but more than 43 causes of eye pain. We use each case as a springboard to generate a differential diagnosis and a thought process based on the signs and symptoms. Some of the cases are not classic, but most of our patients don't always follow the book.

We have tried to give the International Classification of Headache Disorders whenever possible. For a complete listing of these disorders please see: International Headache Society Headache classification ICHD 3 beta. Cephalalgia 2013; 33(9):629–808.

We sincerely hope that you will enjoy this book and, after reading it, feel more comfortable serving our patients with eye pain.

Minneapolis, MN — Michael S. Lee
Salt Lake City, UT — Kathleen B. Digre

Acknowledgements

I would like to thank my loving wife, Mina, and my children, Sam, Nate, Isaac, and Esthergrace, who mean the world to me. Your faith and your support make all the difference and you are truly a gift and a blessing from above. Thanks to Yong and Soo Lee and Hyung and Kilja Kim for your loving support and sacrifice. I would also like to thank Nicholas Volpe, Simmons Lessell, Joe Rizzo, Mike Siatkowski, and Andy Lee who have mentored me along in my career. Greg Kosmorsky has taught me a lot about eye pain and about life in general. Finally, I would like to thank my coauthor, Kathleen, who has made writing my first book an extremely positive experience. It has been a pleasure working with you.

Michael S. Lee, MD

I would like to thank people who have really taught me about eye pain and headache. My mentor, James Corbett, instilled in me an enthusiasm for the study of the eye and headache. I have also learned a lot about eye pain and headache from my wonderful colleagues Susan Baggaley, Judith Warner, Bradley Katz, and Alison Crum at the Moran Eye Center, University of Utah. Finally, I would like to thank my wonderful supportive husband, Michael Varner, and children Johanna and Gita Varner for their encouragement. Thanks to you Mike for a wonderful, educational experience writing this book—it has been fun.

Kathleen B. Digre, MD

We both would like to thank our patients who teach us about eye pain in all of its varied forms and keep us wanting to learn more.

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Signs and Symptoms

Case	Diagnosis	VA loss*	Red	White	Ptosis	Eyelid edema	Anisocoria	Proptosis	Tearing	Nasal sxs	Diplopia	Blurry vision	Photophobia	Other comment
1	Dry eye syndrome		(X)									(X)	(X)	
2	Corneal erosions		X						X			X	X	Upon awakening
3	Post-LASIK pain			X									(X)	
4	"Eye strain"			X							(X)	(X)		
5	Intermittent angle-closure glaucoma		X						X			X	X	
6	Blepharospasm			X					(X)			(X)	X	Excess blinking
7	Chalazion		(X)			(X)								
8	Trochleitis			X									(X)	
9	Lacrimal gland tumor			X	(X)	(X)		(X)			(X)			
10	Posterior scleritis	(X)		X								(X)	(X)	
11	Idiopathic orbital inflammatory syndrome	(X)	X		(X)	(X)		(X)	(X)		X	(X)	(X)	
12	Uveitis	(X)	X				(X)		(X)			(X)	X	
13	Conjunctivitis		X			(X)			X			X	(X)	
14	Thyroid eye disease	(X)	(X)	(X)		(X)		X	(X)		(X)	(X)	(X)	
15	Orbital mass	(X)	(X)	(X)	(X)	(X)		X	(X)		(X)	(X)	(X)	
16	Ocular ischemic syndrome	(X)	(X)	(X)			(X)					(X)	(X)	TVL in light

(continued)

Case	Diagnosis	VA loss*	Red	White	Ptosis	Eyelid edema	Anisocoria	Proptosis	Tearing	Nasal sxs	Diplopia	Blurry vision	Photophobia	Other comment
17	Horner syndrome		(X)	(X)	X		X		(X)	(X)				+/− anhidrosis
18	Microvascular cranial nerve palsy			X	(X)		(X)				X			Ptosis and anisocoria w/3np only
19	Migraine			X									X	Aura may cause TVL
20	Medication overuse headache			X										
21	Photophobia		(X)	(X)									X	
22	Trigeminal neuralgia			X										
23	Cervicogenic headache			X									(X)	
24	Ice pick headache			X										
25	Sinus disease			X						X				
26	Tension type headache			X									(X)	
27	Supraorbital neuralgia			X									(X)	
28	Trigeminal autonomic cephalalgia		X		X		X		X	X			X unilat	
29	Cough headache			X										
30	Traumatic headache			X									X	
31	Intracranial hypotension			X							(X)		(X)	Positional pain
32	Giant cell arteritis	(X)	(X)	(X)	(X)	(X)	(X)				(X)	(X)		>50 yo

33	Thunderclap headache			X								(X)	(X)	
34	Meningitis	(X)	(X)	(X)							(X)	(X)	X	
35	Optic neuritis	X		X								X		
36	Idiopathic intracranial hypertension	(X)		X							(X)	(X)	(X)	
37	Carotid cavernous fistula	(X)	X		(X)	(X)	(X)	(X)			(X)	(X)	(X)	
38	Herpes zoster ophthalmicus	(X)	(X)	(X)	(X)	X		(X)			(X)	(X)	(X)	Pain may antedate vesicles
39	Periocular skin cancer	(X)		X	(X)		(X)	(X)			(X)	(X)		
40	Tolosa Hunt		(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	(X)	(X)	
41	Pituitary tumor	(X)		X							(X)	(X)	(X)	
42	Aneurysm	(X)		X	(X)		(X)				(X)	(X)	(X)	
43	Ophthalmoplegic migraine			X	X		X				X		(X)	<10 yo

X = Commonly occurs
(X) = Possibly occurs

Contents

Part IV Neurologic Disorders Causing Eye Pain: Abnormal Eye or Neurologic Exam

Abbreviations

3NP	Third nerve palsy
ABMD	Anterior basement membrane dystrophy
ACE	Angiotensin-converting enzyme
ANA	Antinuclear antibody
APD	Afferent pupillary defect
BB	Ball bullet
BE	Both eyes
C	Cervical
c-ANCA	Cytoplasmic antineutrophil cytoplasmic antibodies
C-C	Carotid cavernous
CAS	Clinical activity score
CBC	Complete blood count
CI	Convergence insufficiency
CISS	Constructive interference in steady state
cm	Centimeter(s)
CN	Cranial nerve
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomographic angiogram
CTV	Computed tomographic venogram
DES	Dry eye syndrome
EBV	Epstein–Barr virus
ED	Emergency department
EMG	Electromyography
ENT	Ear, nose, and throat
ESR	Erythrocyte sedimentation rate
FTA-ABS	Fluorescent treponemal antibody absorption
GCA	Giant cell arteritis
GON	Greater occipital nerve

GPA	Granulomatosis with polyangiitis
Hg	Mercury
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPI	History of present illness
HSV	Herpes simplex virus
ICHD	International Classification of Headache Disorders
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIH	Idiopathic intracranial hypertension
IOP	Intraocular pressure
IV	Intravenous
IVIG	Intravenous gamma globulin
kg	Kilogram
LASIK	Laser in situ keratomileusis
LDS	Latter Day Saints
LE	Left eye
LP	Light perception or lumbar puncture
LUL	Left upper lid
mg	Milligram (s)
MIDAS	Migraine Inventory Disability Assessment Score
mL	Milliliter(s)
mm	Millimeter(s)
MOH	Medication overuse headache
MR	Magnetic resonance
MRA	Magnetic resonance angiogram
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NMO	Neuromyelitis optica
NOVEL	Neuro-ophthalmology Virtual Educational Library
NSAIDS	Nonsteroidal anti-inflammatory drugs
OD	Right eye
OIS	Ocular ischemic syndrome
OS	Left eye
OU	Both eyes
p-ANCA	Perinuclear antineutrophil cytoplasmic antibodies
Pcomm	Posterior communicating
PCR	Polymerase chain reaction
PD	Prism diopter
PEK	Punctate epithelial keratopathy
PET	Positron emission tomography
POTS	Postural orthostatic tachycardia syndrome
prn	As needed
PSP	Progressive supranuclear palsy

PST	Pulse synchronous tinnitus
RAI	Radioactive iodine
RAPD	Relative afferent pupillary defect
RCVS	Reversible cerebral vasoconstriction syndrome
RE	Right eye
RF	Rheumatoid factor
RNA	Ribonucleic acid
RNFL	Retinal nerve fiber layer
RPR	Rapid plasma reagin
SOV	Superior ophthalmic vein
SR	Sustained release
SSA	Sjögren syndrome-related antigen A
SSB	Sjögren syndrome-related antigen B
SSRI	Selective serotonin reuptake inhibitor
SUNA	Short unilateral neuralgiform headache attacks
SUNCT	Short unilateral neuralgiform headache attacks with conjunctival injection and tearing
TAC	Trigeminal autonomic cephalgia
TB	Tuberculosis
TBUT	Tear break up time
TED	Thyroid eye disease
TMJ	Temporomandibular joint
TRAB	Thyroid receptor antibody
TSI	Thyroid-stimulating immunoglobulin
TVL	Transient vision loss
u	Units
VDRL	Venereal Disease Research Laboratory
VZV	Varicella zoster virus
WHO	World Health Organization
x/d	Times per day

Part I
Ophthalmic Disorders Causing Eye Pain: Relatively Normal Examination

Case 1

History of Present Illness

A 63-year-old woman with a history of strabismus status-post childhood corrective surgery describes pain in both eyes for the last 6 months. She describes an aching pain that is absent when she first awakens then worsens as the day progresses. It is symmetric, daily, and is getting worse occurring more frequently and earlier in the day. She was given eye exercises and prisms without improvement. Nothing initiates the pain, but reading seems to worsen it. Closing her eyes makes it better. Over-the-counter NSAIDs are not beneficial. She endorses occasional redness and occasional tearing. The pain has an aching quality, does not radiate, and measures three out of ten at its worst. She denies blurred vision, ptosis, photophobia, and diplopia.

Past medical and ocular history Osteoarthritis Atrial fibrillation Depression Hyperlipidemia Hypertension Right-sided congestive heart failure Rosacea	*Past surgical history* Total knee arthroplasty
	Family history Mother—Progressive supranuclear palsy
	Review of systems Easy bruising
Medications Furosemide Sertraline Metoprolol Warfarin Vitamin D Spironolactone Atorvastatin	*Social history* One glass of wine daily No smoking or drug use Retired professor

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Examination
Acuity with correction Right eye: 20/20 distance and near Left eye: 20/25 distance, 20/20 near
Pupils Equal, round, reactive, without an afferent pupillary defect
Intraocular pressure Right eye: 17 mmHg Left eye: 18 mmHg
External exam Rosacea, mild ptosis of the left upper lid
Eye alignment and motility Normal motility Orthophoric in distance 3 PD exophoria at near Convergence amplitudes 30 PD for distance, 40 PD near Near point of convergence to nose
Slit lamp examination Blepharitis Mild nuclear sclerosis Tear break up time 4 s BE No foreign body seen
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

The fact that the pain is intermittent, bilateral, and symmetric would argue away from a fixed orbital process, where I would expect the pain to be constant and unilateral. There are no other features of orbital inflammation such as persistent or worsening redness, proptosis, or chemosis. Her pain is not present in the morning and worsens as the day goes on suggesting this is not a more sinister process. While the patient has a small eye misalignment (exodeviation), this would not constitute a convergence insufficiency (CI). Typically, the deviation in CI (see Case 4) is 10 prism diopters greater at near than distance. Her exodeviation is too small to really call it CI. The patient has very normal convergence amplitudes, well over what is needed to overcome the small misalignment at near. Her near point of convergence is also normal. Although her symptoms are worse with reading, which could suggest CI, she has tried prisms and convergence exercises without benefit.

The mild pain and aching quality sound most consistent with dry eye syndrome (DES). It is important to note that DES is the most common cause of eye pain! In

my experience, most patients with dry eye-related pain describe generally mild, aching, pressure, or pulling sensation. Some say it radiates behind the eye and others say eye movement worsens it. It would be highly unusual for DES to cause sharp, stabbing or pounding pain or for it to be severe. Many patients note that the pain seems to wax and wane with the day. When patients wake up, their corneas have been protected all night and then become painful with exposure to wind and evaporation especially with reading. Interestingly, sometimes DES pain is unilateral. Many patients will note other symptoms of DES such as burning, blurry vision, tearing, redness, and foreign body sensation but not all will. Examination may show punctate epithelial erosions, early tear break up time (TBUT), blepharitis, or abnormal Schirmer's tear testing (Fig. 1.1). In other cases, the slit lamp examination can appear quite unremarkable. In many, a topical anesthetic will greatly improve the pain. However, patients with chronic DES-related eye pain of several months duration may not enjoy improvement. This occurs because of upregulation of pain modulating proteins within the cornea. Looking at her medications, she is on two diuretics, a beta blocker and a SSRI, which may worsen DES.

We know that she has rosacea, blepharitis, and an early TBUT. Rosacea can cause inflammation of the eyelid margin and disruption of the meibomian glands, which reduces tear quality. We could see if a topical anesthetic substantially improves the pain. We could also measure her tear production. Given the strong history and physical, I would favor treating with artificial tears 4–6 × /day, washing the eyelids with hot water, using warm compresses, fish oil or flaxseed oil (omega 3 oils) 2 × /day for 1 month then 1 × /day, humidifying her environment, and drinking a lot of water. At bedtime, the patient can also use ocular ointment. If this does not benefit her, then I would add topical corticosteroids 3–4 × /day tapering by one drop each week. If she had improvement, but not resolution with the corticosteroids, then I would try topical cyclosporine 2 × /d. I would also consider punctal plugs and doxycycline 100 mg 2 × /day. More extreme measures could include scleral contact lenses, which put a layer of tears between the lens and the cornea, or even autologous serum eye drops.

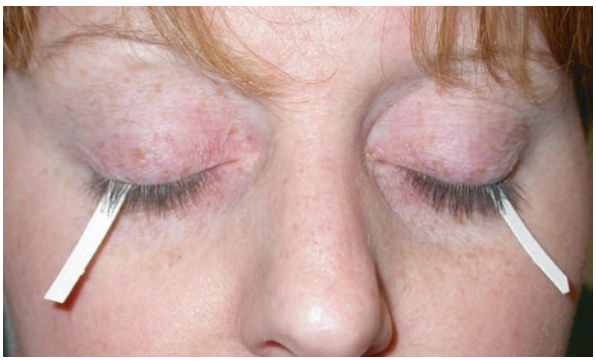

Fig. 1.1 Schirmer tear testing. Some practitioners put anesthetic in and others do not. The strips are placed in the lower fornix and left there for 5 min. After they are removed the degree of wetting is measured using a ruler. Less than 5 mm is considered significantly reduced

Neurologic Perspective: Dr. Digre

I agree with Dr. Lee, that this is dry eye. There are many conditions to at least consider that could be co-morbid in this patient. I would want to be sure she does not have underlying migraine. While she is 63 years old, her migraines may have tapered off, but individuals with previous migraine could be more susceptible to the pain of dry eyes. In addition, in my practice, dry eyes can worsen migraine patient's headaches. I would also be sure that she has no other neurological symptoms. Her mother had progressive supranuclear palsy (PSP) and degenerative neurological disorders can be associated with decreased blinking. While it is not known to be inherited, movement disorders such as PSP and Parkinson disease are frequently associated with both dry eyes and complaints about reading and mild convergence insufficiency. Finally, I would also ask about dry mouth as a symptom of Sjögren's disease which often affects middle-aged women. I frequently do a Schirmer's test. While this is sometimes negative, even when I know the patient has dry eyes, it is often helpful to know how dry the eyes are. As for other testing, if she had dry mouth, I might draw Anti SS A (Anti Ro) and Anti SS B (Anti La) antibodies often seen with Sjögren's disease. Because these labs can be negative with Sjögren's disease, I would consider lip biopsy, if I were very suspicious.

With the lack of any other neurological symptom or examination finding, I would not recommend an MRI scan for this patient. Setting out a written treatment plan is often helpful—outlining the steps to take in improving dry eyes. We frequently recommend warm soaks if there is blepharitis, frequent preservative free tears, and gels or ointments at night. Following up with the patient is also important since further treatment may be helpful. The importance of treating this now and getting DES under control is that, left untreated, this can lead to trigeminal nerve damage and neuropathic pain, resulting in more severe pain, which is much more difficult to treat, so primary prevention of further damage is important.

Non-ophthalmic/Non-neurologic Perspective

The history here will most likely lead you to the diagnosis. You may or may not have a topical anesthetic in the office or emergency room. The pain, if it is going to resolve, will do so within a minute. Staining the cornea with fluorescein may show small, punctate dots of green (aka punctate epithelial erosions or keratopathy) consistent with dry eye. You can use the blue filter on the slit lamp if you have one or, on the direct ophthalmoscope, view the cornea using the +10 lens (green 10). Generally speaking, the visual acuity should be normal or near normal (20/25).

Artificial tears are over the counter. There are two kinds, those with preservatives and those without preservatives. Either one can be used, but some patients develop sensitivity to the preservatives. When asking the patient to wash the eyelids with hot water, this is directed at rubbing gently along the base of the eyelashes where the

meibomian glands sit. A warm wash cloth over the eyes is also effective. We often ask patients to do this in the shower. We would not favor a non-ophthalmologist giving out corticosteroid eye drops or a topical anesthetic to take home. There are too many risks with an incorrect diagnosis. We would recommend a referral to an ophthalmologist for a correct diagnosis.

Follow Up

The patient's pain resolved with topical anesthetic in the office. She used artificial tears and lid hygiene regularly. The pain persisted, and she tried topical corticosteroids. These did not help substantially. With continued use of the artificial tears and eyelid hygiene and humidification of her environment, her pain resolved spontaneously over several months time. *Final Diagnosis: Dry eye syndrome*.

For Further Study

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Case 2

History of Present Illness

A 75-year-old woman complains of bilateral eye pain. She describes the pain as burning, itching, and constant. Approximately every few weeks, when she awakes she has severe right eye pain. She describes it as sharp with a foreign body sensation, and her vision seems blurred at that time. The pain seems to happen as soon as she opens her eye and she is afraid to open her eyes in the morning. Both the blur and the pain resolve slowly over a few hours. With these sharp pains, her eye waters and it appears reddened. A hot towel and artificial tears make this feel better. The left eye seems normal otherwise. She denies any history of trauma or contact lens use.

Past medical and ocular history Hypercholesterolemia Osteoarthritis Atrial fibrillation Anxiety Reflux Hypertension	*Past surgical history* Cataract surgery BE Blepharoplasty BE Tonsillectomy Tubal ligation Gallbladder removal
	Family history None
Medications Pravastatin Escitalopram Losartan Estradiol Omeprazole Zolpidem Warfarin	*Review of systems* Longstanding joint pain, seasonal allergies, anxiety
	Social history Never smoked, no alcohol, homemaker

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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal, round, briskly reactive, no APD
Intraocular pressure Right eye: 19 mmHg Left eye: 17 mmHg
External exam 3 mm ptosis right upper lid 2 mm ptosis left upper lid
Eye movements Normal
Slit lamp examination Anterior basement membrane dystrophy (ABMD) BE Punctate epithelial keratopathy (PEK) BE Intraocular lenses BE
Visual field Normal
Fundus examination Mild drusen consistent with macular degeneration
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

Previously, in Case 1 we discussed dry eye. The patient has signs PEK and symptoms (constant burning and itching) of dry eye syndrome. I believe this is the cause of the constant dull pain that she describes. It almost sounds like she has corneal abrasions but she likely is not scratching her right eye while she is asleep several times.

However, dry eye syndrome (see Case 1) typically feels better in the morning and it does not cause sharp, acute pain. We should examine the patient for lagophthalmos (eyes still partially open after closing gently), which can cause pain in the morning, but the exposure keratopathy of lagophthalmos usually does not cause severe, sharp pain. This scenario above would be most consistent with recurrent corneal erosions. Most commonly, a patient notes a history of corneal abrasion with a sharp object such as a paper cut or a fingernail. The abrasion elevates a layer of the corneal epithelium, which does not cement itself back down well. When patients sleep, the eyelid dries to and sticks to the corneal epithelium slightly. When the patient opens their eye, the eyelid pulls that unstable epithelium off—hence the severe eye pain. This classically improves over a few hours. Oftentimes, the patient

will arrive at the eye doctor with no *obvious* corneal defects (subtle ones are often present). In the case herein, the patient denied trauma. However, she has ABMD, a condition of abnormal corneal epithelial basement membrane, which can lead to poor adherence to the epithelium and corneal erosions. Dry eye syndrome also represents a risk factor for erosions.

The first line of therapy for preventing erosions is an over-the-counter lubricant eye ointment placed in the eye(s) before going to sleep. This prevents the eyelid from sticking to the epithelium. One could consider a bandage contact lens as a protective barrier. If these do not help, then one could denude the faulty epithelium. Other alternatives include lasering the epithelium and basement membrane (phototherapeutic keratectomy) or stromal micropuncture (using a 25-gauge needle to scar the epithelium down).

Neurologic Perspective: Dr. Digre

The diagnosis of recurrent erosions or keratitis would be very hard for a neurologist to make, since it is really seen at the slit lamp and often with fluorescein strips. Erosions could be considered especially with the history of stinging pain first thing in the morning. The red eye should be a clue to send the patient to an ophthalmologist for a diagnosis. The other clue for me that this is a problem with the cornea is the intermittent blurred vision—there is no loss of vision, but blurring also in association with pain. As a first pass, one might start with ointment at night and more tears throughout the day. Sometime I have prescribed moisture chamber glasses. However, a referral to an ophthalmologist is probably the most important step.

Some have advocated using proparacaine drops—but I think these should be avoided unless the patient is under the care of an ophthalmologist. The other caveat is that these individuals frequently have other corneal pathology.

Non-ophthalmic/Non-neurologic Perspective

You may not have access to or expertise with the slit lamp to identify a subtle epithelial change or ABMD. Much of this diagnosis is based on the history—awakening with red, painful, tearing, blurry eye that resolves spontaneously over a few hours. A history of corneal abrasion in the affected eye is gravy. This is not consistent with angle closure glaucoma. If you do not see a corneal abrasion, there probably is not one. Pearl: Sometimes we see a provider "paint" the fluorescein strips on the cornea and it can look like a corneal abrasion (Fig. 2.1a, b). The fluorescein should be placed on the inside lower eyelid and the stain spreads when the patient blinks (Fig. 2.1c).

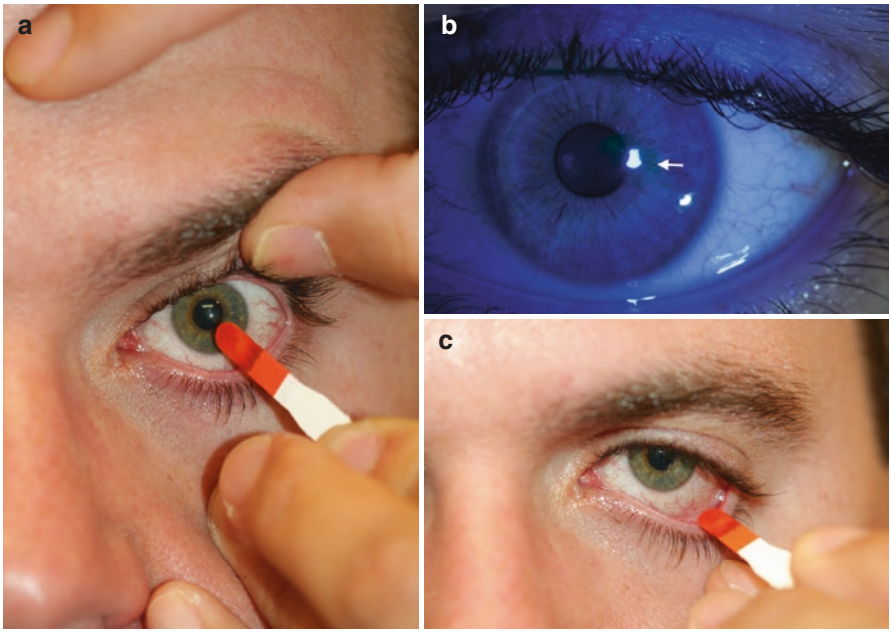

Fig. 2.1 Instilling fluorescein. (**a**) The provider is erroneously placing fluorescein on the cornea. (**b**) This leads to stain on the cornea than can look like a corneal abrasion. (**c**) Proper instillation of fluorescein on the insider of the lower eyelid. When the patient blinks, this will spread fluorescein over the cornea in the tear film

Follow Up

The patient used a lubricant eye ointment at bedtime and enjoyed significant improvement in episodes of recurrent corneal erosions. On occasion, she would forget to put the ointment in and would redevelop attacks. *Final Diagnosis: Recurrent corneal erosions.*

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Case 3

History of Present Illness

A 30-year-old woman underwent bilateral laser in situ keratomileusis (LASIK) surgery 8 months ago. About a month following the surgery she developed pain in both eyes. She describes it mostly as burning and "hurting." It is made worse with wind and computer use. She was given the following eyedrops: artificial tears, preservative-free artificial tears, olopatadine, cyclosporine ophthalmic emulsion, a topical corticosteroid, and a topical nonsteroidal over the ensuing months without benefit. She had punctual plugs placed in all four puncta and was given moisture goggles to sleep at night. Despite these efforts, she rates her pain at seven out of ten by the end of each day. She denies a history of migraine and endorses mild to moderate photophobia. She wears sunglasses outside but not inside.

Past medical and ocular history Fibromyalgia Hypothyroidism	*Past surgical history* LASIK both eyes
Medications Levothyroxine Sertraline Clonazepam Vitamin D Lubricant eye gel	*Family history* Macular degeneration—mother
	Review of systems Negative
	Social history Nonsmoker Social drinker Secretary

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Examination
Acuity without correction Right eye: 20/20 Left eye: 20/20
Pupils Equal, round, brisk, no afferent pupillary defect
Intraocular pressure Right eye: 16 mmHg Left eye: 17 mmHg
External exam Dermatochalasis of upper eyelids No pain to palpation around the eyes Mild lagophthalmos BE
Eye alignment and motility Normal
Slit lamp examination A few punctate erosions both eyes (BE) Unremarkable LASIK flap/scar BE 1+ conjunctivochalasis BE 1+ papillary reaction BE Reddened and irritated skin along the upper and lower lids
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

The burning history could certainly be consistent with dry eye syndrome. Certainly, a high proportion of patients after LASIK complain about increased dry eye symptoms. I will say that seven out of ten pain is a little high for dry eye, but we have all seen patients with pain exaggerate their pain score. She has been treated with plugs, lubrication, moisture chamber, and anti-inflammatories without ANY benefit, which would argue away from corneal surface concerns. I would see if a topical anesthetic in the office helps with her pain, which would support an ocular surface issue. If it were helpful, then one could consider autologous serum or a scleral contact lens. We have already had a dry eye (see Case 1) case and so this cannot be the answer. ☺

The papillary reaction is mild and would be more indicative of an allergic issue associated with itching instead of pain. Conjunctivochalasis is a common condition where excess folds of the conjunctiva lie between the globe and the eyelid margin. You can see the folds laying on the lower eyelid margin. Conjunctivochalasis can be

asymptomatic or cause symptoms of dry eye or mild aching pain. Again, the seven out of ten pain would be high for conjunctivochalasis. In the absence of a diagnosis, I have seen ophthalmologists consider resection of the folds, but I am not convinced this is the answer here.

While I had alluded to the dry eye symptoms following LASIK surgery, there is a growing movement that these are neuropathic symptoms. When a LASIK flap is cut and the corneal stroma is ablated, corneal nerves are damaged. Neuropathic pain can be burning and patients may have allodynia, where light touch induces pain. The eyelids rub the cornea with every blink and may be interpreted as a foreign body sensation, but this could be allodynia. In many cases, the symptoms of dry eye improve as the corneal nerves heal. However, as with nerve injury in other surgical procedures, some patients experience persistent neuropathic pain. The corneal nerves may not grow back properly leading to persistent pain. One way to identify this is with confocal microscopy. Alternatively, one could begin treatment with gabapentin to see if there is any benefit.

Neurologic Perspective: Dr. Digre

When I see patients like this, I look to see if they have a family or self history of migraine, fibromyalgia, or other chronic pain problem. I think some individuals with these pain conditions are just extra pain sensitive. A recently reported paper by Shtein et al. is really important—when we see patients with more symptoms than findings, we need to think about central sensitization similar to what we see in migraine. In their study, they took 48 patients with dry eyes, 23 patients with fibromyalgia, and 26 healthy controls. The dry eye patients were further divided between concordant (dry eyes looked dry) and discordant (dry eye complaints but normal examination). Of course Schirmer's were actually lowest in dry eye patients, but also in fibromyalgia patients. Ocular Surface Disease Index scores were equally raised in dry eye and fibromyalgia patients. The discordant group also had decreased visual quality of life scores that were very similar to the fibromyalgia patients and the concordant dry eye patients were more like healthy controls!

So, my thinking is that she has a central pain disorder that makes her more likely to have these complaints than a typical dry eye person. Fibromyalgia occurs in 2–8% of the population and occurs in women. Their functional MR brain imaging shows similar structural changes seen in patients with chronic pain and migraine.

Treatment for these kinds of cases for me is difficult. First, I tend to maximize tears and good lid hygiene. Gabapentin would be helpful for her fibromyalgia as well as her eye symptoms. If she is light-sensitive, we recommend FL-41 tint since it seems to block the wavelength that is least tolerable for light-sensitive people. On occasion, I have had to recommend sympathetic blockade for these individuals since the eye pain acts a little like sympathetically maintained pain (reflex sympathetic dystrophy) or complex regional pain syndrome.

Non-ophthalmic/Non-neurologic Perspective

The story is going to be in the history of LASIK or other corneal incision followed by symptoms of pain a few to several weeks later. The pain often increases as time progresses. I think you can think of this like a post-surgical neuroma, where the nerve endings grow back in an anomalous fashion. Most ophthalmologists do not have access to a confocal microscope, so I do not expect you would either. A trial of gabapentin for 2–4 months may be reasonable. If the ophthalmologist and you agree that this is apt to be neuropathic pain then a referral to a neurologist or a pain specialist may be reasonable. My guess is, these patients will not go to a non-ophthalmologist since they had LASIK and then develop eye pain, so you may be off the hook.

Follow Up

The patient underwent confocal microscopy and this showed a closed corneal nerve loop instead of the normal branching pattern (Fig. 3.1). The patient was diagnosed with post-LASIK neuropathic pain and was begun on gabapentin 300 mg pills three times a day. The pain gradually improved over the course of several weeks.

As I review the current literature, there was a case report of a patient with neuropathic eye pain and vitamin B12 deficiency who improved with supplementation. Other patients have received typical treatments for neuropathic pain including pregabalin and carbamazepine with success. One could consider a sympathetic block in these cases. There have been a few refractory patients who have tried a spinal cord stimulator or a pain pump in the area of C1. *Final Diagnosis: Post-LASIK eye pain***.**

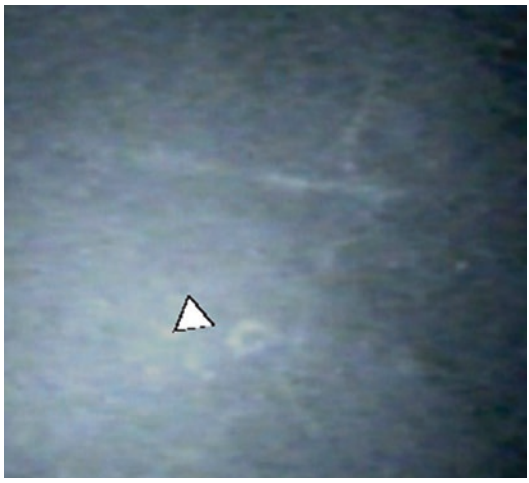

Fig. 3.1 Confocal microscopy demonstrates a subtle corneal loop (*arrowhead*) indicating abnormal regrowth following LASIK resection (Courtesy Stephen C. Kauffman, MD, PhD)

For Further Study

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Case 4

History of Present Illness

A 29-year-old man complains of left eye pain with prolonged near work for the past several months. The pain begins after reading for several minutes and spreads to his frontal region and the right eye unless he stops reading. If he does not read, he does not really develop pain. He describes it as an ache that worsens to a 5/10 at its worst. The clarity of his vision in each eye is unaffected. He denies double vision, ptosis, oscillopsia, eye redness, and epiphora. He does not wear glasses, but has recently purchased over-the-counter readers, which did not help.

Past medical and ocular history Chronic sinusitis	*Past surgical history* Sinus surgery
Social history 1–2 beers daily, occasionally smokes marijuana but not cigarettes, salesman	*Family history* No history of migraine, no eye disease Mother has glaucoma
Medications None	*Review of systems* Negative

Examination
Acuity without correction Right eye: 20/20 distance and near Left eye: 20/20 distance and near
Cycloplegic refraction Right eye: +0.25 Left eye: Plano
Pupils Equal in size, briskly reactive, round

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Intraocular pressure Right eye: 20 mmHg Left eye: 19 mmHg
External exam No ptosis, no proptosis, normal appearance
Eye motility and alignment Normal eye excursions, both eyes Normal pursuits and saccades Orthophoric in the distance in all gazes 12 prism diopter intermittent exotropia at near Near point of convergence 20 cm (Fig. 4.1)
Slit lamp examination No blepharitis No keratopathy or tear film dysfunction
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Fig. 4.1 The patient is focusing on the examiner's finger as it is brought closer to the nose. At this point, 20 cm away, the patient's right eye is focused on the finger, but the left eye has just deviated off the finger. This patient has an abnormal near point of convergence consistent with CI

Discussion

Ophthalmic Perspective: Dr. Lee

This patient gives a story most consistent with "eyestrain," where folks complain of bilateral eye tiredness or aching that can radiate to the temples or the frontal region with prolonged reading. Nowadays, you might hear it called "Computer Vision Syndrome" as well. Sometimes this story could be consistent with dry eye syndrome (see Case 1), and this should be ruled out. Eyestrain is a wastebasket term that includes uncorrected hyperopia, over-corrected myopia, poor accommodation, or eye misalignment at near. Eye evaluation should include a good refraction at

distance and near pushing plus. Patients younger than 45 may require a cycloplegic refraction to determine any hidden hyperopia or overminus. Cover testing with a near target may show a exo- or hyperdeviation. A Maddox Rod can help identify cases of tiny hyperdeviations that may be difficult to observe.

The patient herein has a convergence insufficiency pattern—full eye movements, exodeviation greater at near, and a distant near point of convergence. Typically, the exodeviation measures at least 10 PD more at near than distance. Normally, the eyes can converge on a target at <8 cm. Convergence insufficiency (CI) in this age group most commonly results from head trauma or is idiopathic. He denies trauma, and there is no need to pursue neuroimaging for *isolated* CI. Management usually involves pencil pushups, where one looks at a target and brings it closer to the eyes until it becomes double or blurred. The goal is to strengthen convergence by doing these exercises hundreds of times a day. In our experience, most patients do not have the discipline to do these. Other options include giving base in prisms for reading, formal therapy with a trained orthoptist, computer-based convergence programs, patching an eye for reading (not ideal) and surgery (rarely performed). Monovision could be considered for presbyopic patients unable to tolerate the options above.

Neurologic Perspective: Dr. Digre

When I see someone with this history I do three things. First, I go over the migraine history, because MANY patients with this disorder often are visually sensitive and have migraine (see Case 19). Sometimes you have to ask, "you mean you have never had a headache?" and then "did this headache ever make it hard for you to do your work?" "were you ever light or sound sensitive with your headache?" I also ask whether the reading problem is all types of reading material (like computer screens, tablets, television, or books) in all forms of lighting—fluorescent lighting and computer vs incandescent bulbs. Then on examination, I first look at acuity—and see if this patient could be a latent hyperope (meaning they are far-sighted). I look really carefully for dry eyes and sometimes perform a Schirmer's test. We are a computer using generation, and when we are on the computer, we blink less frequently, which can set up dry eyes in someone you would not suspect. I agree that looking for convergence insufficiency or divergence insufficiency is also important. Sometimes we look at convergence and divergence amplitudes—how much reserve does a person have. For example, we can use a prism bar and push it up and down base in or base out to test these amplitudes. Third I treat. If they have modest dry eyes, I stress lubrication at the computer screen. If they are also light-sensitive, FL-41 glasses can be helpful (see Case 21). I do stress pencil push-ups and sometimes even pressure points that were once developed by the Chinese for embroiderers for a living (see Fig. 4.2). The exercises have been tested in children to prevent myopia and accommodation with minimal benefits, but for eye strain in some individuals they may be more helpful.

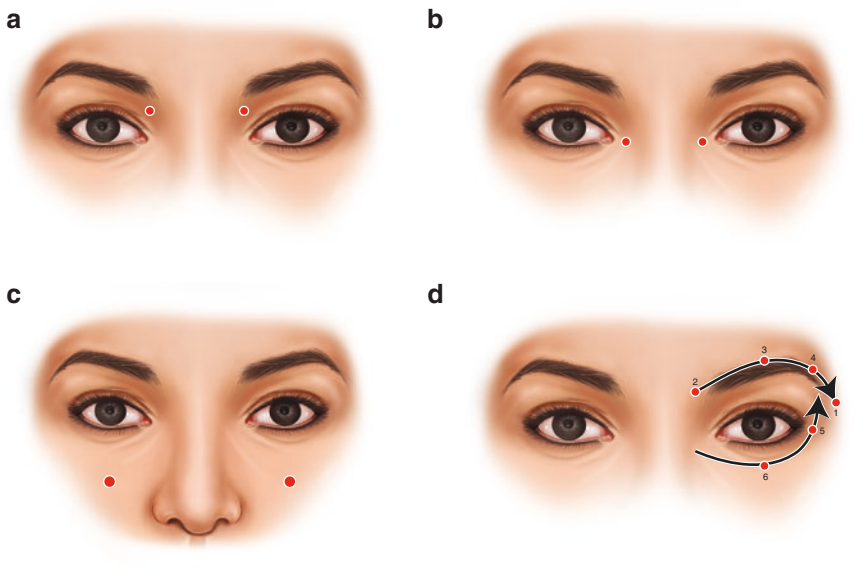

Fig. 4.2 Steps to Chinese exercises for eye strain. (*1*) Perform exercises in the morning and afternoon. (*2*) Do not push on your eye balls (*3*) Press the pressure point until an ache feeling occurs and repeat about eight times each time. (**a**) Push just under your eye brows (Zhan Zhu Point). (**b**) Massage the bridge of your nose (Fu Jing Ming Point) (**c**) Press on your center of your cheek (Si Bai Point). (**d**) Rub around your eye—first along your eye brow then a lower half circle below your eye

Non-ophthalmic/Non-neurologic Perspective

When a patient complains of pain or headache with prolonged reading, consider that they may have eyestrain. In your office, you could consider having the patient stare at a near target such as your nose at 1/3 of meter. Alternately, covering the eyes may show a shift of the eyes as you go back and forth. If the eye shifts toward the nose, then that is consistent with an exodeviation as seen in CI. If the eye shifts up or down, then that is consistent with a hyperdeviation such as a fourth nerve palsy. You can also have the patient look at a target and bring the target to the nose. As you watch the eyes, they should converge on the target as it gets closer. If you see one of the eyes deviate outward as you bring it closer, then that distance is the near point of convergence. You could consider offering the patient convergence exercises, if the eye movements are otherwise full. In the absence of an eye misalignment, the patient will need to get a good refraction at distance and near with an ophthalmologist or optometrist.

Follow Up

The patient received a diagnosis of CI and was given pencil pushups. He reported noncompliance with the exercises. He was given the options of visiting with an orthoptist, using a computer convergence program, and base-in prisms. He was told that prisms might make him dependent on the glasses and that he may see double at near without the prisms. After consideration of all the factors, he elected to receive a prescription for reading glasses with six base-in prism in each lens. He reported significant improvement in his symptoms. *Final Diagnosis: Convergence insufficiency causing "eyestrain".*

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Case 5

History of Present Illness

A 56-year-old woman noted left, intermittent periorbital and orbital pain for 7 months. It occurs suddenly and can wake her from sleep. However, it occurs at all times of the day approximately twice weekly, lasting 30–120 min. She denies a trigger. She endorses a history of temporal mandibular joint issues and believes this is related. Blurred vision coincides with the eye pain each time and she notes mild nausea and photophobia, but denies osmophobia or phonophobia. The blurry vision does not occur independent of the eye pain. She denies seeing sparkles or lights. She has a history of severe diabetic retinopathy status post vitrectomy in the right eye 2 years ago. Her right upper lid has drooped since that surgery. She has had extensive laser for neovascularization related to the diabetes to both eyes.

Past medical and ocular history	*Past surgical history*
Diabetes mellitus Addison disease Hyperlipidemia Hypertension Agoraphobia with panic disorder No history of migraine	Kidney transplant 1984 Pancreas transplant 2002 Heart bypass 2001
Social history	*Family history*
Unemployed, never smoked, former alcoholic	No eye disease Strong family history of diabetes, hypertension, and hyperlipidemia No family history of migraine

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Medications	*Review of systems*
Hydrocortisone	Earaches from the wind
Prograf	Shortness of breath
Cellcept	Constipation
Actonel	Joint pain
Aspirin	Itchy skin
Atenolol	Depressed mood
Diazepam	Easy bruising
Percocet	Numbness of hands and feet
Prozac	Difficulty walking from leg weakness
Lipitor	

Examination
Acuity with correction Right eye: 20/200 Left eye: Hand movements; near vision 20/40
Pupils Constricted, barely reactive, round, equal in size
Intraocular pressure Right eye: 16 mmHg Left eye: 19 mmHg
External exam Symmetric ptosis and dermatochalasis of both upper lids
Eye movement/alignment Normal
Slit lamp examination Chronic blepharitis all four lids Intraocular lens right eye, dense cataract left eye with Phacodonesis No evidence of rubeosis Anterior chamber: Deep right eye, shallow left eye
Visual field Constricted right eye, unable left eye
Fundus examination Optic nerve pallor both eyes Numerous and dense laser scars both eyes
Neurologic examination Numbness both feet, 4/5 strength in legs, poor proprioception of toes bilaterally

Discussion

Ophthalmic Perspective: Dr. Lee

This patient sounds like she could have migraine (see Case 19)—she has episodic eye pain associated with concomitant blurred vision, nausea, and photophobia. The pain is side locked. However, she is older than the average bear to have first onset migraine and does not have a history of migraine. The story is funny in that

Table 5.1 Drugs causing angle closure glaucoma

Tricyclic antidepressants
Non-tricyclic antidepressants (e.g., escitalopram, fluoxetine, mirtazapine, venlafaxine, buproprion)
Anticholinergics
Acetazolamide
Topiramate
Promethazine
Ranitidine
Cabergoline
Cimetidine
HCTZ

she notes the blurred vision and eye pain begin at the same time and are of sudden onset plus they can wake her from sleep. Auras usually take minutes to reach a peak. Her acuity is better at near than at a distance—and this is induced myopia that she never had before. When one looks at her physical examination, she has a shallow anterior chamber in the left eye along with phacodonesis (excessive movement of the lens).

The history and exam are certainly consistent with intermittent angle closure glaucoma (ACG). She denies a trigger; however one should inquire about whether sudden exposure to light, lying down, or taking medications (anticholinergics, antidepressants, antihistamines, and adrenergics) seems to initiate these attacks. She happens to be on fluoxetine (Prozac), which has been associated with ACG. See Table 5.1. Risk factors for angle closure include female gender, smaller eyes (hyperopia), older age, and Asian or Indian descent, topiramate use. She denies red eye or tearing, but these can accompany ACG. Normally, we think of acute ACG as a one-time event, where the patient presents to the ER with prolonged eye pressure elevation that does not remit until the patient receives drops, lasers, or surgery. In some cases, the angle can open and the pressure comes down spontaneously and recurs intermittently as in this case. We have seen intermittent ACG misdiagnosed as migraine by neurologists because of the similarities in historical features.

These patients should be instructed to avoid provocative medications and to have a laser peripheral iridotomy to prevent further attacks. In some cases, if the lens is very large, cataract extraction may be necessary.

Neurologic Perspective: Dr. Digre

This is a new headache in an older woman. Anyone presenting with a new headache needs to be evaluated for a secondary cause, especially when she never really had headaches before. The visual blur and pain would suggest to the neurologist that there may be an ocular problem (e.g., corneal erosion (see Case 2)) and that the patient should be seen by an ophthalmologist.

The temporal mandibular joint (TMJ) dysfunction confounds the history as well. TMJ is diagnosed when someone has demonstrated joint disease that is demonstrated by imaging and/or clinical examination—for example, the individual cannot open the mouth more than 2–3 fingerbreadths. The pain is usually associated with jaw movements, which is not part of the history here. TMJ dysfunction is greatly over-rated and while she may think this is the cause—look for another cause. The nocturnal wakening could suggest hypnic headache especially in an older person, but we are told this pain comes at all times of the day and night.

For sure, this woman should have a good eye examination—and I would definitely want a slit lamp examination since her acuity is down 20/200, hand motions PLUS she has diabetes. Too many red flags here for my liking. The ophthalmologist finds a narrow angle on the left side. This could suggest angle closure.

Differentiating migraine and intermittent acute angle closure can be tricky. If this woman had a previous migraine history, we might have thought she had migraine as the cause of pain. The clues for me that this is not migraine is that it occurs in the same eye and that the blur and the pain are simultaneous. Migraine aura is not typically just a blur—it often as a progression over minutes and it occurs in both eyes. Aura is often colored or has zig-zag lines and often the pain will occur after the visual disturbance. The nausea with the pain can also confuse the neurologist since we usually associate nausea with migraine. The only other thing to worry about is ocular ischemia that could cause pain and visual blurring. A fluorescein angiogram may be helpful looking at an arm to retina time. Finally, always consider giant cell in any older individual with a new headache (see Case 32).

Non-ophthalmic/Non-neurologic Perspective

The history will be essential in distinguishing ACG and migraine. There may be an atypical feature that may guide you. Most patients with migraine experience the blurred vision of an aura before the pain begins. The blur usually progresses over minutes and subsides over minutes. Typically, the aura of migraine lasts less than an hour. However, a new headache in an older person should always alert you that there could be a secondary cause. Keep in mind that migraine is common and intermittent ACG is uncommon.

You can also take a penlight and shine it from the side of the anterior chamber parallel to the iris. If the chamber is deep, then the light will uniformly illuminate the iris. If the chamber is narrow, it may cast a shadow on the nasal side of the iris (Fig. 5.1).

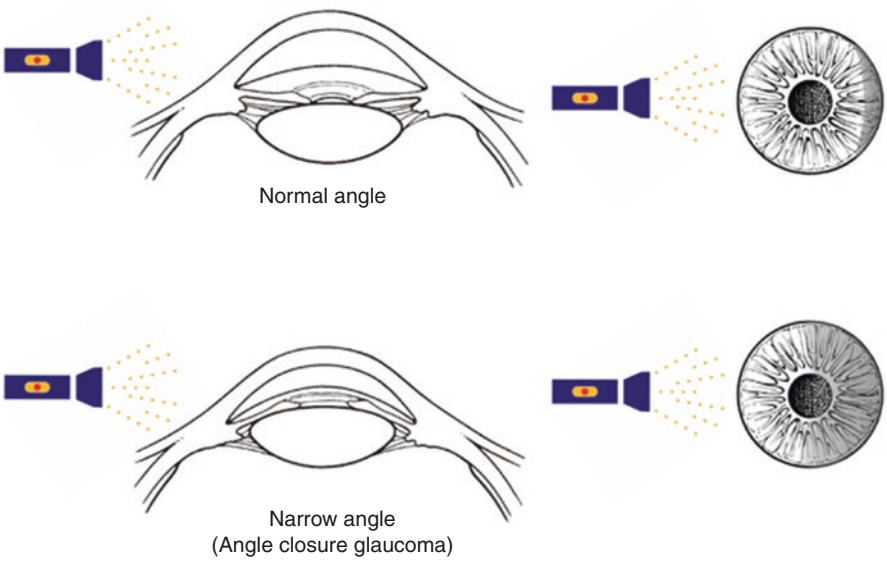

Fig. 5.1 Shining a light from the side in a normal angle will produce no shadow. If the angle is shallow, there may be a shadow. From Digre and Corbett, Practical Viewing of the Optic Disc. Butterworth-Heineman, 2001 (with permission)

Follow Up

Compression goniscopy showed an occludable (appears closed, but can open the angle with pressure) anterior chamber angle with areas of peripheral anterior synechiae. She was diagnosed with intermittent angle closure glaucoma likely related to the mobile lens in the left eye. The patient underwent laser peripheral iridotomy (LPI) followed by uncomplicated cataract extraction. The episodic eye pain resolved after the LPI. *Final diagnosis: Intermittent angle closure glaucoma*.

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Case 6

History of Present Illness

A 59-year-old 6th-grade teacher presents with eye pain and difficulty keeping her eyes open. She reports she was diagnosed with dry eyes in 2014 by an optometrist and treated with cyclosporine ophthalmic solution (Restasis) for 8 months without relief. During this time, she noticed that she had trouble keeping her eyes open at work as though she was sleepy and she had frequent blinking that would worsen in bright light. When driving she has been so bad that she has pulled off of the road to rest her eyes. She noticed more and more trouble making eye contact. She has a dull ache in both eyes that sometimes worsens at the end of the day; she has also noticed significant light sensitivity. An ophthalmologist diagnosed blepharospasm 1 year before and tried botulinum toxin A, which helped somewhat. She has noticed some adventitial mouth movements for years. She wants to know if there is anything else to do.

Past medical and ocular history Diagnosed with head tremors 12 years before treated with propranolol Migraine with aura once each year; more recently only an aura without headache Anxiety for 30 years Hyperlipidemia	*Past surgical history* Neck fusion, ankle surgery, gallbladder surgery, hysterectomy
Medications Alprazolam Artificial tears four times each day Cyclosporin eye drops twice daily Propranolol	*Family history* Father with tremor Amyotrophic lateral sclerosis in several family members Cancer in her mother
Social history Married with two children No alcohol or tobacco	*Review of systems* Mild weight gain Breakouts of a rash on her face

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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal with no RAPD
Color vision (HRR) 9/9 bilaterally
Stereo vision Perfect
External exam Minimal rosacea changes of her skin
Eye alignment Normal
Slit lamp examination Meibomian gland dysfunction in both eyes
Visual field Normal to confrontation
Fundus examination Normal
Neurologic examination Mildly diminished movement of her forehead; frequent blinking, frequent lip movements. After squeezing her eyes tightly, she had some difficulty opening them again. The rest of her examination was normal
MR scan Imaging done 2–3 years before showed a normal brain MR and aside from the fusion of the neck, and normal neck MR

Discussion

Neurologic Perspective: Dr. Digre

This patient has the diagnosis of blepharospasm and apraxia of eye lid opening. She also has co-morbid dry eye symptoms, photophobia (see Case 21), head tremor, and some mouth movements (oral-facial dystonia or Meige syndrome).

Blepharospasm is a primary dystonia associated with frequent blinking, squeezing, often heralded with symptoms of dry eye and photophobia. It is the most common form of dystonia and occurs typically more frequently in women and in the fifth to sixth decade. As in our patient, many patients have other movement disorders such as oral facial movements/dystonia or tremor. Many patients have a trick (putting their finger to the eye, singing, reading) to keep the eyes open and not spasming. Our patient did not know of any trick. Visit the Neuro-ophthalmology Virtual Educational Library (NOVEL) where you can view many example videos. For a typical case of blepharospasm with apraxia of eyelid opening see http://content.lib.utah.edu/cdm/singleitem/collection/EHSL-Moran-Neuro-opth/id/71/rec/5.

The first symptoms are usually a scratchy, gritty feeling to the eye and frequently dry eyes (see Case 1) are diagnosed. Photophobia is present in most of these patients. Interestingly, many patients with dystonia and blepharospasm have increased frequency of depression and anxiety like our patient. Some patients with blepharospasm also have apraxia of eye lid opening—described often as the inability to keep the eyes open even when doing such activities as driving. In addition, about one-third of patients can have oral-facial dystonias as she does.

The diagnosis is made clinically with typical symptoms such as our patient and findings of increased blinking, sometimes squeezing. The pain in the eyes in this disorder is probably the dry eye symptoms but it is usually mild. A feeling of grittiness is frequently described and treating the dry eye portion may help some, but the movement disorder continues. In fact, some have speculated that the frequent blinking may exacerbate the dry eye feeling. Rosacea has been reported in 15% of patients with blepharospasm. Occasionally, the pain can be severe and has been associated with corneal neuropathy. These cases may require more aggressive therapy.

The cause of blepharospasm is thought to be a lack of inhibition from malfunctioning of the basal ganglia. Indeed lesions in the basal ganglia, thalamus, and brainstem have been associated with symptomatic blepharospasm. However, most blepharospasm has no obvious changes in the brain. Rarely, further testing is required such as EMG or MR scan—EMG only if there is a doubt about the diagnosis and MR scan if there are other focal neurologic findings.

Treatment with botulinum toxin has been the mainstay in the last 30 years. There are several varieties of botulinum toxin, but the two approved by the FDA currently are onabotulinum toxin and incobotulinum toxin, but there are several others that have been used in Europe and here including: Abobotulinum toxin, Rimabotulinum toxin B. The drug has been highly successful in most patients. There have been few side effects—worsening dry eyes, ptosis. Reinjection occurs variably from person to person but 3–6 months is typical. We also address the dry eyes, by using frequent preservative-free tears frequently and even ointment at night. The light sensitivity can be treated with FL41 tint, which has been studied in blepharospasm and can often reduce blinking and light sensitivity. Infrequently, surgical treatment is necessary for blepharospasm.

Apraxia of eyelid opening is often more difficult to treat and frequently botulinum toxin is helpful. Other drugs have been tried including Aripiprazole which has been reported helpful in Apraxia of eye lid opening associated with Parkinson disease. Sometimes lid crutches are helpful for the apraxia.

Ophthalmic Perspective: Dr. Lee

This is a diagnosis you could make in the grocery store. If you watch the videos, you can see that patients with blepharospasm have uncontrolled spastic eyelid closure. The muscles around the eyes (orbicularis oculi) are contracting. Meanwhile, in

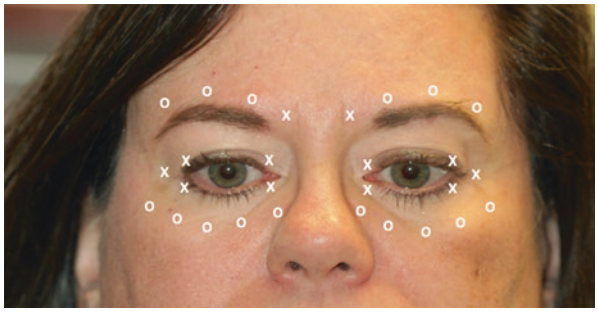

Fig. 6.1 Injection sites for botulinum toxin A injections. *X* typical injection sites of 2.5–5.0 units, *O* additional injection sites for refractory symptoms

apraxia of eyelid opening, the eyes appear passively closed. The patients note that they feel too "weak" to open them.

Many patients do well with botulinum toxin A injections. One could give 2.5 units or 5 units at locations along eyebrows, along the eyelashes, and next to the lateral canthus in the area of the "crow's feet." Generally, physicians do not give more than 100 units at any given sitting, but some of my patients have received as many as 150 units. Figure 6.1 shows the typical locations of injections (x) and some accessory ones (o). Some patients find the botulinum injections painful because the eyelid skin is so thin and sensitive. We will sometimes use a 32-gauge needle or topical lidocaine to numb the skin. The lidocaine needs to sit about 30–45 min on the skin. In other cases, patients have requested oral anxiolytics or oxycodone to take before the injections.

Patients may also have significant degrees of dermatochalasis and ptosis. These patients can undergo a limited orbicularis oculi myectomy, where muscle is removed from around each eye. This is often not covered by insurance, but is billed as a functional ptosis repair while orbicularis is also removed. Myectomy does not eliminate the need for botulinum toxin but can reduce the frequency and the dose required.

Patients with apraxia may require a frontalis sling, where the eyebrows are surgically attached to the eyelids using cadaver fascia lata or silicone slings.

Non-ophthalmic/Non-neurologic Perspective

Primary care physicians can recognize blepharospasm and will likely need the help of an ophthalmologist who is most likely to care for these patients. These patients do not require an MRI unless other neurological features are present. Historically, they were diagnosed with a nonorganic or anxiety issue and treated with oral anxiolytics. In some cases, patients note significant improvement with these agents, but generally require botulinum toxin or surgery.

Follow Up

We treated our patient with continued onabotulinum toxin, FL41 tint for the light sensitivity, and aggressive dry eye therapy (preservative free tears, ointment at night, continued the cyclosporin drops). The apraxia of lid opening could be controlled by singing—she had never recognized that she had a trick. While she was not symptom-free, she became somewhat more functional. *Final diagnosis: eye pain from blepharospasm.*

For Further Study

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Case 7

History of Present Illness

A 61-year-old man complained of new, gradual-onset, left-sided eye pain for 2 days. It is annoying, aching pain that feels like a bruise. The left lower eyelid is tender. The pain is rated as a 2/10. The eye and eyelid does not look red or swollen. There is no effect on vision or double vision. The patient denies ptosis. He has a history of physiologic anisocoria, discovered 15 years prior on routine examination. There is no tearing, proptosis, nasal symptoms, or migraine symptoms. The pain seems like it is perhaps worse with eye movement and it is gradually getting worse. He denies trauma.

Past medical and ocular history Hypertension Hypercholesterolemia History of soft contact lenses Occasional migraine headaches Seasonal allergies History of traumatic iritis RE 10 years ago	*Past surgical history* Wisdom teeth removed as a teen
Medications Atorvastatin Metoprolol Multivitamin Nasal steroid spray Krill oil	*Family history* Father—High cholesterol, diabetes, hypertension Mother—High cholesterol, glaucoma suspect Brother—High cholesterol, diabetes
Social history Married, never smoked, 1–2 drinks a day, 3–4 days a week	*Review of systems* Mild, chronic neck and shoulder pain Dermatographism Difficulty sleeping No fever, chills

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Examination
Acuity with correction Right eye: 20/15 Left eye: 20/15
Pupils Normal
Intraocular pressure Right eye: 14 mmHg Left eye: 15 mmHg
External exam Dermatochalasis
Eye alignment and motility Normal
Slit lamp examination No injection, chemosis, uveitis
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

This is not apt to represent a headache syndrome. This patient has mild localized tenderness of the left eye and more focused on the left lower eyelid. However, the external examination appears fairly unremarkable. It has only been a day or two, and it is possible that this represents forme fruste preseptal cellulitis or stye. I would palpate over the lacrimal gland (superotemporal eyelid) and the trochlea (superonasal eyelid). I would also look at the lacrimal gland to see if it is enlarged. We are told that he does not have uveitis, but in some cases, iritis can present with mild tenderness. I would also consider a foreign body. The patient wears contact lenses and occasionally contact lenses become "lost" under the upper eyelid. I would evert the eyelids, and if no cause is found, then I would double evert the eyelid with a Desmarres lid retractor. I would also sweep the upper fornix to make sure that no foreign bodies have hidden there.

If we cannot find a cause, then I would recommend hot compresses and artificial tears and observation…basically ordering the test of time. Time will tell whether this represents something more sinister. I do not have anything to push me toward a scan or blood work. I would not order a CBC or give antibiotics.

Neurologic Perspective: Dr. Digre

Palpation around the eye is always a great idea in eye pain like this. A few things I do would be to palpate the trochlea since trochleitis can cause pain and it is easy to palpate. I would also gently palpate the lid of the left eye to see if I could find some focal tenderness. Also, to rule out a vascular or migraine cause I frequently compress the superficial temporal arteries or superior and inferior orbital arteries to see if this improves the pain. If it does, my experience suggests that this is migrainous or vascular. While this man has migraine, he is not complaining of any migraine features like light and sound sensitivity or nausea. This does not sound like any trigeminal autonomic cephalgias—it is a new pain for him. I would keep looking at the eye!

This sure sounds like a foreign body in the eye. And I agree with lid eversion. I would also check for dry eyes since sometimes individuals complain about this type of pain with dry eyes.

Non-ophthalmic/Non-neurologic Perspective

With such a normal looking eye and lack of other findings, I would recommend flipping the eyelid. To flip the upper eyelid, you have the patient look down, then you grab the eyelashes with your hand. The patient continues to look down, while you push down on the eyelid crease and pull up on the eyelashes. A video of this can be seen at this link: https://www.youtube.com/watch?v=XU-hZ4ryx48. To sweep the upper fornix, you can put a numbing drop in the eye, have the patient look down, and sweep a proparacaine covered cotton tip under the upper eyelid. If you are comfortable looking for uveitis, then I would use a slit lamp. If not, then consider sending the patient for an eye exam. This is not an emergency!

Follow Up

The patient's lower eyelid was everted and there was a localized area of redness with a white spot in the center. This was sitting along the conjunctiva running on the inside of the eyelid (Fig. 7.1). This is consistent with an early chalazion. The eyelid was not swollen (yet) and there was no localized, erythematous external bump (yet). After proparacaine was given, the patient had the chalazion "popped" using two cotton tips. The pain resolved after a day or two.

The eyelid contains a firm, rubbery tissue called the tarsus. Meibomian glands in the tarsus can become occluded and swell. Initially, the swelling appears on the conjunctival surface of the eyelid and later become visible externally. They can be painful acutely and painless, if they become chronic. Normally, these drain on their

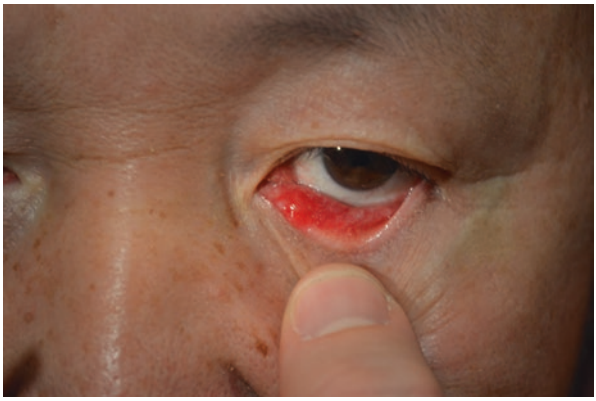

Fig. 7.1 The lower eyelid is everted and shows a focal area of redness and elevation nasally along the conjunctival side of the eyelid consistent with an acute stye (Courtesy Ali Mokhtarzadeh, MD)

own, while some persist and may require an incision and drainage. Local injection of corticosteroids is another option. If they are recurrent in the same location or not located along the tarsus, then it may require biopsy to rule out other causes. *Final diagnosis: chalazion*.

Digre's last thought: Interestingly, chalazion contrary to a lot of people's belief can and do cause eye pain. We recently reviewed eye pain in two large eye centers and it was definitely in the top 5 causes of eye pain going to ophthalmology. There is not a lot of literature about pain in this disorder.

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Case 8

History of Present Illness

A 36-year-old, morbidly obese man noted pain behind his right eye and along his right temple for 3 months. It is constant with intermittent worsening for several hours at a time. The pain worsens with eye movement upward and with touching the eye. He denies vision loss, tearing, redness, eyelid swelling, double vision, or intracranial bruit. He has significant photophobia, but no phonophobia or osmophobia. He denies nausea or vomiting. He notes a history of temporal mandibular joint (TMJ) issues. He underwent an MRI and MRV brain, which showed a partially empty sella. He has tried prednisone starting at 100 mg daily with taper over several weeks, rizatriptan, and acetazolamide without benefit.

Past medical and ocular history	*Past surgical history*
Diabetes mellitus	Sinus surgery
Hypertension	Colonoscopy
Gastric ulcer	Appendectomy
Sleep apnea	Cholecystectomy
Depression	

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Medications Simvastatin Losartan Trazodone Prednisone 10 mg Lamotrigine Insulin Fluoxetine Clonazepam Vitamin D Rizatriptan Cetiritzine Multivitamin	*Family history* Diabetes Hypertension Migraine
Social history Never smoked, casual drinker, works at a computer all day	*Review of systems* Dry mouth Pain with chewing Shortness of breath with exertion Diffuse joint pain Diffuse muscle aches Low back pain Diarrhea on and off for years Reflux type pain for past few weeks

Examination

Acuity with correction Right eye: 20/25-1 Left eye: 20/20
Pupils Equal, round, briskly reactive, no afferent defect
Color vision Normal
Intraocular pressure Right eye: 19 mmHg Left eye: 21 mmHg
External exam No edema, no redness, no ptosis Severe tenderness to palpation deep to the right superomedial orbital rim
Eye motility and alignment Normal, but pain with eye movement up and down when looking to the left
Slit lamp examination Normal, no injection, corneal staining
Visual field Normal
Fundus examination Normal, no diabetic retinopathy
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

"Pain with eye movements" often represents a knee-jerk reaction for optic neuritis. Indeed, optic neuritis can also have tenderness to palpation of the globe. However, in this case, the patient is not complaining of visual loss nor demonstrating evidence of optic nerve dysfunction (color vision loss, afferent pupillary defect, visual field defect, acuity loss). The pain from optic neuritis may last up to 2 weeks, so this would be incredibly atypical. Other causes for pain with eye movements would include myositis (inflammation of an extraocular muscle), trochleitis, or orbital inflammation/infection. Of course, pain is such a squirrely symptom that patients with migraine, dry eye, and occipital neuralgia may complain of pain with eye movement as well—i.e. the symptom is not specific!

The patient is not demonstrating evidence of orbital inflammation such as proptosis, eyelid edema, conjunctival redness, or swelling. This could represent myositis or trochleitis. The trochlea is a fibrous band in the superomedial orbit through which the superior oblique tendon passes. Some patients may suffer inflammation of the trochlea and develop acute on chronic pain, worsened by eye movement. The patient herein has exquisite tenderness over the area of the trochlea, which strongly supports the diagnosis. Often, inflammation of the trochlea cannot be observed on neuroimaging or ultrasonography and is predominantly a clinical diagnosis. Myositis can affect the muscle belly or tendinous insertions of any of the six extraocular muscles. This causes enlargement and enhancement of the affected muscle on CT, MRI, or orbital ultrasound.

Normally, I would not order an MRI since I feel strongly that this is trochleitis. However, since we have it, I would take a look at the MRI for any missed eye muscle inflammation or fat stranding in the orbit. If this appears normal or if I do not have an MRI, then I would offer the patient an injection of corticosteroids to the trochlea. In many cases, patients are worried about an injection to the periocular region so I might offer a course of oral steroids or indomethacin. If the patient fails this, then they often opt for the injection at that point. I inject 0.5–1.0 mL of triamcinolone 40 mg/mL using a 25-gauge ½ in. needle. Triamcinolone is a suspension, so you cannot use a 30-gauge needle because it will not pass through. There have been case reports of periocular injections causing central retinal artery occlusions, so others use dexamethasone 4 mg/mL. Dexamethasone is short acting and triamcinolone is long acting, which is why I like to use it. Some of my colleagues mix the corticosteroids with 0.5 mL lidocaine 1 or 2% (without epinephrine) in the same syringe for a total of 1 mL. Lidocaine, if injected into an eye muscle will cause severe myotoxicity. Fortunately, it is the tendon that runs through the trochlea and there is a lower chance of a myotoxic event.

If you are going to give the injection, make sure the needle is directed superomedially and you draw back before injecting since the supraorbital vein lies temporal to the trochlea. Generally, the injection does not hurt, it does not bleed, and does not get infected. More than one injection may be required, but I like to wait at least 30 days between injections. It is my belief that everyone is entitled to get trochleitis once in their life and do not require a workup. If it is recurrent, then one could consider evaluation for rheumatoid arthritis, lupus, and sarcoidosis.

Table 8.1 ICHD 3 Diagnostic criteria for trochleitis

A.	Periorbital and/or frontal headache fulfilling criterion C
B.	Clinical and/or imaging evidence of trochlear inflammation
C.	Evidence of causation demonstrated by *at least two of the following*:
	1. Unilateral ocular pain
	2. Headache is exacerbated by movement of the eye, particularly downward in adduction
	3. Headache is significantly improved by injection of local anesthetic or steroid agent into the peritrochlear region
	4. In the case of a unilateral trochleitis, headache is localized ipsilateral to it
D.	Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Neurologic Perspective: Dr. Digre

Trochleitis is not rare, but it is not common either. The ICHD 3 beta suggests that the diagnosis can be made by having the pain resolve after an injection of the trochlea (see Table 8.1 for ICHD 3 criteria). In fact, he really meets all of the criteria for trochleitis. It is important to know that trochleitis can also worsen migraine. He does not really sound like he has migraine headache (even though he has a family history of migraine), and that is probably why the rizatriptan was not successful. However, trochleitis can also contribute to migraine. In fact, the patients that I have seen usually have underlying migraine. Having migraine does not keep an individual from having trochleitis and looking for causes that make headaches more chronic can really be helpful—get rid of the trochleitis and the continuous irritation of the trigeminal nerve, and the chronic migraine may improve. Many of the cases reported by Smith et al. had concurrent migraine. The other condition that he has is TMJ. However, in this case the pain would not be in the eye, but in the jaw. I think the key here was palpation of the trochlea during the examination that helped to make the diagnosis. It is also important to not over diagnose trochleitis. One study showed that individuals with migraine had tenderness around the trochlea and this is not trochleitis, but they propose that migraine causes sensitization of the superior oblique muscle and this irritation may worsen migraine.

Non-ophthalmic/Non-neurologic Perspective

We think it is important to palpate around the eye in patients with eye pain especially in the area of the trochlea, the lacrimal gland, the supraorbital, and infraorbital nerve (Fig. 8.1). Usually, the eye should appear white and quiet as in this case. There often is no swelling in the superonasal eyelid. The key to the diagnosis will be palpation of the trochlear region and the history of pain with eye

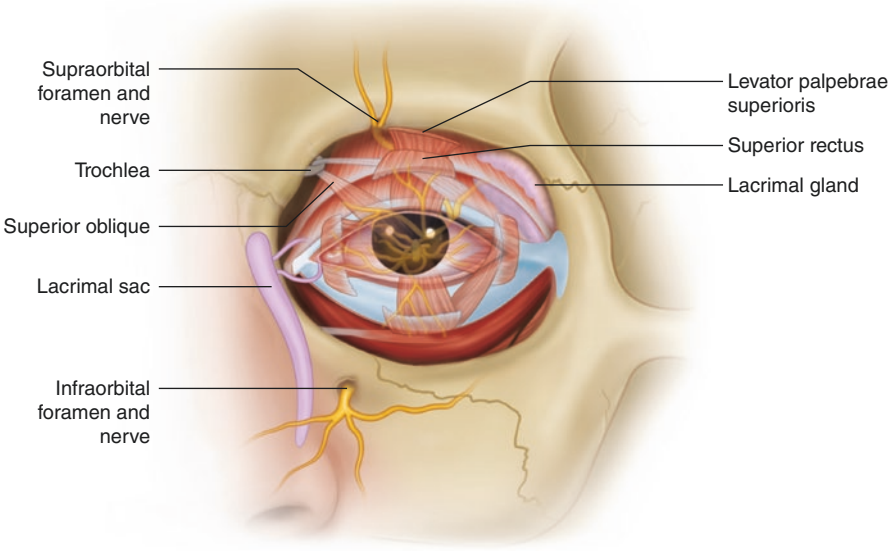

Fig. 8.1 Anatomy of trochlea. The trochlea sits under the superonasal orbital rim. Note the location of the supraorbital and infraorbital nerves, which can become inflamed in other disorders. The lacrimal gland sits under the superotemporal orbital rim

movements. Not all ophthalmologists or pain specialists will deliver this trochlear injection so you may want to ask around before sending the patient to someone. Neurologists may not be familiar with the diagnosis and usually will not give periocular injections.

Follow Up

Review of his MRI showed that the trochlea was not imaged (not uncommon) on the axial or coronal views. The patient elected for a trial of indomethacin without benefit. An injection of 1 mL of triamcinolone 40 mg/mL on a 25-gauge ½ in. needle was delivered to the area of the patient's trochlea. There was no bleeding. The patient noted gradual improvement in the pain over the course of 1 week. He returned for a repeat injection 1 month later because of a recurrence of pain (not to the same level as before). He remained pain-free at 6 months follow up. *Final diagnosis: trochleitis or primary trochlear headache.*

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Case 9

History of Present Illness

A 22-year-old woman developed pressure pain in the right eye × 3 months. It was tender to palpation and she felt like there was lump in the right upper eyelid. She notes that she had mild double vision when looking to the right and that her vision seems mildly blurred in that right eye. She tried hot compresses and a steroid-antibiotic ointment on the right upper lid, but the pain and the lump did not improve. Overall the pain has not changed substantially. She has a history of migraines, but these have not changed recently. She denies any migraine accompaniments (light or sound sensitivity or nausea) with this eye pain. She has a history of a blocked tear duct in the right eye for which she underwent a probing and irrigation at 8 months of age.

Past medical and ocular history Per HPI	*Past surgical history* Per HPI
Medications Sumatriptan prn headache Ondansetron prn headache Birth control	*Family history* Grandfather—Macular degeneration
Social history Manages meetings and events Does not smoke or drink	*Review of systems* Completely negative

Examination

Acuity with correction Right eye: 20/150 improving with pinhole to 20/20 Left eye: 20/20
Pupils Normal
Intraocular pressure Right eye: 17 mmHg Left eye: 20 mmHg

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External exam 3 mm proptosis, right eye (Fig. 9.1a) Firm lump in the superotemporal area right eye, inferior to the eyebrow and superior to the tarsus
Eye alignment and motility 25% deficit of abduction and elevation, right eye Right esotropia and hypotropia in right and upgaze Orthophoric in primary gaze
Slit lamp examination Normal
Visual field Normal
Fundus examination Choroidal folds in the macula, right eye
Neurologic examination Normal facial sensation Otherwise unremarkable

Discussion

Ophthalmic Perspective: Dr. Lee

She has developed blurred vision likely from something pushing on the back of the eye causing hyperopia. She also has double vision and is unable to move her eye up and to the right, suggesting that she has a mass there. The photo shows mild edema of the fat above the eyelid and below the orbital rim. There is mild ptosis of the right upper eyelid. The eyes appear straight as she looks straight ahead (Fig. 9.1a). It seems likely that she has a lacrimal gland mass.

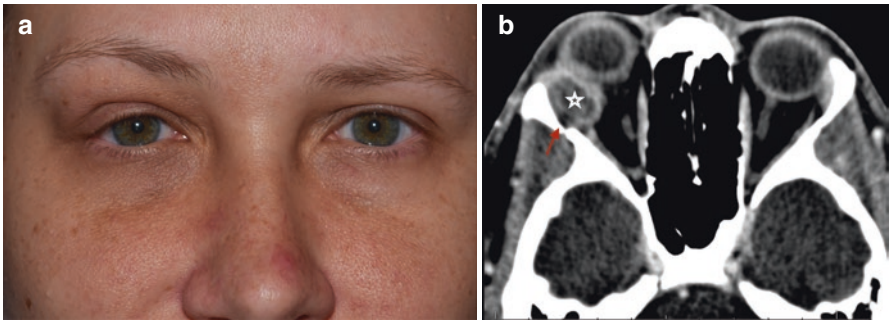

Fig. 9.1 (**a**) External images of the face show subtle enlargement of the brow fat above the eyelid. The right upper eyelid shows mild ptosis. (**b**) Axial CT of the orbit shows a cystic mass in the area of the lacrimal gland, lateral and posterior to the right globe (*star*). There is erosion of the lateral orbital wall (*red arrow*)

The most common would be a benign mixed tumor given the firmness of the tumor. Adenoid cystic carcinoma is in the differential, but these are usually much more painful because of neural invasion. The average age is 40 years, so our patient is young to have that. The differential could also include lymphoid hyperplasia, lymphoma (not this firm), sarcoidosis (not this firm), infection (usually more obvious), and other epithelial malignancies or metastases. See Fig. 8.1 for relationships of the lacrimal gland and adjacent anatomy. We should really start with CT of the orbit to look better at the bony orbital involvement and consider an excisional biopsy. MRI does not give us a good view of the bone, but would be acceptable to show lacrimal gland involvement. If there were more pain, redness, or a hot looking abnormality then one might consider antibiotics for an orbital cellulitis or corticosteroids for lacrimal gland inflammation. This would not be consistent with a preseptal lesion, because it is causing double vision. The double vision pushes us that there is something in the orbit.

Neurologic Perspective: Dr. Digre

First, her decreased vision is related to her choroidal folds in her macula; her vision was correctable to 20/20 with pinhole and she has no RAPD. This is one more reason why anyone with changes in the vision and eye pain needs a full, dilated eye examination. Then she has diplopia—just looking at her, you can see something is wrong because there is fullness over the lateral aspect of her orbit and that this diplopia is not from a cranial nerve abnormality. Imaging is the first step in determining the cause and CT of the orbit with bone windows would be what I would order. Fortunately for her, the slight discomfort she is experiencing is not making her migraines worse. Many of my patients with any kind of secondary pain will have worsening of migraines. If the discomfort got worse, I would suggest an anti-inflammatory medication (e.g., ibuprofen or naproxen).

Non-ophthalmic/Non-neurologic Perspective

This patient started with mild “eye” ache with some tenderness to touch of the right upper eyelid area. Just hearing the story, the most common thing to consider would be a stye. She tried hot compresses and eye ointment without benefit and now we are 3 months later. Early on styes can present with just some mild eyelid edema, but these are usually very close to the eyelid margin. In this case, she has some mild edema of the area inferior to the eyebrow, which would not be a stye since it does not involve the tarsus. This is the area of the right lacrimal gland. If you pull up on the eyelid and have the patient look down, you can get a better idea of whether the lacrimal gland is enlarged. In many cases MRI is better than CT, but with lacrimal gland disorders, it is better to get a CT orbit.

Follow Up

The patient underwent an orbital CT (Fig. 9.1b). This showed a 2.5 × 2.0 × 2.6 cm enhancing mass in the area of the lacrimal gland with adjacent orbital roof erosion. She underwent an excisional biopsy of the lacrimal gland, which showed adenoid cystic carcinoma, basaloid type.

Historically, the 5-year survival was 17–20% with chemotherapy, radiation, and exenteration. With neoadjuvant intra-arterial doxorubicin and cisplatin, the survival rate has improved to 57–100%. The patient underwent intra-arterial therapy followed by orbital exenteration (removal of the eye and all of the orbital contents) and radiation therapy. Two years later, she experienced a recurrence in her right mandible. This was resected and she remained in remission at 4 years follow up. *Final diagnosis: adenoid cystic carcinoma of the lacrimal gland*.

Digre comment: Adenocystic in a 22-year-old is very rare. This case reminds us that we must be ever vigilant and that all tumors of the orbit and lacrimal gland need work up.

For Further Study

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Case 10

History of Present Illness

A uveitis specialist sent a 13-year-old boy for eye pain. He had normal development. He started with eye pain at age 4 and was treated for allergies for 2 years. At age 6, he was diagnosed with non-granulomatous uveitis and was evaluated for systemic disease but none was found. He started having eye pain—usually one eye at a time occurring 1–2 times each year from age 6 to 12. He was treated with naproxen and prednisolone acetate drops for minor ocular inflammation. In between his bouts of inflammation, he was pain-free. At age 12 he developed episcleritis in the right eye and intermediate uveitis. Treatment with meloxicam and systemic prednisone completely quieted his eyes down. He had an orbital ultrasound and MR scan looking for orbital inflammation, but none was found. His work up included normal CBC, CMP, ESR, lysozyme, ACE, ANA, quantiferon gold, HLA B27, Serum IgG4, ANCA, and MPO. He had a negative RPR, FTA, toxoplasmosis, and toxocara titer. He was seen by a rheumatologist who started methotrexate and began tapering the steroids. When steroids were tapered to 5 mg, the eye pain recurred without increased ocular inflammation. Repeat ultrasound showed minimal scleral thickening. An orbital specialist evaluated him and no orbital disease was found. He was referred to neuro-ophthalmology for further evaluation since he had eye pain and no active uveitis or episcleritis.

The pain was a steady, constant ache in the left eye—he had no headache. He had no light or sound sensitivity and it did not worsen with activity, but sometimes the eye would tear. The pain lasts hours to days; and a cool rag over the eyes sometimes worsens it. A burst of 60 mg of prednisone would quiet the pain, but when he tapered below 15 mg, the pain would recur. Most of the time, it would occur in the left eye but he had bouts of right eye pain. His vision he says is normal.

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_10

Past medical and ocular history Non-granulomatous uveitis	*Past surgical history* Inguinal hernia repair
Medications Calcium/Vitamin D Cellcept 500 mg Prednisone 15 mg	*Family history* Mother with migraine
Social history 7th grade	*Review of systems* Otherwise negative

Examination
Acuity with correction Right eye: 20/20-2 Left eye: 20/20
Pupils 5 mm OD, 6 mm OS in darkness; 4 mm OD, 5 mm OS in light; No RAPD
Color vision (HRR) 8/10 OD and 9/10 OS
Stereo vision Normal—9 circles by Titmus Test
Intraocular pressure Right eye: 17 mmHg Left eye: 17 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination One deep scleral vessel mildly enlarged left eye, otherwise normal without cell or flare
Visual field Normal to confrontation
Fundus examination Normal optic disc with 0.2 cup to disc ratio; normal macula and vessels
Neurologic examination Normal neurological examination

Discussion

Neurologic Perspective: Dr. Digre

My first thought was—is this migraine coming on when the patient has a history of inflammatory uveitis. His mother had migraine and he could not read in the car (often seen in migraine). However, he had NO headache whatsoever, no migraine features of light and sound sensitivity, no nausea, no worsening with activity. I also thought about a form of cluster or autonomic cephalgia, but the pain could be on the right or left side, lasted hours to days and completely went away after being on high dose steroids.

We also wondered about scleritis or episcleritis, but his imaging (MR, ultrasound) were said to be normal. He had no active uveitis. His intraocular pressures were normal. I tried him on indomethacin in case this was an unusual case of hemicranias continua. There was only a partial response.

Ophthalmic Perspective: Dr. Lee

Recurrent uveitis would be the most common situation causing eye pain, but the slit lamp examination was normal. However, I think inflammation of "something" seems likely given the steroid responsive nature of his pain.

Episcleritis and anterior scleritis cause eye redness, but episcleritis is not very painful while scleritis often becomes increasingly painful. If it is not clear, then a drop of 10% neosynephrine will blanch the vessels in episcleritis but will not affect deeper vessels in scleritis. Why is this important? As a general rule, episcleritis is not associated with a systemic disease. Scleritis can be idiopathic or associated with a systemic condition and also lead to visual loss.

In the absence of eye redness, then one could consider posterior scleritis or even orbital inflammation. Often inflammation of the orbit will cause orbital signs such as diplopia and ophthalmoplegia, proptosis, chemosis, and eyelid edema. Sometimes, myositis will cause eye pain with eye movements with a white and quiet eye.

Non-ophthalmic/Non-neurologic Perspective

Scleritis is not a frequent cause of eye pain. This is a situation where having an ophthalmologist examine the patient can be very helpful. Think about scleritis or eye inflammation in patients with autoimmune disease who have new onset of eye pain or red eye.

Follow Up

This is when I went back to the MR scan to review carefully**.** The MR scan showed faint enhancement of the sclera and also the perioptic nerve sheath (Fig. 10.1). The indomethacin helped a little, but did not stop the eye pain. We also repeated his ultrasound, and now he had classic findings of posterior scleritis. Posterior scleritis will only be visible on imaging of the posterior globe—as in this case on the MR scan.

Table 10.1 gives the ICHD 3 beta criteria for scleritis and eye pain/headache. Scleritis can often be misinterpreted as one of the autonomic cephalgias. But as in this case, indomethacin was only partially helpful. Scleritis can occur in children as well.

In a large review of scleritis, Lavric et al. reported that scleritis was more common in women (71%), less likely to be bilateral (15.8%), and often associated with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematous,

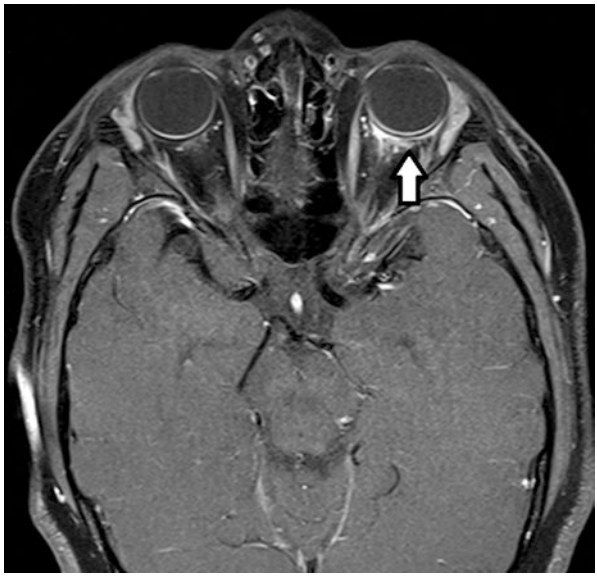

Fig. 10.1 Axial, postgadolinium T1 MRI of the orbits shows mild enhancement of the posterior sclera in the left eye (*arrow*). There is also perineural enhancement at the nerve/sclera junction

Table 10.1 ICHD 3 beta headache attributed to ocular inflammatory disorder

Diagnostic criteria:
A. Periorbital headache and eye pain fulfilling criterion C
B. Clinical, laboratory, and/or imaging evidence of ocular inflammatory diseases such as iritis, uveitis, cyclitis, scleritis, choroiditis, conjunctivitis, or corneal inflammation
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to the onset of the ocular disorder
2. Either or both of the following:
(a) headache has significantly worsened in parallel with worsening of the ocular disorder
(b) headache has significantly improved or resolved in parallel with improvement in or resolution of the ocular disorder
3. Either or both of the following:
(a) headache significantly improves with topical application of local anesthetic agent to the eye
(b) headache is aggravated by pressure applied to the eye
4. In the case of a unilateral eye disorder, headache is localized ipsilateral to it
D. Not better accounted for by another ICHD-3 diagnosis
According to the ICHD 3Beta—Description: Headache caused by ocular inflammatory conditions such as iritis, uveitis, scleritis or conjunctivitis and associated with other symptoms and clinical signs of the disorder
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

angiitis and or infection. Relapses occur in about 1/3. Pain in the eye is present in over half; fewer (about 1/3) have blurred vision and light sensitivity is not common. Sometimes one can see subtle disc swelling and even folds in the retina and serous retinal detachment in posterior scleritis. Occasionally there can be longer lasting pain (neuralgiform type) that challenges treatment.

In this case, he could not be tapered below 15 mg prednisone daily. If a patient cannot get below 7.5 mg prednisone daily, then we would consider asking a rheumatologist to institute a steroid-sparing agent. The patient might also benefit from a periocular steroid injection to reduce the systemic load. *Final diagnosis: posterior scleritis*.

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Part II
Ophthalmic Disorders Causing Eye Pain: Abnormal Eye Exam

Case 11

History of Present Illness

The patient is a 49-year-old, right-handed, special education teacher. She presented initially with spells of kaleidoscopic prisms centrally in the right eye 2 days before she was seen. At this point she had no pain, but a dull ache over the right eye. She was treated with aspirin and the spells resolved. About 10 days later she presented to the emergency room with severe right eye pain. The pain was worse with eye movements and she denied any visual loss. She did have some mild swelling around the eyelid and some tearing, but the pain was really severe.

Four years before she presented with diplopia and eye pain. Her examination at that time showed an esotropia (eye crossing) and a mild hypertropia (vertical misalignment). Imaging showed inflammation of the medial rectus muscle. She was diagnosed with orbital myositis, treated with steroids and diplopia and pain resolved.

While she has had migraines in the past, the pain does not feel like migraine.

Past medical and ocular history Wrist fracture Previous orbital myositis Migraine in the past	*Past surgical history* History of uterine ablation for dysfunctional bleeding
Medications Vitamin C	*Family history* Her mother died at age 60 from complications of multiple sclerosis; heart disease in father
Social history Currently single with 3 children Non-smoker No alcohol	*Review of systems* Otherwise feels healthy

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Examination in the Emergency Room
Acuity with correction Right eye: 20/20 with correction Left eye: 20/20
Pupils 6 mm in darkness and 3 mm in light 7 mm in darkness 4 mm in light No RAPD
Intraocular pressure Right eye 20 mmHg Left eye 21 mmHg
External exam Normal—Hertel 14 OU at base of 92 Right eye: She had 1+ erythema and edema of upper and lower eyelid and mild resistance to retropulsion
Eye alignment She had −1 limitation of downgaze in the right eye but was full in other directions. While she was orthophoric in primary gaze she had a small less than 4 diopters of right hypertropia in downgaze
Slit lamp examination Mild chemosis of right eye only. LE was white and quiet. No cell or flare either eye
Visual field Normal
Color vision Ishihara 13/13 OU
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective: Dr. Digre

This patient has visual disturbances and then presents with severe eye pain. Her initial presentation of kaleidoscopic vision was not associated with any eye pain, and it was thought that this could be a migrainous phenomenon so a baby aspirin was started which often improves migrainous aura. At that time she also had a fluorescein angiogram because of the unilateral nature of the visual change, and this was normal.

When she presented to the ER 10 days later with severe pain with eye movements, our first reaction is—this must be optic neuritis. However, she had absolutely no other signs of an optic neuropathy (normal vision, no RAPD, normal fields, and normal color vision).

There are only a few things that could cause eye pain with movement and normal optic nerve function—inflammatory conditions like thyroid eye disease, sinus disease,

cellulitis or infections, vasculitis like granulomatosis with polyangiitis (Wegener's), and sarcoid can all cause pain. Optic perineuritis (inflammation around the optic nerve, without demyelination) can also present like this. Other findings to look for include proptosis, chemosis (inflammation of the conjunctiva), scleral show, lid lag, and swelling around the eye. See Table 11.1.

Thyroid orbitopathy is the most common orbital disorder but it is usually not that painful. The next most likely thought would be idiopathic orbital inflammation, also known as orbital pseudotumor, or orbital myositis. It really is the most common cause of a painful orbital process. While it occurs at any age and sex (women slightly more than men), it often occurs in middle age. When it occurs in children, it is often bilateral, and has evidence of uveitis and even disc edema. The onset can be slowly gradual to acute or subacute. Imaging has been very helpful in defining idiopathic orbital inflammatory disease. Orbital ultrasound is very sensitive to subtle inflammatory disease, but one needs a competent orbital echographer. CT of the orbits with contrast may show enhancing enlarged muscles or a mass in the orbit. MR scan of the orbits with fat saturation and gadolinium enhancement also may be diagnostic—muscle involvement usually does NOT spare the tendon (vs. thyroid ophthalmopathy which does). Further it has several distinct patterns: muscle only involvement where single muscle or multiple muscles are enlarged and enhancing, lacrimal gland enhancement, and sometimes the sclera will also enhance. The optic nerve sheath can also be involved and this is often called peri-neuritis. Sometimes it is very difficult to distinguish optic peri-neuritis from optic neuritis. However, optic neuritis almost always causes visual loss, a relative afferent pupillary defect (RAPD) and change in color vision, while optic peri-neuritis may have NO evidence of optic nerve dysfunction. If the enhancement has intracranial extension and cranial nerves are also involved, this is idiopathic cavernous sinus inflammation and called Tolosa Hunt Syndrome. Occasionally idiopathic orbital disease can be fibrotic and this type does not always respond to steroids.

Optic perineuritis can be a component of idiopathic orbital inflammation and is very painful—especially with eye movements. While most of the time it is self-limited with good recovery, secondary causes such as granulomatosis with polyangiitis and Behçet's disease can cause severe visual loss.

While there are no official diagnostic criteria, some have suggested: acute orbital pain including pain with eye movements, one or more muscles enlarged in the orbit evident on CT or MR scan, in the face of absent thyroid disease, scleritis or uveitis, normal visual acuity, and a prompt response to steroid therapy.

Aside from imaging, other labs to consider include: CBC, ESR, ANA, ANCA, IgG4, syphilis serology, and lumbar puncture may be helpful to diagnose a secondary cause.

Occasionally a biopsy is needed to make the diagnosis of idiopathic inflammatory disease—for example, when it is not clear if this is a lymphoproliferative (lymphoma), metastatic, or sarcoid orbital disease. The idiopathic form may occur after respiratory or viral illness, may cluster with other immunological disorders (e.g. Crohn's disease).

Recently, IgG4 disease has been recognized to cause idiopathic inflammatory conditions of the orbit and many other organs (e.g. pancreas, salivary glands,

Table 11.1 Causes of orbital inflammation/proptosis and eye pain

Cause	Pain	Symptoms	Signs	Imaging	Laboratory	Comments
Thyroid—most common orbital disorder	Usually mild or absent	Dry eyes, eyes unusually prominent eyes, diplopia	Proptosis, lid retraction, lid lag; muscles usually involved in order include inferior, medial, superior, lateral, obliques	Enlargement of the muscle, but spares tendon	T4, TSH, TRAB, TSI	Most common cause of orbital inflammation; watch for optic nerve compromise; may need orbital decompression or radiation; occasionally steroids helpful
Orbital myositis (idiopathic inflammatory disease)	Can be acute and very painful Pain with eye movement	Usually unilateral eye pain, diplopia, and redness by muscle insertion	Mild proptosis	One muscle, can involve perio-optic nerve, and mass like in the entire orbit; muscle tendon is NOT spared; enlarged lacrimal glands	CBC, ESR, CRP	Steroids are usually helpful
Tolosa Hunt Syndrome	Painful	Diplopia	Cranial nerve palsy—III, IV, VI	Usually shows abnormality into the cavernous sinus	Usually need to rule out malignancy	Look for malignancy, or lymphoproliferative disorder; steroids usually resolve true Tolosa Hunt Syndrome
Sarcoid	Variable but can be painful	Diplopia	Any pattern of muscle involvement; can involve optic nerve	Enhancement of orbital structures; lacrimal glands	ACE, CXR, Chest CT	After diagnosis, treatment with steroids
Vasculitis (e.g. Granulomatosis with polyangiitis (Wegener's disease))	Painful	Diplopia, Red eye	Unilateral or bilateral muscle involvement; episcleritis, scleritis, uveitis	See orbital enhancement and often sinus disease	ANCA, UA	Steroid treatment cyclophosphamide, and rituximab
Infectious (cellulitis)	Painful	Red eye, fever	Proptosis, usually unilateral, chemosis	Can involve whole orbit; image sinuses	Increased WBC; culture and biopsy	Staph, Strep, mucor, aspergillosis; Treat with antibiotic, antifungal, occasionally need surgery
Metastatic disease to orbit	Variable pain	Diplopia	En-ophthalmous, proptosis	Mass in the orbit with bony erosion	Imaging; PET body scan for primary	Breast and lung most frequent

thyroid, etc.). It is often treated with rituximab and steroid treatment can sometimes delay the diagnosis.

Treatment of idiopathic orbital inflammatory disease is usually corticosteroids in doses of prednisone 1 mg/kg for 2–3 weeks with a slow taper. The pain often readily responds and the diplopia improves later. If patients do not respond to this, consider biopsy or another diagnosis or the fibrotic type. Steroid-sparing agents include azathioprine, methotrexate, and infliximab. If the pain recurs or is insufficiently treated with steroids consider other anti-inflammatory medications including naproxen, indomethacin, or gabapentin. Recurrences can occur as well in less than half—but do not be surprised if the inflammation recurs.

Ophthalmic Perspective: Dr. lee

The swollen eyelids could suggest a preseptal cellulitis, but the reduced eye movements here indicate an orbital process. With the pain and redness, you should think about orbital infection vs. orbital inflammation. Some clues to an orbital infection would include fever, elevated white count, and sinus disease on neuroimaging. A CT scan might show a subperiosteal abscess, which would definitely push you toward infection. If this is seen, then the patient will need surgical removal of the abscess. In some cases, you just cannot tell if this is infection vs. inflammation. The safer thing to do is to treat with antibiotics first for 1–2 days. If there is no improvement or worsening, then consider prednisone.

There is no clear evidence for how much steroids and how long to treat with steroids for orbital inflammation, so I will give you my management plan, which differs slightly from Dr. Digre. I treat with 60–80 mg prednisone orally for 1 week. If the inflammation resolves and stays away, then I observe and do not do a systemic workup. If it recurs, then I restart the prednisone and taper slowly over 6–8 weeks. If it recurs again, then I pursue a biopsy because I am most worried about lymphoma. We generally think of lymphoma as painless, but it can be painful. If the biopsy is negative, then I might offer the patient an even longer taper of steroids, orbital radiation (2000 cGy over 10 days), or immunosuppression with a steroid-sparing agent. If the patient is very intolerant of steroids, one could consider injection of 40 mg of triamcinolone in the peribulbar region. I also pursue a systemic workup as described above for recurrent orbital inflammation.

Non-ophthalmic/Non-neurologic Perspective

Orbital inflammatory disease is not rare. The most common symptom is diplopia and pain. The signs are usually proptosis, lid retraction, scleral show, and variable extra-ocular movements. Always check visual acuity and look for an RAPD—if there is loss of vision, and an RAPD, then refer the patient for further evaluation for an optic neuritis. The most common orbital disease is thyroid ophthalmopathy

which is usually not that painful. If you see signs of orbital disease and pain, be thinking about other orbital inflammatory disease, of orbital myositis, or orbital pseudotumor is the most common. See Table 11.1.

Follow Up

The history of a previous myositis 5 years before made the suspicion for orbital inflammatory disease. Her evaluation showed an MR scan that showed enhancement of the orbit and perioptic nerve (Fig. 11.1). Extensive laboratory studies showed: Normal CBC, ESR, CRP, RPR, RF, ACE, anti-thrombin elevation, and factor V Leiden and ANCA. Her protein C was mildly elevated. She was treated with prednisone 60 mg which quickly stopped her pain. She was seen back in clinic 10 days later and her examination now was normal—no evidence of a phoria, or chemosis or redness to the eyes. The prednisone was slowly tapered by 10 mg each week. She remained recurrence free for the last 6 months. *Final diagnosis: idiopathic orbital inflammatory syndrome*.

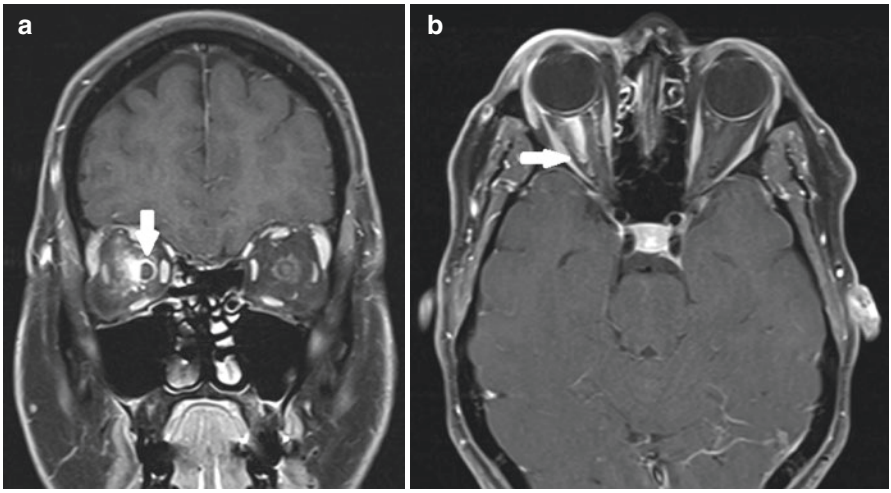

Fig. 11.1 (**a**) Coronal T1 with fat saturation showing the enhancement of the optic nerve sheath (*arrow*) and surrounding orbital tissue. (**b**) Axial T1 with fat saturation showing enhancement of the optic nerve sheath (*arrow*). Note there is mild evidence of proptosis compared to the opposite orbit

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Case 12

History of Present Illness

A 58-year-old woman began complaining of gradually worsening right eye pain for 6 years. She was diagnosed with dry eye syndrome. Artificial tears and warm compresses help to some degree. The pain is a deep ache in and behind the right eye which can increase to 5/10 at times. The pain is intermittent lasting several weeks at a time and then gradually resolving. She notes mild tearing, but no foreign body sensation or itching. She has a history of classic, right-sided migraine headache for the past 20 years. Brain MRI 5 years ago was normal. She has significant photophobia with the eye pain but denies nausea, vomiting, or phonophobia.

Past medical and ocular history Back pain Osteoarthritis in the knees and hips Hypertension	*Past surgical history* Cataract removal right eye 2 years ago
Medications Atenolol Nasonex Alprazolam Sumatriptan	*Family history* Father—Heart disease Brother—Glaucoma, brain tumor, heart Disease Sister—Rheumatoid arthritis
Social history Former smoker (pack a week × 10 years, quit last year) Does not drink Retired Salvation Army worker	*Review of systems* Overactive bladder Shortness of breath Arthritis Panic attacks Numbness in back and arms Some incoordination

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_12

Examination
Acuity with correction Right eye: 20/25 Left eye: 20/20
Pupils Slightly sluggish, equal, no afferent pupillary defect
Intraocular pressure Right eye: 14 mmHg Left eye: 17 mmHg
External exam Unremarkable
Eye alignment and motility Normal
Slit lamp examination 1+ conjunctival injection BE Fine, diffuse endothelial keratic precipitates BE 2–3+ white blood cells BE Old cells in anterior vitreous No posterior synechiae
Visual field Normal
Fundus examination Mild cup to disc asymmetry (0.4 RE and 0.5 LE) Otherwise normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

Generally speaking dry eye does not cause 5/10 eye pain. Additionally, she has not improved significantly with dry eye treatment. Her corneas do not show evidence of dry eye as well. Although the patient has a history of right-sided migraine and migraine can cause eye pain, generally migraine headaches do not last weeks at a time. The main diagnosis here relies upon the slit lamp examination. The conjunctival injection, keratic precipitates, and white blood cells in the anterior chamber are most consistent with a bilateral anterior uveitis. One final nonspecific clue is that patients with uveitis can be quite photophobic because the inflammation irritates the iris. This tends to hurt when the iris constricts to light. I do not know why she only complained of right eye pain when she had bilateral findings.

We like to divide uveitis into granulomatous vs. nongranulomatous inflammation. Granulomatous uveitis shows larger keratic precipitates called “mutton fat” (Fig. 12.1). This distinction helps guide the work-up. For instance, the most frequent differential diagnosis of granulomatous disease includes tuberculosis, sar-

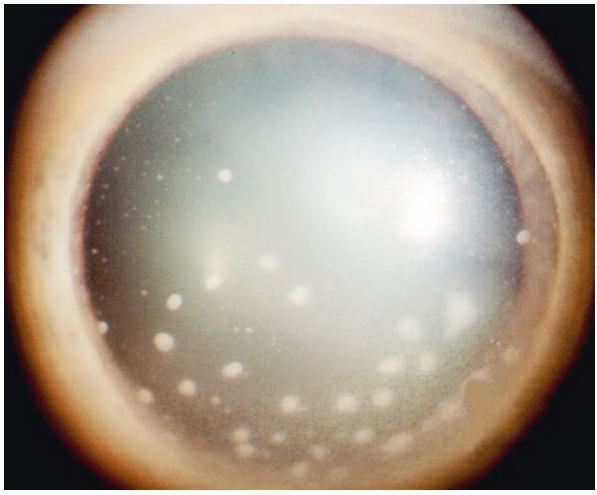

Fig. 12.1 Slit lamp examination shows a pharmacologically dilated pupil. There are several large, white lesions on the back of the cornea consistent with mutton-fat keratic precipitates seen in granulomatous uveitis

coidosis, syphilis, Lyme, toxoplasmosis, and granulomatosis with polyangiitis (Wegener's). The most common differential overlaps for nongranulomatous disease and includes syphilis, sarcoidosis, ankylosing spondylitis, lupus, and rheumatoid, and tubulointerstitial nephritis, and herpes simplex. Rarely, multiple sclerosis can also cause granulomatous or nongranulomatous uveitis. Fifty percent of patients have idiopathic uveitis, but if the above workup is negative and the patient has recurrent disease, then I will send the patient to a uveitis specialist.

A systemic workup is indicated for granulomatous uveitis, bilateral uveitis, and recurrent uveitis. Patients with a first-time attack of nongranulomatous disease in one eye may sometimes be treated without a workup. Treatment often includes topical corticosteroid eye drops. This is often begun empirically before testing for infectious disorders comes back. I like to start with prednisolone acetate 1% every hour while awake for a week followed by a taper to 6x/d for a week and reducing by 1 drop/day every week for 6 weeks. If they have a recurrence on this regimen, then I restart the drops with a slower taper over months. In some cases, recurrent and recalcitrant uveitis requires the use of depot steroid injections, implantable steroid, and systemic immunosuppression including oral prednisone, tumor necrosis alpha inhibitors, and methotrexate.

Neurologic Perspective: Dr. Digre

Really the only thing one would see on examination if a slit lamp exam was not done was some conjunctival injection. So, without a slit lamp exam this could be confused with a lot of other things like dry eyes or even migraine—which can go on for weeks at a time in certain individuals (but usually they have a history of migraines that are prolonged in duration). The sluggishly reactive pupils may be

another clue that an ocular process is occurring. The other clue is complaint of photophobia—Photophobia is a symptom that requires an explanation. We are told that she has no phonophobia, nausea and this pain does not feel like her migraine. So, something is wrong. The most common ocular causes of photophobia are dry eyes and iritis; other causes of photophobia would be blepharospasm (Case 6), which will have characteristic eyelid closure; and migraine should be diagnosed by history.

Once uveitis is diagnosed by slit lamp, looking for underlying causes is important as Dr. Lee has pointed out. While this patient does not seem to have a severe headache accompanying her uveitis, there are some uveitides that go with meningitis that can have headaches associated with them. See Table 12.1 for a partial list.

Table 12.1 Uveitis and meningitis syndromes (adapted in part from: Allegri et al. J Ophthalmic Vis Res. 2011;6:284)

Infectious
Virus (Herpes, cytomegalovirus, herpes zoster, West Nile virus, HIV virus
Bacterial: Bartonella Henslae (cat scratch disease), Whipples
Myocobacteria: Tuberculosis
Spirochete: Lyme disease, Syphilis, Leptospirosis
Protozoa: Toxoplasmosis, pneumocystis cariii
Autoimmune
Polyartereritis nodosa
Polyangiitis (Wegener's granulomatosis)
Sjögren's syndrome
Rheumatoid arthritis
Systemic Lupus erythematosus
Sarcoidosis
Vogt-Koyanagi Harada disease
Behçet's disease
Acute multiocal placoid pigment epitheliopathy
Neoplasm
Lymphoma
Demyelinating disease
Multiple sclerosis
Acute disseminated myelitis

Non-ophthalmic/Non-neurologic Perspective

Uveitis really requires a good slit lamp exam to make the diagnosis. Sometimes, the patient will have injection next to the colored part of the eye called limbal flush. The rest of the conjunctiva appears relatively white. This can be suggestive of uveitis, but is not a specific sign. Patients with mild eye redness without discharge and photophobia may have uveitis and may need a slit lamp exam.

Follow Up

This patient was diagnosed with uveitis. Her workup included a normal ANA, ACE, RPR, HLA-B27, urinalysis, ESR, RF, and chest X-ray. She was started on prednisolone acetate 1% as described above and her uveitis was resolved at her 6 week return. The pain resolved slowly over about a week or so after treatment was begun. She was diagnosed with idiopathic anterior uveitis and did not suffer a recurrence. *Final diagnosis: anterior uveitis*.

For Further Study

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Case 13

History of Present Illness

A 23-year-old woman developed a red and painful right eye. The pain was described as burning, worse when she blinked, and better when she closed her eye and kept it closed. She rated it as 4 out of 10. She endorsed tearing and eyelid crusting in the morning. She denied ptosis, stuffy nose, or runny nose. The symptoms worsened over the course of 3 days and then similar symptoms began in the left eye. She visited her primary care doctor and was prescribed an antibiotic drop four times daily. The symptoms improved approximately 1 week after onset, but then worsened again in both eyes. Every day, the pain, redness, and irritation seem worse. Her primary care doctor ordered an MRI, which was normal. A methylprednisolone dose pack did not improve her symptoms.

Past medical and ocular history Normally wears soft contact lenses but cannot tolerate them since the redness began	*Past surgical history* Tonsillectomy as a child Myringotomy tubes as a child
Medications Gentamicin eye drops Oral contraceptives	*Family history* Mother has optic disc drusen Sister has migraines and wears glasses
Social history Pre-school teacher Smokes socially Drinks alcohol socially	*Review of systems* Negative

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_13

Examination
Acuity with correction Right eye: 20/25 Left eye: 20/25
Pupils Equal, briskly reactive, no APD
Intraocular pressure Right eye: Soft to palpation Left eye: Soft to palpation
External exam Bilateral eyelid redness and trace edema
Eye alignment and motility Normal
Slit lamp examination 2+ injection Diffuse punctate epithelial keratopathy (PEK) BE Mild chemosis BE Follicles in inferior fornix BE (Fig. 13.1)
Visual field Normal to confrontation
Fundus examination Normal
Neurologic examination Normal

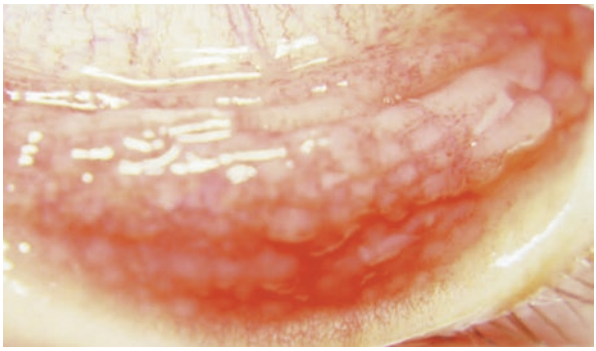

Fig. 13.1 External photograph shows an everted lower eyelid. Note the multiple pinkish "bumps" on the palpebral conjunctiva consistent with follicles

Discussion

Ophthalmic Perspective: Dr. Lee

Red eye, pain, and watery discharge sounds like conjunctivitis. There are multiple forms of conjunctivitis including allergic, viral, bacterial, mechanical, contact lens related, toxic, and immune-related. Allergic conjunctivitis usually starts in childhood, affects both eyes, and an adult is generally aware of these seasonal issues. This patient wears contacts, so you have to worry about corneal infections.

Ophthalmologists are usually very concerned about acanthomoeba (an extremely painful corneal infection) often seen in a contact lens wearer with recent hot tub use. Patients can also become contact lens intolerant, but this usually starts with both eyes and is not so acute or angry as this.

The most common form of conjunctivitis is adenoviral. Her story of starting in one eye and then spreading to the other is a classic one. The symptoms of morning crusting are also extremely consistent. Typically, viral conjunctivitis resolves spontaneously after several days. Exam findings may include PEK and follicles as seen in this patient. Normally, we ask these patients to use preservative free artificial tears, cool compresses, and meticulously wash their hands to avoid spreading it. I often advise patients use paper towels at home to avoid spreading it to the other eye or another family member. The diagnosis is usually clinical and presumed viral unless other findings such as severe pain, purulent discharge, excessive discharge, or the symptoms last more than 4 weeks. If atypical, then cultures (blood and chocolate agar) and gram stain should be performed.

The fact that she got better and then got worse might suggest that she has something other than viral conjunctivitis. However, the patient was placed on gentamycin, which can cause a toxic reaction to the cornea and conjunctiva called medicamentosa. This reaction can occur within days or weeks of eye drop use and may relate to preservatives. Usually the symptoms continue to worsen for as long as the patient uses the drops. Stopping the drops and adding preservative free artificial tears often helps most patients. Severe cases may require use of NSAID drops or steroid eye drops. These patients often do very well.

Neurologic Perspective: Dr. Digre

Red eye, eye pain and serous or purulent discharge usually signifies eye inflammation or infection. Traditional wisdom states that viral conjunctivitis presents with itchy red eye, little pain and may have a cold, runny nose or congestion, whereas bacterial conjunctivitis often presents with discharge (purulent), and may have chemosis, eyes glued shut in the morning and no other illness. The differential diagnosis of a red eye is important to review here. See Table 13.1. The most common are dry eye, blepharitis, and conjunctivitis.

The important part for me as a neurologist is to look for warning signs of something really serious—either serious eye disease like uveitis, corneal abrasion, scleritis, or neurological disease (dissection, fistula). What I look for is decreased vision and red eye needs urgent evaluation. Significant photophobia rarely occurs with conjunctivitis and if this is present I am more concerned. If the cornea appears hazy in conjunction with a red eye, I immediately refer them to ophthalmology. Other symptoms include unequal pupils, or any muscle imbalance or complaint of diplopia.

I usually do not treat conjunctivitis with medications—but recommend tears and cold/warm compresses—and see their ophthalmologist if it does not get better. I also recommend the individual to stop wearing contact lenses if they are and avoid heavy make up.

Table 13.1 Differential diagnosis of a red eye

Ocular causes
Conjunctivitis
Allergic
Viral (usually adenovirus)
Bacterial
Blepharitis
Dry eye
Episcleritis and scleritis
Foreign body
Corneal abrasion
Iritis
Anterior uveitis
Keratitis
Subconjunctival hemorrhage
Medication use that irritates cornea
Neurological causes of the red eye
Carotid dissection and Horner's syndrome
Carotid/dural cavernous fistula
Ophthalmic vein/cavernous sinus thrombosis
Herpes zoster ophthalmicus
Tolosa hunt
Meningitis
Trigeminal autonomic cephalgias

Non-ophthalmic/Non-neurologic Perspective

One of my best friends is a family doctor who developed likely viral conjunctivitis and insisted upon getting antibiotic eye drops despite my protests. Daycares often mandate that a child with "pink eye" receive antibiotic eye drops for 24 h before returning. It is very challenging not to give patients antibiotic eye drops for what is most likely viral conjunctivitis. However, keep in mind that they can develop a toxic reaction to the eye drops and it may seem like they are getting worse. If it occurs, you can tell the patient that s/he has medicamentosa, which has a good outcome with removing the drop. This is not the same as an allergy and the drop does not need to be placed on their allergy list.

Follow Up

The gentamicin eye drops were discontinued and the patient started preservative-free artificial tears 4–6 times daily. The patient's symptoms began to improve after 1 day and completely resolved after 4 days. *Final diagnosis: conjunctivitis complicated by medicamentosa*.

For Further Study

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Case 14

History of Present Illness

A 32-year-old white woman noted 2 months of periocular swelling, tearing, and redness of both eyes. She noted constant eye pressure behind both eyes worse with far eccentric upgaze. Closing the eyes did not improve the pain. Nonsteroidals did make the pain better but it did not resolve it. The pain had been the same without worsening or improvement over the past 2 months. She denied any visual loss or diplopia.

Past medical and ocular history None	*Past surgical history* None
Medications None	*Family history* Father—Hyperlipidemia, prostate cancer, skin cancer Mother—Hypothyroidism
Social history One glass of wine daily Never used tobacco Works as a cook at a military base	*Review of systems* Negative

Examination

Acuity with correction Right eye: 20/20-1 Left eye: 20/20
Pupils Equal, brisk, no APD
Intraocular pressure Right eye: 14 mmHg Left eye: 14 mmHg

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_14

External exam Mild eyelid retraction both upper eye lids Margin reflex distance = 5.5 mm BE Hertel exophthalmometry 21 mm BE
Eye alignment and motility 25% symmetric elevator deficit BE Orthophoric in all gazes
Slit lamp examination 1+ chemosis and trace injection BE
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

Initially, one might assume that this is a dry eye case, which could be a contributing factor. However, close inspection of the figure shows mild eyelid edema LE greater than RE (Fig. 14.1) and some mild eyelid retraction BE. The combination of the eyelid edema and eyelid retraction really point toward thyroid eye disease (TED). The top limit of normal for Hertel exophthalmometry in a Caucasian woman is 20 mm, which would also make her suspicious for TED.

Now when I was in residency, I remember clearly being told that TED does not cause pain and if you see pain in a patient with orbital signs and symptoms, then you should think about something else. I held onto that mantra for a long time until I became a faculty member and started keeping track of the clinical activity score (CAS, Table 14.1), which is a standardized methodology for determining how active TED is. The first two points include spontaneous retrobulbar pain and pain on vertical gaze. Therefore, I have changed my tune that TED can definitely cause pain and is an indicator of activity.

I would have told this patient that the problem begins with an overactive immune system that attacks the thyroid gland as well as the orbital tissues including the eye muscles. Even if one removes the thyroid gland with surgery or radioactive iodine, the immune system is still overactive and can attack the eyes. In the majority of cases, the hyperthyroidism and orbital signs occur within 6 months of each other. There are definitely a significant number of Graves' patients who do not develop ophthalmopathy. In some cases, there may be isolated TED, and the patient is euthyroid. Normally, TED runs a course of getting worse, getting better, and then stabilizing but not returning back to normal baseline eye appearance, known as Rundle's curve. The time to reach stability is usually 1–3 years and can be several years in some cases. Sometimes it can be quite disfiguring and in others it may hardly be noticeable.

In mild cases, such as this, I would advise her to get thyroid function tests and a thyroid stimulating immunoglobulin (TSI). I would advise her to avoid smoke and secondhand smoke, which could worsen the course of the disease. I would ask her to

Fig. 14.1 External photographs show bilateral upper eyelid retraction. Normally, the upper eyelids cover the iris by about 1 mm. She also has very mild upper eyelid edema of the left upper eyelid

Table 14.1 Clinical activity score. One point for each and a score of 3+ = active TED

Spontaneous retrobulbar pain
Pain on attempted up- or downgaze
Redness of the eyelids
Swelling of the eyelids
Redness of the conjunctiva
Swelling of the conjunctiva
Inflammation of the caruncle or plica semilunaris

take selenium 100 micrograms twice daily and use artificial tears regularly. I would see her back at 4–6 month intervals sooner if she develops vision loss in either eye.

In moderate to severe cases, I might initiate IV steroids 500 mg weekly × 6 weeks followed by 250 mg weekly × 6 weeks. I might also give radiation therapy, 2000 cGy in 10 fractions. I am not a fan of giving oral steroids on a daily basis because I think that patients become very steroid-dependent. Recently, we have been trying pulsed oral prednisone 600 mg weekly by mouth for 6 weeks followed by 300 mg weekly for 6 weeks. For double vision, I either occlude one eye or blur one eye significantly. Patients that want to try a Fresnel prism can, but they understand that this may change with disease worsening. Hot off the presses in May 2017, a recent study in the New England Journal of Medicine showed that teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, reduced proptosis and CAS in patients with active, moderate-to-severe ophthalmopathy compared to placebo. This could be a game changer and could conceivably reduce the time to stabilization of TED.

Once the patient stabilizes for at least 6 months and their CAS score is 2 or below, then I recommend surgical intervention, which can include orbital decompression, strabismus surgery, and eyelid repositioning (in this specific order). Some patients require all of these procedures and some only one or two.

Neurologic Perspective: Dr. Digre

TED is the most common cause of diplopia and I always look for evidence of thyroid eye disease if that is the chief complaint. Pain with thyroid eye disease is not rare and sometimes it can throw us off the track. For example, orbital myositis or orbital inflammatory disease can be in the differential diagnosis of thyroid eye disease. CT

and MR of the orbit are helpful if the typical tendon sparing is present. If the tendon is involved, it may be myositis. I also get orbital ultrasound when it is available, because the ultrasonographer can tell the difference between myositis and TED. Hashimoto's thyroiditis can also be associated with eye pain and TED. A thyroid receptor antibody can be helpful here. If patients have TED and migraine, migraines can be worsened by the thyroid disease and also the pain can be more pronounced.

TED patients do require a good eye examination. I get a baseline visual field as well as good measurements to follow the disease. Almost every thyroid patient gets dry eyes because of the proptosis and I frequently prescribe artificial tears. We order TSI and TRAB as well as thyroid tests.

Treatment of TED is so frustrating for patients because it is a waiting game for the thyroid eye disease to settle down before doing anything. In the meantime, follow the optic nerve function, and be sure the eyes stay lubricated. We try Fresnel prisms for diplopia or we fog a lens. Recently vitamin D has been reported to help.

For pain, we often use a non-steroidal anti-inflammatory since the pain is generally mild to moderate.

Non-ophthalmic/Non-neurologic Perspective

Graves' disease really requires a finding of either a high thyroid auto-antibody or an abnormal radioactive iodine uptake test. I usually start with thyroid function testing and a TSI along with the clinical exam to make the diagnosis. A CT or MRI of the orbit might reveal a large extraocular muscle but usually only if the patient has moderate disease and eye movement limitation. For whatever reason, there is a preferential involvement of the muscles in the following order: inferior, medial, superior, and lateral. So, if you see a scan that shows isolated lateral rectus enlargement, you would be suspicious that this may not be TED. Keep in mind that TED can cause vision loss and even blindness if the eye muscles compress the optic nerve, which requires urgent steroids and/or surgery. TED is best followed by either an orbital specialist or a neuro-ophthalmologist or anyone with strong familiarity and experience with the eye disease.

Follow Up

This patient had an elevated TSI and was diagnosed with Graves' disease. She is euthyroid on methimazole treatment. The literature supports that thyroidectomy causes less TED activity than radioactive iodine (RAI). She and her endocrinologist are debating the pros and cons of definitive treatment. If she opts for RAI, then I would recommend prednisone treatment before, during, and after to try to mitigate TED worsening. The patient is to follow up in 4–6 months sooner if she loses vision in either eye. *Final diagnosis: Thyroid eye disease*.

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Case 15

History of Present Illness

A 64-year-old Hispanic woman with a history of mixed connective tissue disease and possible rheumatoid arthritis presented with severe eye pain and visual loss. She had previous headaches as a young woman but had none until about 3 months ago, when she began to have pain around her left eye and left side of her head. The pain has steadily increased and is worsened with movement. She had light sensitivity in that eye and preferred to have the left eye closed. She also has had some mild tearing on the left side with the severe pain. About 1 month ago she noticed decreased vision in her left eye. She thinks her visual loss is getting worse. She may have had a cold the week before the onset of her symptoms.

Past medical and ocular history Diabetes for many years—Type II Anemia Hypertension Hypothyroidism History of Bell's palsy	*Past surgical history* Lung biopsy for hemoptysis showed pulmonary vasculitis 5 years before; she had been on methotrexate and prednisone in the past—Now none for long period of time
Medications Albuterol inhaler Benazepil Glipizide Metformin	*Family history* Negative
Social history Married, works as a cleaning lady; three children; does not speak English; never smoked; no alcohol	*Review of systems* Fatigue

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_15

Examination
Acuity with correction Right eye: 20/25 Left eye: 20/400
Pupils 2 mm OD and 2.5 mm OS in light 4 mm OD and 3.5 mm OS in darkness 1.2–1.5 log u RAPD in the left eye
Color vision (HRR) 9/9 OD 0/9 OS
Stereo vision None
Intraocular pressure Right eye: 19 mmHg Left eye: 19 mmHg
External exam 2 mm ptosis on the left
Exophthalmometry (Hertel) 18 OD and 21 OS at a base of 99 mm (Fig. 15.1) Mild resistance to palpation on the left
Eye alignment and motility 35 diopters of exotropia with limitation of adduction, elevation
Slit lamp examination Mild blepharitis OU with Meibomian glad dysfunction OU. Mild conjunctival injection OU; anterior chamber no cell; nuclear sclerosis OU and cortical cataract mild; no vitreal cell
Visual field OD: Normal; central scotoma on the left with constriction and depression
Fundus examination Normal OU with no edema or pallor; 0.2 c/d ratio; mild retinal artery attenuation
Neurologic examination Normal except for a very mild postural tremor on outstretched arms; corneal sensation intact
Optical coherence tomography Minimal decrease in RNFL OS

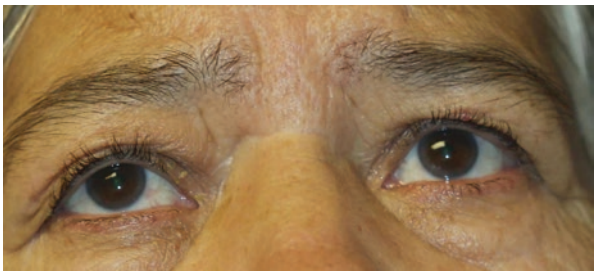

Fig. 15.1 External photograph shows proptosis of the left eye

Discussion

Neurologic Perspective: Dr. Digre

Because of the loss of vision, pain and proptosis, imaging must be done to determine where the problem is. The possibilities are orbital apex (with visual loss and partial cranial nerve 3, 4, 6), less likely superior orbital fissure, which may not have visual loss, and cavernous sinus, which would have multiple cranial nerve including V1 and V2 involvement. The fact that her corneal reflex was intact and that she did not have a sixth nerve palsy, I was thinking orbit not cavernous sinus. In these cases, careful cranial nerve examination is also important—especially the fifth nerve (check the corneal reflex) and fourth and sixth. She looked a little like a partial third nerve palsy, but it certainly was not complete. All of her other eye findings—meibmonian gland dysfunction and dry eye would not account for visual loss or this much pain.

Anytime there is pain and proptosis, it is important to think about an orbital lesion. The most common cause of proptosis is thyroid disease, but there is too much pain for that. In a diabetic, we worry the most about sinus disease especially an infection such as orbital mucormycosis or other fungus like aspergillosis. Fungal infections, unless treated promptly, could potentially kill the patient, so urgent evaluation is required. Orbital cellulitis usually is associated with more flagrant edema around the eyelids, which our patient did not have. Orbital tuberculosis could also be considered.

I would get an MR scan with orbital views and fat saturation and based on these findings, decide what to do. Is the mass in the orbit alone or in the sinuses is the first question. If in the sinuses, consider a referral to ENT for endoscopy and biopsy and culture. If it is in the orbit, the characteristics of the mass may be helpful. Many slow growing tumors do not usually cause pain but can cause visual loss and proptosis. The pain here suggests that this is either quickly growing or an invasive lesion—such as a metastatic tumor (breast in women and lung in men are most frequent). Lymphoma while normally painless is also a consideration.

Other things to consider would be inflammation. Sarcoid must be on the differential diagnosis since it can cause visual loss, but does not always cause pain. She did have pulmonary vasculitis 5 years ago, so this could also be inflammation such as granulomatosis with polyangitis (GPA, formerly known as Wegener's granulomatosis). Giant cell arteritis can rarely present as proptosis and visual loss. Idiopathic inflammatory disease is also a possibility.

An urgent MR scan was ordered. We also ordered laboratory studies: CBC, Chem 27, Hemoglobin A1C, ESR, c-ANCA and p-ANCA, and C-reactive protein.

Ophthalmic Perspective: Dr. Lee

Notice in the history that proptosis was not something about which she complained. I would say that most folks do not notice this when they have ptosis as well, since the eyelids mask this appearance unless it is extreme. Even if her lid were in a normal position, she may not make much of it. However, if the eyelid were retracted, patients

often describe that as bulging. Many people are a bit asymmetric and studies of Hertel exophthalmometry show that a 1 mm difference is acceptable; uncommonly, normal individuals have up to 2 mm difference and anything more than that is likely pathologic. The patient here has 3 mm of difference. One way to distinguish between a restrictive process vs. a cranial neuropathy is the speed of the saccades. If you ask the patient to adduct quickly, then a restrictive process will have a quick saccade but limited excursion, and a cranial neuropathy will have a slowed saccade.

I would agree that neuroimaging is warranted. MRI may be the same or better than a CT orbit, but CT would be an acceptable first step since they are so easy and quick to get. CT will also help us identify bony destruction, which could suggest a malignancy with a solid tumor. In this case, I would advocate for contrast especially as infection is on the differential.

Other potential tests would include serum IgG4, Lyme, Ehrlichiosis, and a urinalysis, but a lot of it depends on what the imaging shows.

Non-ophthalmic/Non-neurologic Perspective

For a primary care physician, the most important thing is to recognize proptosis. First view the patient while seated from above or the worm's eye view—does one eye appear proptotic? Second is to recognize visual loss. Besides the patient's complaint—check visual acuity and look carefully for a relative afferent pupillary defect. If present, this patient needs further evaluation with imaging and probably a neuro-ophthalmology consult.

Follow Up

The MR scan showed a large mass engulfing the orbit involving the optic nerve (Fig. 15.2). There was no evidence of naso-sinus disease. Because of the progressive visual loss, a biopsy was obtained. She was also placed on prednisone after the biopsy and she was supposed to return, but she went to visit relatives in Mexico. The biopsy showed inflammation consistent with but not diagnostic of GPA. Quantiferon Gold was negative, ESR and CRP were elevated. Her pANCA and cANCA were positive—this is GPA of the lung and orbit. About 6 weeks later she returned, and on prednisone her Visual acuity was 20/25 + 3 OD and 20/30 OS and her motility completely normalized, she still had an RAPD OS but it had become smaller, and she had no ptosis. Her visual field had also improved. She is followed by rheumatology and monthly Rituximab and tapering steroids. A follow-up MR scan shows the left mass in the orbit and also a mass developing on the right side as well. *Final diagnosis: orbital mass from GPA*.

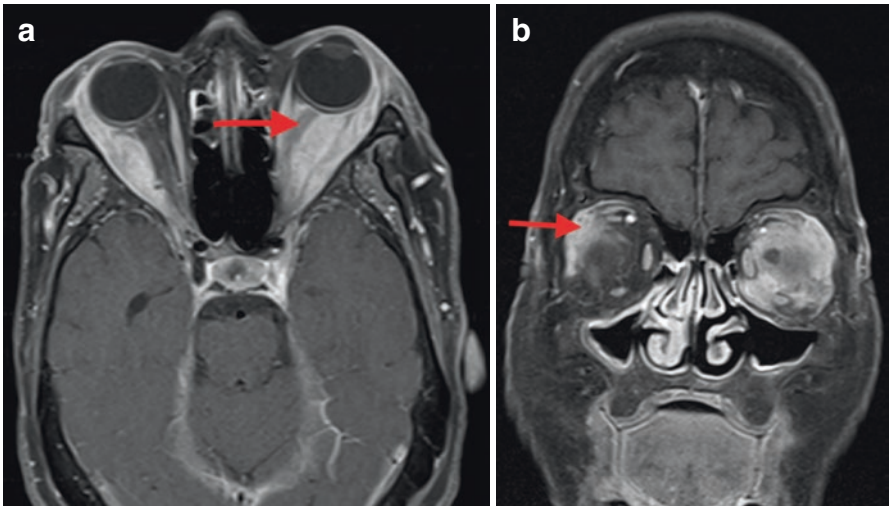

Fig. 15.2 MR scan axial and coronal views. (**a**) Axial view: This is a T1 fat saturated view with gadolinium enhancement. Notice the normally black fat is replaced by diffusely enhancing mass bilaterally. On the left side the left optic nerve is displaced (*arrow*). (**b**) Coronal view, fat saturated with gadolinium enhancement shows complete loss of the fat by an infiltrating mass on the left and enhancement especially around on the lacrimal gland on the right (*arrow*)

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Case 16

History of Present Illness

A 64-year-old man notes a pressure sensation for the past few months in his left eye occurring about once per week mostly upon awakening lasting about an hour. He does not take anything for the pain. There is mild pain to move the eye. It is becoming more frequent. He has a history of a TIA 18 years ago where the entire right side of his body went numb for a few minutes. The workup was negative at that time. He has a history of cerebral palsy with right lower extremity weakness. He denies vision loss or diplopia. He denies jaw claudication, weight loss, anorexia, fatigue, or scalp tenderness. He describes a delay of about 5 min in dark adaptation in his left eye when coming inside from bright sunlight.

Past medical and ocular history High cholesterol Hypertension Diabetes—diet controlled Amblyopia LE Glasses since 6 years old	*Past surgical history* Carpal tunnel surgery
Medications Gemfibrozil HCTZ Multivitamin Fish oil	*Family history* Mother—glaucoma and cataract in her 70s
Social history Disabled Does not smoke or drink	*Review of systems* Hands and feet always feel cold Hands tingle in the morning

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_16

Examination
Acuity with correction Right eye: 20/25 Left eye: 20/60
Pupils Round, equal, briskly reactive, no RAPD
Intraocular pressure Right eye: 24 mmHg Left eye: 19 mmHg
External exam Dermatochalasis of the upper eyelids
Eye alignment Normal
Slit lamp examination A few cells floating in the anterior chamber No iris neovascularization
Visual field Subtle superonasal step on automated perimetry BE
Fundus examination 0.55 CDR RE, inferotemporal notching 0.65 CDR LE, inferotemporal notching Normal nerve and macula Multiple hemorrhages in the midperiphery (Fig. 16.1)
Neurologic examination 3/5 Strength in RLE

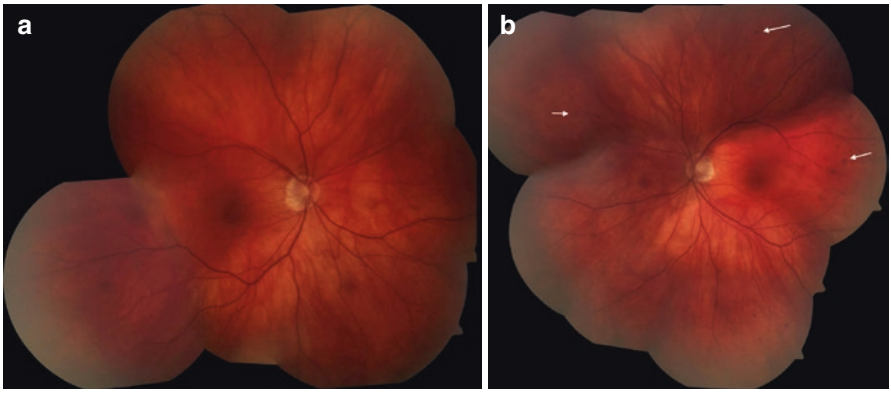

Fig. 16.1 Composite photographs of the fundus show a (**a**) normal fundus right eye and (**b**) hemorrhages in the midperiphery (*arrows*) left eye

Discussion

Ophthalmic Perspective: Dr. Lee

From a historical standpoint, the eye pain is not that specific. However, the delayed light adaptation in the left eye only is intriguing. This symptom can manifest as day

blindness too and occurs with severe carotid stenosis or a central retinal abnormality. When you add in the multiple mid-peripheral retinal hemorrhages and the cells in the anterior chamber, then this is most consistent with ocular ischemic syndrome (OIS). I would just caution the ophthalmologist that you might attribute the cells to post-dilation effect, but it is only unilateral. Usually post-dilation cells are bilateral and pigmented. Also, if you only look at the macula and nerve, then you might miss the hemorrhages, then the diagnosis is not so easy. The patient also has a superonasal step and a notch, elevated intraocular pressure (IOP) and a family history of glaucoma suggesting that he also has glaucoma, which has nothing to do with the eye pain. Note that the IOP is lower in the LE, which can be seen in OIS presumably due to ischemia of the ciliary body.

Some patients with OIS complain of more constant or boring pain. Other signs include iris neovascularization, ipsilateral and unilateral cataract, and macular edema. In some cases, patients with diabetes may have very asymmetric retinopathy with worse disease on the contralateral side.

Given the rather classic findings of OIS, an imaging study of the carotids should be performed. My preference is to obtain an MRA neck and brain so that we can see the entire carotid and intracranial vascular system to the eye. I have seen intracranial carotid stenosis causing OIS with a normal carotid ultrasound.

Neurologic Perspective: Dr. Digre

This guy is a "vasculopath" with hypertension, diabetes, and high cholesterol—at least he does not smoke. He also had a transient ischemic attack 18 years ago and his entire right side went numb. On neurological examination he clearly has lower extremity weakness on the right side. This is ominous for a problem in the left carotid artery.

The loss of vision with light is indeed curious—and should alert the astute clinician that there is possible ischemia. Other symptoms of disrupted blood flow to the retina are transient visual loss or progressive visual loss, which this patient did not have. Ischemia can also be positional—more visual loss upright and less lying down or brought about by exercise.

The pain associated with ocular ischemic syndrome may not be severe. Some have reported the pain to get better lying down indicating better blood flow. If the intraocular pressure is really high, the pain could be confused for acute glaucoma.

Other signs to look for include changes in the cornea, iris neovascularization and of course cells in the vitreous. In the retina, narrowing of retinal arteries and dilated veins can occur. Sometimes there are cotton-wool spots in addition to the mid-peripheral hemorrhages. If we had not been told about the light—the retinal findings could mimic diabetic retinopathy or central retinal vein occlusion.

The visual field is important to review and fluorescein angiography can be helpful if there is doubt about the diagnosis. The choroid will have delayed filling or delay in the arteriovenous filling and can be a helpful sign.

The evaluation of these individuals is urgent imaging. Because he has right lower extremity weakness, which we presume to be due to cerebral palsy, I would check with previous exams to be sure this is not new. However, because he has a history of

transient ischemic attack, I would recommend an MR with diffusion weighted imaging (DWI) to be sure he has not had an acute stroke. Arterial imaging is also really important, since if there is less than 100% occlusion, then treatment with stenting, carotid endarectomy would be considered. MRA or CTA should be done of the head AND neck since the stenosis can be in the internal carotid artery anywhere even intracranially. Rarely, digital substraction angiography is required to fully visualize the carotid artery and the ophthalmic artery. Also of importance is to check an ESR and CRP—giant cell arteritis has been known to cause OIS.

Treatment of OIS is based on getting the right diagnosis and knowing what lesion is causing the ischemia. Maximizing medical control of hypertension, diabetes, and cholesterol would also be helpful. Carotid artery endartectomy or carotid artery stenting could be advised if there is not complete occlusion of the carotid artery in the neck. If the stenosis is intracranial, stenting has been attempted with success. Rarely, external carotid to internal carotid arterial bypass is recommended. For sure, I would also treat the raised intraocular pressure. Sometimes the retinopathy also needs photocoagulation.

This is an eye pain you do not want to miss since the patient could have a stroke or be at risk for death.

Non-ophthalmic/Non-neurologic Perspective

A patient with day blindness or poor dark adaptation can be assessed with the photostress test. In a darkened room with one eye covered, the patient looks into a bright light for 10 s. The patient should be able to see two lines above their best acuity line within 30 s (e.g., if the eye saw 20/20 then it should see 20/30 within 30 s). A positive test is not specific and could suggest OIS or a retinal condition. The cells in the anterior chamber are usually very subtle and require an experienced examiner. These should not be mistaken for uveitis causing pain (the clue here is history of day blindness, midperipheral hemorrhages).

Follow Up

The patient underwent an MRA neck and brain, which showed 100% blockage of the left carotid artery within the neck (Fig. 16.2). This was confirmed with arteriography. If there was severe, less than 100% stenosis of the extracranial carotid artery, then endarterectomy or stenting could be considered. With 100% stenosis, the patient was offered antiplatelets. He has been followed at regular intervals for the development of iris or retinal neovascularization (if present, then would receive panretinal photocoagulation). Finally, the patient was diagnosed with glaucoma and referred to his primary ophthalmologist for management. *Final diagnosis: ocular ischemic syndrome secondary to complete carotid occlusion*.

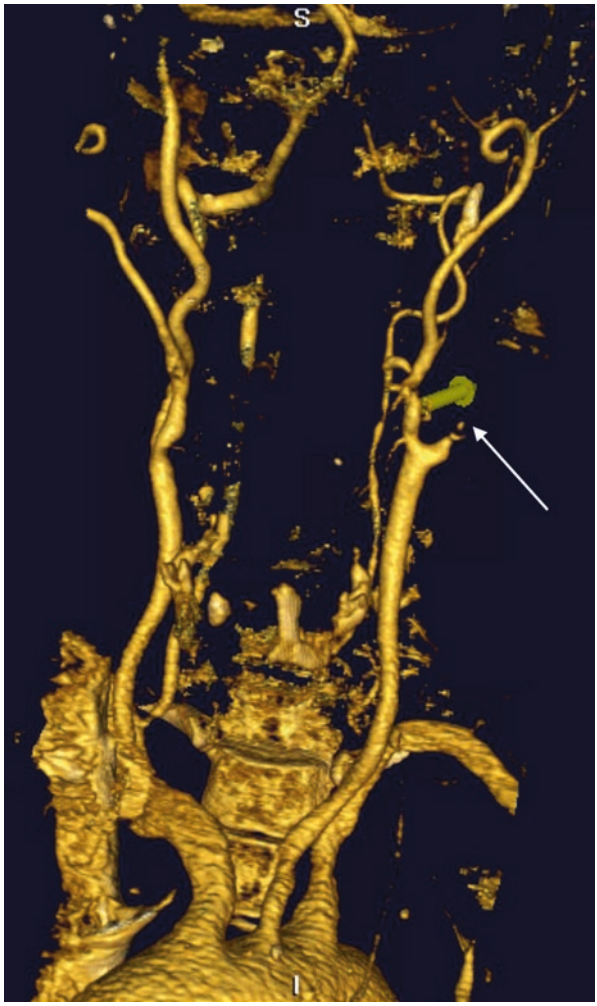

Fig. 16.2 Three-dimensional rendering of the carotid circulation. Note that the left carotid artery is completely missing indicating complete occlusion (*arrow*)

For Further Study

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Case 17

History of Present Illness

A 62-year-old man developed a severe burning pain around the right eye and the right side of his head. Initially, he thought it was due to sinus infection, which he had in the past. Two years before, he had a bicycle accident and dislocated his shoulder but denied head trauma. The pain was continuous and not associated with light or sound sensitivity or nausea or vomiting; occasionally the pain is bad enough that he will lie down. As a youngster, age 12, he was shot with a b-b gun and still has a copper BB behind his right eye and near the optic nerve.

Past medical and ocular history Fatigue and muscle aching—Worked up for polymyalgia rheumatica but this was negative Previous sinus infection Barrett's esophagus Hypothyroidism Essential hypertension	*Past surgical history* Knee surgery twice; tonsillectomy
Medications Metoprolol 100 mg each day Multiple vitamin Omeprazole 20 mg Vitamin D 1000 I.U.	*Family history* Diabetes in father and sister Hypertension in brother and mother
Social history No smoking or alcohol; married Social worker for LDS church	*Review of systems* Occasional fatigue

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Examination
Acuity with correction Right eye: 20/25 Left eye: 20/20-2
Pupils OD: 2 mm light and 4 mm darkness OS: 3 mm light and 6 mm darkness Dilation lag on the right (Fig. 17.1)
Color vision 9/9 BE Ishihara
Stereo vision Reduced; 1/3 animals on Titmus test
Intraocular pressure Right eye: 23 mmHg Left eye: 23 mmHg
External exam No ptosis
Eye motility and alignment Full excursions Comitant 10 prism diopter exophoria (long standing)
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal disks 0.3 cup to disk ratio in both eyes
Neurologic examination Normal facial sensation The rest of the exam was normal

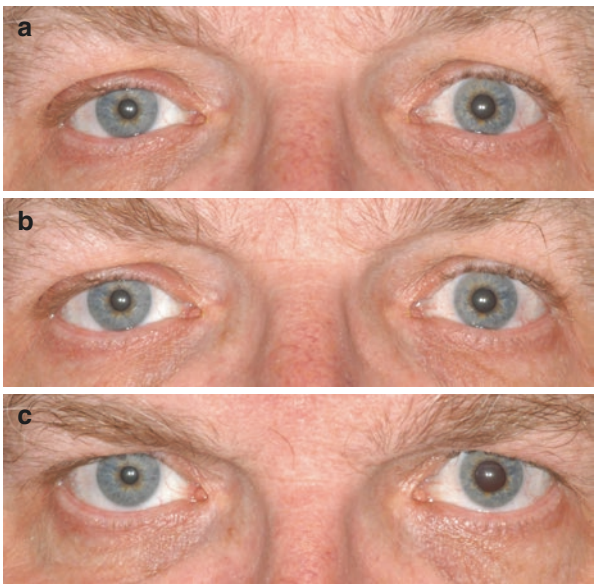

Fig. 17.1 External photographs show very mild ptosis on the right. Note that the palpebral fissure is smaller on the right. There is anisocoria at (**a**) 5 s after turning off the lights, which becomes less obvious at (**b**) 15 s. This difference is known as dilation lag. (**c**) Thirty minutes after instillation of 5% cocaine eye drops, the anisocoria becomes more obvious. This is a positive cocaine test, diagnostic of a Horner syndrome

Discussion

Neurologic Perspective: Dr. Digre

In every patient with eye pain, I look carefully at the pupils to see if there is a Horner's syndrome (small pupil, ptosis, upside down ptosis, and dilation lag) since many headache syndromes are associated with a Horner's or partial Horner's syndrome. To look for a Horner's syndrome I look for three things: First—assess the size of the pupil in light and darkness. Typically, the Horner's patient will have more anisocoria in darkness than in light. Second, I look for a dilation lag—you can do this in a dimly lighted room with a flashlight below the chin and turn the overhead light on and off, looking to see if the smaller pupil is slow to dilate. Third, I look for ptosis on the side of the smaller pupil—both superior lid ptosis but also upside down ptosis (lower eyelid is higher). In this case the Horner's syndrome was subtle since he really did not have any appreciable ptosis.

This man fits the syndrome of paratrigeminal oculosympathetic syndrome (sometimes called Raeder's syndrome)—a painful Horner's syndrome. It is typified by pain in V1 or V2 and a Horner's pupil. See Table 17.1 for the ICHD 3 beta definition of paratrigeminal oculosympathetic syndrome. This is a new headache in someone who does not have headaches.

Painful Horner's syndrome can occur in an acute Cluster headache attack—and I have seen this several times—a painful Horner's in the ER and after all testing, it was the first attack of cluster headache. Imaging is critical since carotid dissection or middle cranial fossa lesions (e.g., cavernous sinus disease) could also present this way.

Sometimes, the Horner's is so subtle that I am not sure it is a Horner's; then I perform pharmacologic testing. Here photographs of the pupils before and after drop testing are very helpful. I will apply cocaine (which blocks norepinephrine reuptake and therefore dilates the normal pupil) 5% when available to each eye and wait 30–60 min to see if both pupils dilate equally—if one pupil fails to dilate, it is a positive test. If there is more than 0.8 mm of anisocoria after the testing, Horner's pupil is diagnosed.

Table 17.1 ICHD 3 Beta: Paratrigeminal oculosympathetic syndrome (Raeder's syndrome)

Diagnostic criteria:

A. Constant, unilateral headache fulfilling criterion C
B. Imaging evidence of underlying disease of either the middle cranial fossa or of the ipsilateral carotid artery
C. Evidence of causation demonstrated by both of the following:
    1. Headache has developed in temporal relation to the onset of the underlying disorder
    2. Headache has either or both of the following features:
        (a) Localized to the distribution of the ophthalmic division of the trigeminal nerve, with or without spread to the maxillary division
        (b) Aggravated by eye movement
D. Ipsilateral Horner's syndrome
E. Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Sometimes cocaine is not available and the apraclonidine test is used. In this pharmacologic test, we take advantage of adrenergic hypersensitivity since apraclonidine is a weak adrenergic agent. In this case, a drop is instilled in each eye. After waiting for 30–40 min, you will see a reversal of anisocoria (that is the Horner's pupil will appear larger than the non-Horner's pupil).

When available, I like to localize the Horner's as a second- or third-order neuron Horner's pupil. It helps me order the appropriate imaging. In this test hydroxyamphetamine (which releases any norepinephrine from the iris terminal which causes dilation in a normal pupil and in a first or second order Horner's pupil) is instilled in a separate session (usually 1–2 days apart from the previous testing). You wait 30–40 min and a third-order Horner's will show NO dilation to hydroxyamphetamine. When the Horner's syndrome is acute, you may want to skip this test, since getting to imaging is critical to prevent stroke.

To determine if the Horner's is acute—the history is helpful—sudden onset of pain and changes in the eyelid or pupil. I usually look at old photographs—if a patient has a driver's license and has had a smaller pupil on that side for years, the emergency of the pupil is lessened. If the Horner's pupil is acute, I order imaging—usually MRI and MRA since I am most worried about a carotid dissection. In this man's case, he had a BB to the eye, so only a CT could be done, but a CTA was also ordered.

Ophthalmic Perspective: Dr. Lee

In the ophthalmologist's office, a technician often evaluates patients and then dilates the patient prior to seeing the physician. In cases of eye pain, it is critical that the technician evaluates the pupil and eyelid, because if they dilate the patient, then you will never find the Horner syndrome and may miss the carotid dissection. Since this is an acute oculosympathetic disruption, some patients may have other autonomic signs or symptoms such as ipsilateral conjunctival injection, tearing, lower intraocular pressure, nasal congestion, or an abnormally close near point of accommodation. These other symptoms are transient and may only be there for hours to days. Patients with autonomic symptoms can sometimes be mistaken for conjunctivitis or trigeminal autonomic cephalgia. Keep in mind that 20–40% of folks can have physiologic anisocoria. If your cocaine test is negative (both pupils dilate equally) then the patient likely has headache plus physiologic anisocoria.

If the neuroimaging is normal and this is not part of an autonomic headache, the Horner syndrome is generally idiopathic and permanent. Patients can undergo eyelid surgery (Mullerectomy) for repair. Because the pupil and eyelid are supersensitive to alpha 1 agonists, I have asked individuals to try over-the-counter tetrahydrozoline (Visine) to reverse the lid and pupil findings for cosmesis.

As with all things medicine, differing opinions exist. Personally, I do not localize a Horner syndrome with hydroxyamphetamine as described by Dr. Digre. I usually

image the entire oculosympathetic axis. If the scan is normal then I do not pursue further workup, since idiopathic Horner syndrome is not uncommon.

Non-ophthalmic/Non-neurologic Perspective

If you suspect a painful Horner's syndrome and it is acute, it is a relative emergency to prevent a stroke from occurring. Imaging will be critical to ensure that this is not a carotid dissection. Most patients do not have the full triad and will not endorse the anhidrosis. The radiologist needs to know that you are looking for a carotid dissection, or they may not protocol the scan properly.

Follow-Up

Normally, I would have ordered an MR on this patient, but because of the BB shot, a CT scan was done. The CT showed the expected B-B pellet behind the right eye and a double lumen sign consistent with a carotid artery dissection (Fig. 17.2). He was placed on aspirin 81 mg and did well without further problems. Horner's syndrome can be the presenting sign of carotid dissection along with headache. *Final diagnosis: Horner syndrome secondary to carotid artery dissection*.

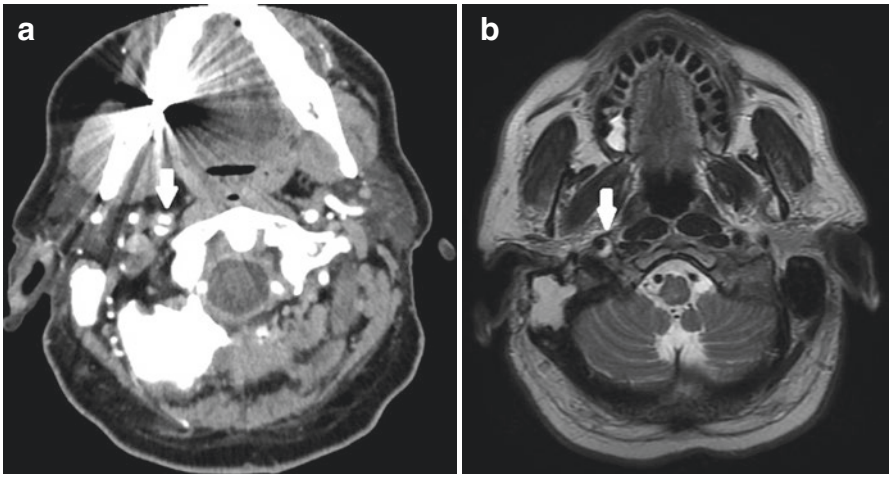

Fig. 17.2 (**a**) CTA in this case showing a carotid dissection with a double lumen (*arrow*). (**b**) Axial T1 MRI of another case shows classic hyperintense crescent typical of a carotid dissection (*arrow*)

For Further Study

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Case 18

History of Present Illness

A 77-year-old woman developed a 6-day history of fever and right eye pain. The fever was low grade, although she did not check her temperature with a thermometer, and it lasted 4 days. The right eye pain is gradually worsening and is currently 8–9 out of 10. It is constant, sharp, and located in, behind and around the right eye. There is no tenderness or pain with eye movement. She denies eye redness, ptosis, or discharge. Three days ago, she developed horizontal binocular double vision. The double vision is worse in the distance and is constant.

Past medical and ocular history Diabetes Hypertension Hypercholesterolemia Hypothyroidism	*Past surgical history* Gallbladder surgery Hip replacement Hysterectomy
Medications Insulin Amlodipine Lisinopril Atorvastatin Levothyroxine	*Family history* Hypertension Diabetes Hypercholesterolemia No migraine
Social history Homemaker Nonsmoker Nondrinker	*Review of systems* Reduced appetite × 4 days Malaise × several days No jaw pain or fatigue No myalgias No arthralgias

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Examination
Acuity with correction Right eye: 20/30 Left eye: 20/20
Pupils Equal, briskly reactive, no APD
Intraocular pressure Right eye: 23 mmHg Left eye: 28 mmHg
External exam No ptosis, redness, normal temporal artery pulses
Eye alignment and motility Esotropia worse in right gaze Abduction deficit, right eye (Fig. 18.1)
Slit lamp examination Cataract RE
Visual field Normal
Fundus examination Cup to disc ratio 0.6 BE, no diabetic retinopathy
Neurologic examination Normal facial sensation and strength Normal hearing to finger rub Color vision normal

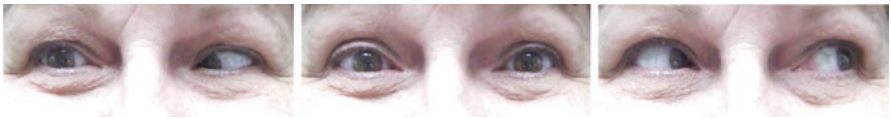

Fig. 18.1 External photographs show a subtle esotropia in primary gaze. She has full motility looking to the left, and she has a right abduction deficit in right gaze consistent with a right sixth nerve palsy (Courtesy of Collin M. McClelland, MD)

Discussion

Ophthalmic Perspective: Dr. Lee

Clinically, this patient has a right, isolated sixth nerve palsy. When it comes to determining whether it is isolated, as one of my colleagues likes to say, "Can you count to 7? They are numbered for a reason." There is no optic neuropathy present (CN II). She does not have a visual field defect, an APD, or color vision loss. There is no ptosis, dilated pupil, or poor vertical movement to suggest a CN III or vertical misalignment to suggest a CN IV palsy. Her facial sensation was normal (CN V) as was her facial strength (CN VII). The oculosympathetics run with CN VI in the cavernous sinus, so we also look for an ipsilateral Horner syndrome (ptosis and small pupil), which she does not have. A cartoon of the anatomy is shown in Fig. 18.2.

Interestingly, she may have had a fever, which could suggest an infectious or a systemic collagen vascular disease. The fever was self-limited, which may argue for a viral cause. She also has significant headache/eye pain. Giant cell arteritis (GCA, Case 32) can cause double vision and a cranial nerve palsy, and it should be on the differential. She has some malaise and anorexia but no jaw claudication. Her temporal arteries are normal. I would favor drawing an ESR and CRP. If these are high, then I would start her on prednisone and obtain a temporal artery biopsy. If these are normal, then I would observe.

In my experience, patients with diabetes are more apt to have a PAINFUL microvascular CN palsy than those without diabetes. Not all do, but some microvascular CN palsies can be painless and it runs the gamut to excruciating. The excruciating ones tend to be diabetic patients. By microvascular, I mean they have a presumptive occlusion of a microvessel that causes the CN palsy. These typically resolve spontaneously over the course of 3–4 months.

There is a debate in neuro-ophthalmology about whether patients over 50 years old with microvascular risk factors and an isolated CN palsy should get an MRI or whether you should observe them for 3 months first. A lot of that debate began in the 1970s and 1980s when it was difficult to get an MRI. Today, my opinion is to scan right away. Neuroimaging is readily available and a lesion may be seen in 1–5% of patients. If the patient cannot afford it or has significant issues with getting it, then I will wait 6 weeks. If the palsy is stable or worse at follow-up, then I would get an MRI. If the palsy is improving and remains isolated, then I will continue to wait. If it does not resolve by 3–4 months, then I will press upon them to get a scan.

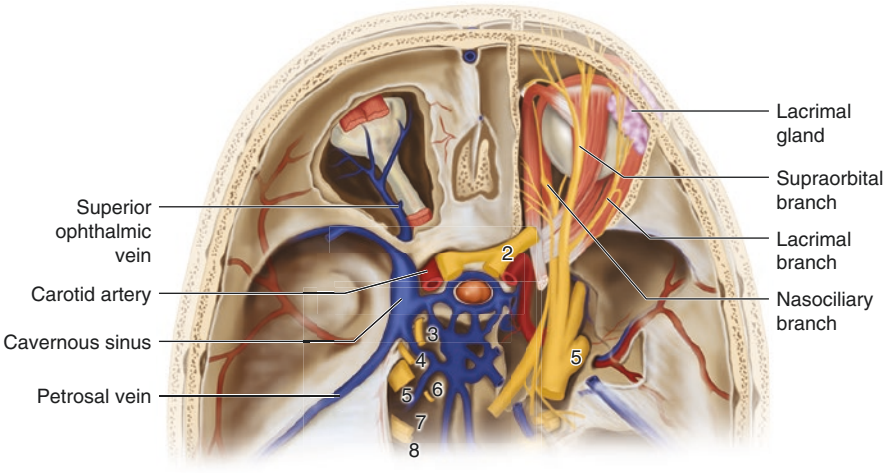

Fig. 18.2 Diagram of cranial nerves 3, 4, and 6. Notice also how many other nerves are nearby, including 5

In this particular case, because she has such significant pain, I would scan her. I am interested to know whether she has a cavernous sinus lesion or orbital inflammation and this could be Tolosa Hunt (Case 40) or idiopathic orbital inflammation (Case 11). I would also treat the pain with non-steroidals or tramadol or in some cases opioids. The pain tends to resolve after a few weeks.

Neurologic Perspective: Dr. Digre

The patient has a painful sixth nerve palsy and she is a vasculopath (hypertension, diabetes, high cholesterol) so this is likely to be a diabetic or microvascular sixth nerve palsy. However, the differential diagnosis of a painful sixth nerve palsy is broader than this. As Dr. Lee points out an older person presenting with a painful cranial nerve palsy needs an ESR and CRP to rule out giant cell arteritis. In this condition, usually the pain is worse with eye movement and their might be proptosis. Be sure to look in the ears and test hearing with a painful sixth nerve palsy. Gradenigo's syndrome is an inflammation/infection of the petrous bone and clivus which causes a sixth nerve palsy and pain and otitis media can be present. This can be serious in an older individual. Other tumors of the petrous bone can be associated with a painful sixth nerve palsy. Be sure to look for a sympathetic defect since a sixth and a Horner's can be indicative of a paratrigeminal defect in the posterior cavernous sinus. Look carefully for subtle signs of a third, fourth, or fifth nerve palsy indicating a cavernous sinus syndrome or lesion. Increased or decreased intracranial pressure can present with a headache and sixth nerve palsy; unlike our patient whose pain is really in the eye this is usually in the head. Be sure to do a complete neurological examination since a slight hemiparesis contralateral to the sixth nerve palsy could be a brainstem stroke or demyelination; while stroke is not usually painful, it can be.

Consider the mimickers of a painful sixth nerve palsy such as: Orbital myositis and thyroid eye disease (see Case 14); while these are not always extremely painful, they can be. Myasthenia, a mimicker of sixth nerve palsy, is almost never is painful. Spasm of the near could look like a sixth nerve, but would not have as much focal unilateral pain. We have also discussed painful third nerve palsies in Cases 42 and 43.

This is why I usually get an MR scan in isolated cranial neuropathy whether it is sixth, third, or fourth (unless there is trauma and a fourth nerve palsy). Sometimes special imaging protocols are available to image these nerves—especially CISS (constructive interference in steady-state imaging).

I usually treat the pain with acetaminophen or non-steroidal anti-inflammatory. Sometimes the pain is bad enough to warrant an opioid, but in the elderly, I try to avoid those.

Non-ophthalmic/Non-neurologic Perspective

I know you are thinking that this is more of a CN palsy/double vision case. But, her main complaint was the pain and not the double vision. This does happen on occasion. The first time I saw a very painful CN palsy, I thought the patient was exaggerating or drug seeking. However, I have seen it enough to know that there are some patients who just have significant pain with microvascular cranial nerve palsies.

Although her intraocular pressure was elevated (less than 21 is normal), this kind of pain would be more consistent with a pressure of 40 or 50+. Patients with pressures in the 30s usually do not have pain.

Follow-Up

Her ESR and CRP were both normal. Her MRI with contrast showed a normal orbit, cavernous sinus, and course of the sixth nerve. She was diagnosed with a microvascular CN palsy. She was placed on tramadol 50 mg every 6 h as needed. At 6 weeks follow-up, her pain was gone and her double vision was substantially improved. At 3 months, her double vision had resolved. Her intraocular pressure was consistently over 21 and she was sent for a glaucoma evaluation. *Final diagnosis: Microvascular sixth nerve palsy*.

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Part III
Neurologic Disorders Causing Eye Pain: Relatively Normal Examination

Case 19

History of Present Illness

This 28-year-old painter in the fine arts presented with a worsening headaches and eye pain. She has a family history of headaches in her mother and cousin. She was carsick as a child and had occasional night terrors. She began having headaches at age 11, and some of those were preceded with visual aura. In high school she had headaches about 2–3 times each month. In college she noticed headaches every weekend and she would have a headache with light and sound sensitivity, and nausea. The headache went from both sides of her neck and radiated to her eyes. She started topiramate and her headaches markedly reduced to about once each month. Three years later, she discovered she was pregnant and stopped the topiramate and her headaches worsened. After delivery she restarted topiramate and onabotulinum toxin and the headaches reduced to once monthly. She again stopped topiramate and the onabotulinum toxin because of a planned pregnancy. After a miscarriage she found herself pregnant again. She presents now with headaches radiating into her eyes. The worst headache starts as a visual aura of zig-zag lines and a central scotoma in both eyes, followed by pain in her neck that radiates into both eyes. The pain is throbbing, with light and sound sensitivity, nausea, and it worsens with activity. The pain lasts 1–3 days. In addition, she has less severe headaches 2–3 times each week associated with pain in her eyes, a pressure feeling associated with light and sound sensitivity but no nausea. Finally, she gets an aura without any headache—these last about 20 min and occur 1–2 times each week. She is not sleeping well, which she attributes to the pregnancy, and she drinks 44 ounces of diet cola beverage. She has been on topiramate in the past, which she is not on during pregnancy. She has tried preventative medications including amitriptyline, magnesium, fish oil, and onabotulinum toxin in the past. She has tried abortive medication including sumatriptan, eletriptan, frovatriptan, ibuprofen, acetaminophen which have not been helpful and isometheptene combination with acetaminophen and

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dichlorphenazone (Midrin) which has been effective. She had an MR scan 4 years ago, and this was normal except for mild maxillary mucosal thickening.

Her Migraine Inventory Disability Score (MIDAS) is 54 indicating significant disability from migraine. Her PHQ 9 (depression scale) was 22 indicating significant depression and GAD 7 (anxiety scale) was 19 indicating significant anxiety.

Past medical and ocular history Miscarriage 1 year ago Hypothyroidism Depression and anxiety	*Past surgical history* D & C after the miscarriage
	Family history Headaches, depression, anxiety
Medications Midrinprn Pre-natal multiple vitamins Synthroid 0.1 mg Sertraline 50 mg each day	*Review of systems* Fatigue, dizziness, chronic light Sensitivity, constipation, back pain
Social history Married, one child	*Allergies* Aspirin causes throat swelling

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils: Large 6 mm OD, 6 mm OS in light; 8 mm OD, 8 mm OS in darkness; equal and no RAPD
External exam Normal
Eye alignment Normal
Visual field Normal fields to confrontation
Fundus examination Normal
Neurologic examination BP 122/76, HR 95, BMI 25 Normal except for mildly increased deep tendon reflexes; she had no change with superficial temporal artery compression, but she did have some cervical and trapezius spasms

Discussion

Neurologic Perspective: Dr. Digre

This woman has three different kinds of headaches including: migraine with aura, migraine without aura, and aura without headache (Acephalgic migraine). The eye pain is associated with both her migraine with and without aura and interestingly

pain starts in the neck and goes to the eyes—where the bulk of her migraines end—behind her eyes. Furthermore she is pregnant.

Migraine is a very common disorder affecting almost 20% of women and 8–10% of men. It is no wonder then, that it would be common in all of our clinics. The diagnosis of migraine is often made with a family history of headaches (usually migraine), car sickness, and night terrors as a child. The characteristics of light and sound sensitivity, nausea and/or vomiting and worsening with activity are key characteristics of migraine defined by the ICHD 3 beta (Table 19.1). She also has a fully reversible aura and central scotoma that precedes some of her headaches followed by a typical migraine headache (Table 19.2). She also gets an aura without a headache (often called acephalgic migraine or migraine without pain) (Table 19.3). Since she is having slightly more than 15 migrainous days in a month, she meets the definition of chronic migraine (Table 19.4). "The ID migraine study" found that headaches that meet 2/3 characteristics from the following have a 96% specificity and 94% sensitivity: (1) moderate to severe headache causing disability, associated with (2) light sensitivity, or (3) nausea.

She also has the common and important comorbidities that accompany migraine including depression and anxiety. Her chronic light sensitivity which has also been associated with chronic migraine as well as higher levels of depression and anxiety could be making her migraines worse. She also is not sleeping well, which makes migraines worse and she has cervical spasm, which can contribute to migraine as well. The excessive amount of caffeine may be interfering with sleep, and the sweetener, NutraSweet found in the cola she drinks has been associated with migraine.

Migraines are usually inherited headaches and, while the exact cause and mechanism is not completely understood, are likely caused by changes in the trigeminovascular complex. The aura component may relate to spreading depression, and the

Table 19.1 ICHD 3 beta criteria for migraine without aura

Diagnostic criteria:

A. At least five attacks 1 fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated) 2,3
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 19.2 ICHD-3 beta criteria for migraine with aura

Diagnostic criteria:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura
Symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal
C. At least two of the following four characteristics:
1. At least one aura symptom spreads gradually over _5 min, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5–60 min 1
3. At least one aura symptom is unilateral 2
4. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded
Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 19.3 ICHD 3 beta criteria for typical aura without headache (migraine without aura, acephalgic migraine, migraine without pain)

Diagnostic criteria:
A. Fulfills criteria for migraine with typical aura (see Table 19.2)
B. No headache accompanies or follows the aura within 60 min
Description: Migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

pain component may be caused by release of inflammatory molecules associated with the dural vessels stimulating trigeminal afferents to the nucleus caudalis (a spinal trigeminal nucleus) and modulated by the thalamus and sensed in the sensory cortex. Because of the involvement of the spinal nucleus, sufferers may experience neck pain as part of the migraine, like our patient. The pain can be unilateral or bilateral, but characteristically occurs in the first division of the trigeminal nerve, and not infrequently involves pain around, in, by the eyes. Neck pain can also be a sign of migraine. This is due to the caudal nucleus extending into the upper cervical spine (See Fig. 23.1 and Appendix 4).

Table 19.4 Chronic migraine ICHD 3 beta criteria

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on >15 days per month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura
C. On >8 days per month for >3 months, fulfilling any of the following:
   1. Criteria C and D for migraine without aura
   2. Criteria B and C for migraine with aura
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

Description: Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Our patient does not need further imaging. Imaging in migraine has a very low yield of any pathology and while MR and CT scans are not contraindicated in pregnancy, they are unnecessary in this case, since her migraines have not really changed in character—only in frequency since stopping her preventatives AND her neurological examination is normal.

If she were not pregnant, we would consider putting her back on the topiramate (100–200 mg) and back to the onabotulinum toxin (every 3 months) since these were successful in the past. Other preventatives that could be considered include: beta-blockers like propranolol, tricyclic antidepressants such as amitriptyline, nortriptyline, imipramine, desipramine and doxepin, calcium channel blockers such as verapamil.

Since she is pregnant, we try to avoid anticonvulsant class drugs since topiramate is a Class D drug (causing neural-tube defects). One could use low-dose aspirin (81 mg) which is very helpful for preventing aura, and can be taken in pregnancy especially after a woman has had previous miscarriage, but our woman has a significant aspirin allergy. Other medications used successfully in pregnancy include tricyclic antidepressant, calcium channel blockers, and beta blockers (all Class C drugs).

In all patients with migraine, pregnant or not, there are some basic treatments that should be counseled: First, limit caffeine to less than 1–2 cups of any caffeinated beverage. Encourage sleep with sleep hygiene—eating at least 4 hours before bed time, do no other activity in bed except sleep and sex, think only about sleep while in bed (those who do, fall asleep faster), stay in bed for 6–8 h every night. Having some "down time" before bedtime with relaxation techniques is also helpful. Frequent exercise, eating regularly is also helpful. In this patient I would also recommend FL-41 tinted lens for her chronic light sensitivity (see Case 21), which successfully reduced migraines in studies. In this case, I would also recommend a Theracane or a device where she could reduce her cervical spasm which can contribute to migraine.

For the acute treatment of migraine, we recommend to prevent nausea with medications such as promethazine 25 mg (tablets and suppositories) or ondansetron

2–4 mg, or metoclopramide 2.5–5 mg; treat the pain with an isometheptene combination drug or a triptan with or without a non-steroidal anti-inflammatory in the first half of pregnancy (the non-steroidal would be contraindicated due to premature closure of the ductusarteriosis in the last one-third of pregnancy).

Ophthalmic Perspective: Dr. Lee

This is a pretty classic migraine story. I do not really have anything to add. An ophthalmologist familiar with giving botulinum toxin A could consider learning the indications and injection patterns. It is pretty straightforward and can be rewarding.

Non-ophthalmic/Non-neurologic Perspective

This woman has migraine with and without aura—treatment could proceed as outlined above.

Follow-Up

We discussed the above-mentioned non-medication treatments. We also increased her sertraline to 100 mg to treat the depression and anxiety. We discussed stopping caffeine and artificial sweeteners. We suggested a low dose of amitriptyline 25 mg at night to aid in sleep. After pregnancy we suggested verapamil and retrying botulinum toxin, topiramate, or both. *Final diagnosis: migraine with aura, migraine without aura, aura without headache*.

For Further Study

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Case 20

History of Present Illness

A 45-year-old sales clerk with a family history of migraine began having headaches in high school. She treated her headaches early on with over-the-counter medications. After the birth of her two children, her headaches increased in frequency to 1–2 headaches each week. She then saw her primary care physician in her mid 30s who diagnosed migraine and while she tried sumatriptan once, she did not like how it made her feel, so the provider prescribed butalbital, acetaminophen, and caffeine, which worked most of the time. However, over the last 5 years her headaches have slowly increased in frequency and severity and over the last 1 year, the headaches are daily with her needing to go to bed at least 1–2 days each week. She takes her triptan at least 2–3 days in a week and the combination analgesic (acetaminophen, butalbital, caffeine) 4 days each week.

The worst headache is focused around her right eye and forehead and can switch to the left side rarely. The pain is throbbing, she has light and sound sensitivity as well as nausea and vomiting for the most severe headaches. The pain is usually worst in the morning and will respond to her acute medication. She denies any tearing, conjunctival injection, rhinorrhea, or ptosis. She is now missing work and fears her job will be terminated. She is also having trouble sleeping, and is somewhat depressed. Her PHQ 9 depression scale is ten indicating moderate depression. Her MIDAS score is 60 indicating severe disability from migraine.

What can we do to help her?

Past medical and ocular history	*Past surgical history*
Hypothyroidism treated	Cholecystectomy
Obesity	Hysterectomy
Depression	
Wears reading glasses	

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Medications Synthroid 0.1 mg each day Sertraline 100 mg each day Prilosec prn Zolpidem prn Acetaminophen, butalbital, caffeine 1–4 every other day Rizatriptan 2–3 days each week	*Family history* Migraine in her mother, maternal grandmother Depression in father
Social history Married with two children; no smoking; rare alcohol use	*Review of systems* Poor sleep; knee pain Snores at night Anxiety about her job

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal without RAPD
Intraocular pressure Right eye: 15 mmHg Left eye: 15 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective: Dr. Digre

We first need to diagnose the problem with this woman. She has migraine (see Case 19), which has increased to near daily headaches—with more than 15 per month signifying chronic migraine. As with many individuals, she started with episodic migraine and then had gradual worsening. She has many risk factors for chronification of her migraines including: her gender, migraine history, attack frequency, obesity, snoring, depression, and frequency of use of medication. See Table 20.1 for risk factors for chronification of migraine.

Table 20.1 Risk factors that lead to chronic migraine

Non-modifiable factors:
Sex (women more frequent)
Migraine history
Low education
Lower socio-economic status
Head injury
Modifiable factors:
Medication overuse*
Attack frequency
How well acute treatment works
Frequent nausea
Stressful life events
Snoring
Depression

*see Table 20.2

Overuse of medication can lead to medication overuse headache (MOH). While migraine is very common chronic migraine occurs in about 3–4% of adults. The combination of chronic migraine and MOH is very debilitating and occurs about 1–2% of the population. Criteria for MOH are listed in Table 20.2. Other names used for MOH include: rebound headache, drug-induced headache, and medication misuse headache.

Medication overuse headache is most prevalent in women in their 40s. Patients most frequently have a previous primary headache disorder like migraine or tension-type headache. Risk factors for the development of MOH are primarily frequent use of an acute rescue medication (ergotamine, triptan, opioid, and combination analgesic). Barbiturates (butalbital), which this woman is on, is notorious for causing MOH. In fact, 70% of patients using barbiturates and 40% of those using opioids develop chronic migraine. Other risk factors include depression and other psychiatric contributions, and frequent migraine.

Treatment rests with withdrawal of the offending medication—sometimes patients need to be detox'ed. Often the addition of a preventive is helpful. Sometimes patients go through withdrawal especially from opiates and butalbital containing compounds. The best evidence suggests stopping the offending agent and starting a preventive such as topiramate or onabotulinum toxin. Coming off the offending medication can be tricky too. Slow tapering off butalbital or switching short acting butalbital to long acting phenobarbital and then tapering is what I would recommend in this patient. Overuse of opiates would require slow taper to avoid withdrawal symptoms. Sometimes the addition of clonidine to fight the opiate withdrawal can be helpful. One can stop ergotamines and triptans abruptly without untoward effects. Education about migraines and how to avoid them, and an acute and preventive treatment plan are critical to stopping this headache.

With education and stopping the offending agent, 50–90% of patients revert to episodic migraine. Teaching non-medication ways to handle pain including lifestyle

Table 20.2 ICHD 3 beta: medication overuse headache criteria

A.	Headache occurring on 15 days per month in a patient with a pre-existing headache disorder
B.	Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache*
C.	Not better accounted for by another ICHD-3 diagnosis

*Regular intake risk varies by class
Ergotamine: More than 10 days per month for more than 3 months
Triptans: More than 10 days each month for more than 3 months
Simple analgesics (acetominophen, aspirin, non-steroidal anti-inflammatory): More than 15 days per month for more than 3 months
Opioids: More than 10 days per month for more than 3 months
Combination analgesic: More than 10 days each month for more than 3 months
Multiple drug classes (any combination of ergotamine, triptans, simple analgesics, NSAID, and/or opioids): More than 10 days per month for over 3 months
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

management and avoidance of trigger factors, mindfulness, and deep relaxation all have been shown to be helpful in some individuals. Finding a migraine-specific treatment like a triptan, sometimes the longer acting triptans like frovatriptan and naratriptan can be helpful in treating patients. Limit acute triptan use to no more than 2 days in a week. Start a preventive such as topiramate, amitriptyline, or onabotulinum toxin. Even in the best of hands, unfortunately, 20–40% of patients can relapse after detox usually within the first 12 months.

Why these headaches occur is not completely understood, but some believe them to have genetic underpinnings. The medications themselves may change the way a person responds to pain medication as well. Clearly this is an area that needs further study and understanding.

Ophthalmic Perspective: Dr. Lee

For the ophthalmologist, it is important to rule out eye disease that could cause pain. Make sure there is no dry eye, uveitis, posterior scleritis, orbital inflammation, etc. More than anything, it is critical to ask how many days per month they are taking analgesics (see Table 20.2) and *recognize* that MOH exists. Referral to a neurologist experienced in headache is important.

Non-ophthalmic/Non-neurologic Perspective

Primary care physicians play a vital role in discovering, diagnosing, and treating MOH since most patients have contact with their *primary care* at least annually. Also, most primary care providers will know all of the medications that a patient has

been prescribed. Just educating people that the medication they are taking is CAUSING their headache is often enough to get individuals to taper off and avoid medication overuse headache. Just knowing about medication overuse and its treatment is one giant step for recovery.

Follow-Up

We educated the patient about chronic migraine and also about MOH. Because of her obesity we started her on topiramate 25 mg at night with slow increase to 50 mg twice daily. We also educated her on lifestyle and the importance of sleep and trigger avoidance. We tapered her off butalbital by putting her on phenobarbital at night 40 mg and slowly tapered her off this medication over 1 month. We added in a longer acting triptan frovatriptan 2.5 mg at onset and repeat in 2–4 h up to 7.5 mg/24 h—to be used no more than 2 days a week. In between we suggested naproxen 500 mg 1 day each week. We also adjusted her antidepressant medication to 150 mg each day to control anxiety and depression. She resumed episodic migraine (so far!). *Final diagnosis: chronic migraine with medication overuse headache*.

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Case 21

History of Present Illness

The patient is a 42-year-old registered nurse, who is referred for eye pain and photophobia. She has a history of rheumatoid arthritis and mild hearing loss. At age 31 she began experiencing bilateral eye pain and headaches associated with severe light sensitivity. Despite having hearing loss, she said sound increased the pain in her forehead. She put blankets on the windows of her house and was only able to leave the house at night. She would experience a squeezing sensation in her eyes that moved to her forehead. She thought they were sinus headaches, and underwent sinus surgery even though the otolaryngologist expressed doubt that the sinuses were causative. She had no relief of the eye pain or improvement of her light sensitivity. Sometimes the pain was so bad that she would cry and vomit. While she felt that her eyes could be puffy, she denied any rhinorrhea, tearing, or redness of the eyes. She also had several stressors at that time including a new diagnosis of rheumatoid arthritis and marital discord. For several years she spent a lot of time in bed. She had to quit working and she wore sunglasses all day, inside and out. She had been treated intermittently in the past with TobraDex eye drops, but these no longer give her relief.

She saw a neurologist who gave her topiramate that caused mental slowing and another medication (that she did not know the name of) made her depressed. She was diagnosed with depression and treated with duloxetine, which helped her mood, but she discontinued this because she worried it caused sinus problems.

Her current symptoms are squeezing eye pain that radiates into her forehead with extreme light sensitivity, mild sound sensitivity, and nausea with rare vomiting. Sometimes she will have daily severe headache and photophobia. She is light sensitive every day all of the time in both eyes. Her eyes feel dry and scratchy every night and she also has dry mouth.

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Past medical and ocular history Rheumatoid arthritis Depression	*Past surgical history* Sinus surgery
	Family history Mother had "sinus headaches" Hypertension, depression
Medications Vitamin C and E and D and cod liver oil Oil of oregano Polymyxin B ophthalmic solution prn Tobramycin (tobrex) prn Dexamethasone 0.1% solution prn Valacyclovir prn	*Review of systems* Joint pain Dry mouth
Social history Married with three children 16 years of education; no smoking; no alcohol	

Examination

Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal and there is no RAPD
Color vision (HRR) 6/6 OU
Stereo vision Excellent stereopsis: 8/9 circles on the Titmus test
Intraocular pressure Right eye: 15 mm Hg Left eye: 15 mm Hg
External exam Normal
Eye alignment Normal
Slit lamp examination She had Meibomian gland dysfunction in both eyes; normal anterior chamber and no cells were seen. She did have 2+ punctate epithelial erosion and tear film debris
Visual field Normal to confrontation
Fundus examination Normal optic disc, macula and retina
Neurologic examination Normal, except that she has allodynia on the forehead when it is touched. She also has mild hearing loss bilaterally.
Schirmer's test 4 mm OD and 5 mm OS; topical proparacaine improved her eye pain

Discussion

Neurologic Perspective: Dr. Digre

This patient presents with eye pain and photophobia, but she also has migraine headaches (see Case 19) and dry eyes (see Case 1). Both dry eyes and migraine can cause photophobia, and while she has been given eye drops in the past, she really had not understood how all of these symptoms could make each other worse. Most folks have a reason for photophobia and for some patients there may be more than one reason—such as dry eyes and migraine. My approach to diagnosing photophobia is this: first, a careful history is essential—I am looking for any central causes of photophobia such as meningitis, pituitary tumor or other clue. If so, I proceed with imaging (MRI) and possibly lumbar puncture. If not, I look for dry eyes. Dry eye symptoms are extremely common and we have found that patients with chronic migraine have more of these symptoms—even where there are no findings of erosions or decreased tear film (such as in our case). Treatment of dry eye symptoms may be helpful to reduce photophobia. I often will instill a drop of anesthetic to the eye, when eye pain is associated with photophobia to see how much the cornea is contributing to the symptoms. This helps with inflammation of the cornea, and corneal neuropathy in many cases. Then I think about the retina—is there hemeralopia (blindness from light) or night blindness, or trouble seeing the stars at night. A dilated examination can pick up retinitis pigmentosa or other retinal dystrophy associated with photophobia. I assess if there is excessive blinking to go along with blepharospasm (see Case 6)—another very common cause of photophobia and these individuals also may have dry eye symptoms. Finally, I am very careful to look for a headache history—since many patients have underlying migraine headache, which makes them more susceptible to photophobia. If I have not found a reason for photophobia, I start over, because there is usually a reason. Coming up with a diagnosis of the cause of photophobia is most important since treatment will frequently be directed toward those cause(s). In this case, I think she has photophobia due to migraine predisposition and dry eyes (Fig. 21.1).

I would recommend maximally treating the dry eyes. Sometimes with meibomian gland dysfunction, warm packs can be helpful. Frequent preservative-free tears can be helpful, and even ointment at night. While we discourage making the house darkened and wearing sunglasses indoors, FL41 tint which blocks blue light (which is the same wave length of the melanopsin pathway) and has been shown to exacerbate photophobia, seems to be helpful in both blepharospasm and migraine. When photophobia and eye pain are so severe, I have found gabapentin 100 mg three times daily and working up to a dose tolerated and efficacious is also helpful. Correcting the migraine component may also be important—treatment of migraine is discussed in Case 19.

The cause of photophobia is not completely understood, but it is very clear that one does not need vision. The melanopsin pathway of intrinsically photoactive ganglion cells synapse in the thalamus and connect with trigeminal afferents from the

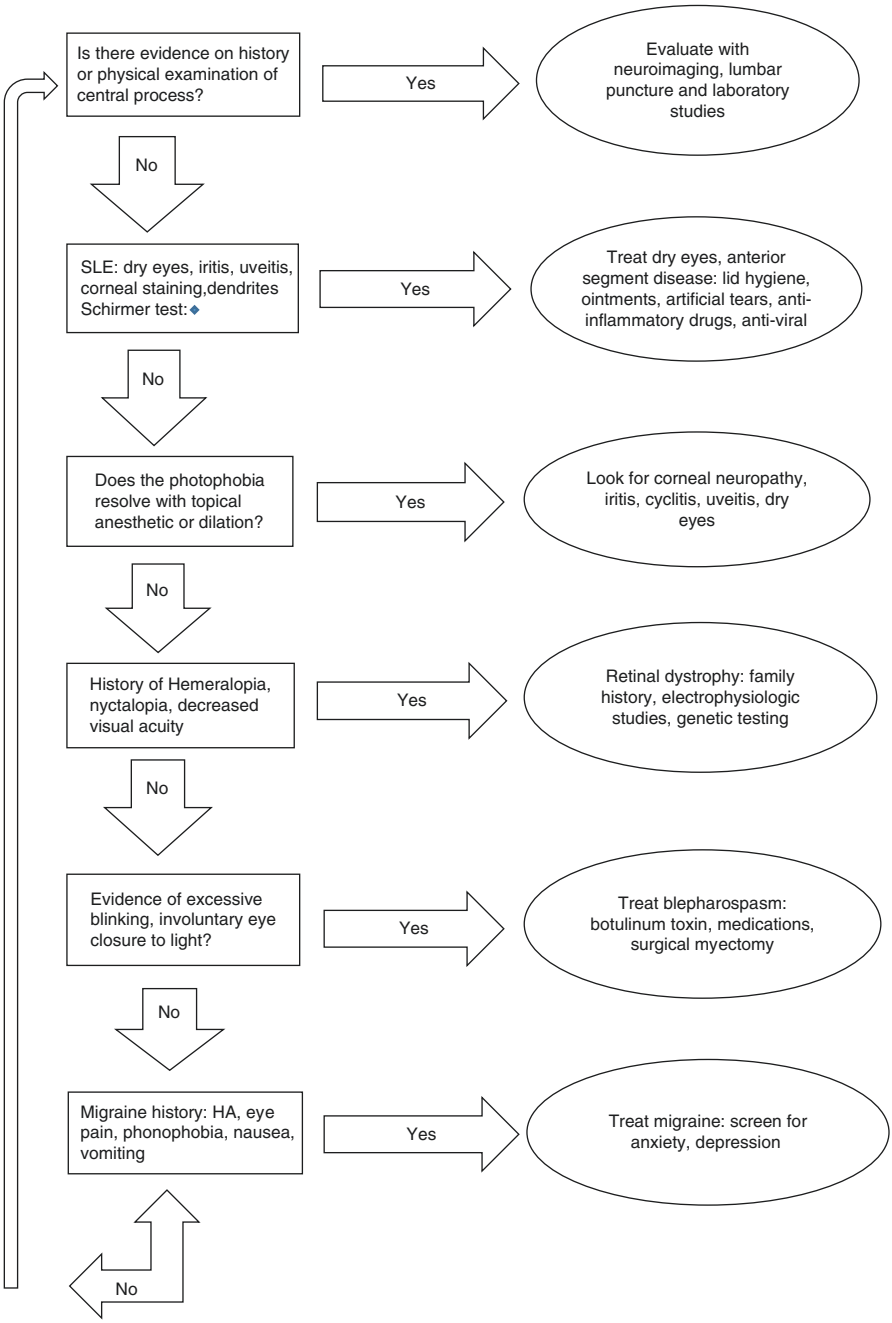

Fig. 21.1 An approach to the patient with photophobia (adapted from Digre and Brennan)

dura and presumably the eye causing the sensation of pain. Why some individuals have lower thresholds is unknown, but it is clear that individuals with blepharospasm and migraine have lower thresholds. One can understand why inflammation from iritis, conjunctivitis, scleritis, and so forth in the eye could affect trigeminal afferents directly and contribute to photophobia. We are beginning to understand why some individuals retreat into the darkness of their homes, and become very depressed too. Clinical studies have shown individuals with interictal photophobia in migraine had more depression and anxiety. Furthermore, newly born fetal animals with only the melanopsin pathway active show signs of anxiety and have increased expression of C-fos in the amygdala when exposed to light at an early stage. These studies show that there may be an emotional component to photophobia. It probably contributes to many providers diagnosing factitious disease among individuals with sunglasses in their waiting room.

Ophthalmic Perspective: Dr. Lee

Wearing sunglasses indoors is not socially acceptable because folks cannot see someone's eyes. Additionally, the sunglasses dark adapt the individual and make them more light sensitive (similar to when we non-photophobics walk outside of a movie theater on a sunny day). Tinted lenses are much more acceptable and the patient generally can see better indoors with them. Keep in mind that a patient can order a light or a heavy FL-41 tint. Many will order a light tint for situations with fluorescent lights and heavy tint for outdoors. There are also wraparound or cocoon frames that block the light from getting in from the sides. Finally, I like to tell patients to try smart lightbulbs. These LED lightbulbs connect to the internet and are controlled by smartphones. You can change the color and set the brightness to something that is more comfortable. There are also some optometrists and opticians who can dispense tinted contact lenses. However, contacts are more difficult if dry eye is a significant component of the photophobia.

Anything that irritates or inflames the cornea or uvea can cause photophobia, which will generally be reflected in a red eye. However, sometimes the redness is subtle or absent. Patients can have uveitis (see Case 12). This will generally cause some blurring of the vision. Definitively evaluating for uveitis requires a slit lamp and dilated fundus examination. I do not know who gave her Tobradex eyedrops, but hopefully it was an eye doctor. The absence of redness or tearing argues against infection so I'm not certain why give her the antibiotic portion of the drops. As we all know, steroids treats a lot of things including dryness and inflammation but it can lead to cataract, high intraocular pressure, or worsen corneal infection. Anyone but an eye doctor should probably avoid prescribing steroid eye drops for more than a week.

Finally, this woman has allodynia of her forehead. This suggest some type of neuropathic pain. Hence, a trial of an anti-epileptic such as gabapentin may be reasonable.

Non-ophthalmic/Non-neurologic Perspective

The primary care physician will definitely need help from an ophthalmologist since making the diagnosis of dry eyes can be challenging. Sometimes the eyes will not even appear red or injected. The primary care physician will feel more comfortable treating the migraine component. For all patients with photophobia, it is reasonable to ask the patient to visit their optical shop and try to purchase FL-41 tinted lenses**.**

Follow Up

We did check Sjögren's antibodies, which were negative. We recommended FL-41 tinted lenses and this improved her symptoms markedly. This patient began using tears during the day and ointment at night. She was instructed that migraine can be worsened by her dry eyes and that some of her dry eye symptoms can accompany chronic migraine. She improved—she is still light sensitive but is able to control symptoms by controlling the dry eyes and treating her migraine and using the tinted lenses. We started her on gabapentin 100 mg at bed time and increased her dose weekly to a tolerated maximum dose of 300 mg three times daily. We suggested that she work with her ophthalmologist on the dry eyes and that she may even need punctual plugs. *Final diagnosis: photophobia.*

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Case 22

History of Present Illness

A 72-year-old woman reports "electric shocks" behind her right eye for the last 2 years. The attacks last only for 1–3 s and can be precipitated by any tactile stimulation such as wind or light touch to the right periorbital region. These attacks lasted 6 months and then completely resolved for 6 months. About 1 year ago, the pains returned. She denied any unilateral tearing rhinorrhea, ptosis, or photophobia. She denies jaw claudication, weight loss, anorexia, and malaise.

Past medical and ocular history Depression Hypertension Hyperlipidemia Possible "mini stroke" after having left upper extremity numbness when lying on it	*Past surgical history* Right eye lid surgery 25–30 years ago Cataract surgery LE 3 years ago
	Family history Non-contributory
Medications Enalapril Multiple vitamins (six different types)	*Review of systems* Sometimes trouble sleeping
	Social history Widowed; drinks two glasses of wine each day. No smoking

Examination

Acuity with correction Right eye: 20/25 + 1 Left eye: 20/20-3 Near vision 20/20
Pupils Equal and no RAPD
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg

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External exam Normal
Eye alignment Normal
Slit lamp examination 1+ nuclear sclerosis RE, PC-IOL LE, with inferior corneal scar LE
Visual field Normal
Fundus examination Normal
Neurologic examination Normal; normal corneal reflex

Discussion

Neurologic Perspective: Dr. Digre

The key features in this case are: unilateral, stabbing, severe but brief (less than 1–2 min) pain, in the same spot and triggered by something innocuous like wind on the face. Pain lasting seconds to less than 1–2 min in the eye has a broad differential. These can be divided in primary headache disorders including trigeminal autonomic cephalgias and also trigeminal neuralgia. See Table 22.1.

The primary headache disorders that are brief include ice pick pain (see Case 24)—this pain is very brief but does not necessarily need to be in a trigeminal distribution and frequently occurs holocranially. It is also not triggered. SUNCT and SUNA both have autonomic features and this patient has none (Case 28).

Ocular conditions can also cause brief stabbing pain, but aside from her old corneal scar on the opposite eye, she has no other ocular disease such as dry eye or corneal dystrophy. She also is not light sensitive, which would usually accompany a trigeminal mediated ocular pain like iritis or corneal disease.

We are left with the possibility that this is some type of neuralgia. The most common is trigeminal neuralgia, also known as tic douloureux. Other neuralgias like nasociliary neuralgia (pain around the nose) and supraorbital neuralgia (above the eye, see Case 27) are less common. Trigeminal neuralgia (Table 22.2) is not rare and is more common as individuals age (with over three-quarters over age 50) and slightly more common in women than men. The key features are that it is brief (usually less than 2–3 min), is limited to one side of the face (it is almost always unilateral), and can be precipitated by what seems to be innocuous stimuli—like brushing teeth, combing hair, or wind blowing on the face. The other characteristic is that it has a refractory period—that once discharges have occurred, there is a time when touching the same spot produces no pain. The distribution is most frequently in the V2, followed by the V3 and the V1 distribution (so eye pain or periorbital pain can occur). There are not usually any autonomic symptoms. The neurological examination is almost always normal—and the corneal reflex is present. When there is anesthesia or loss of corneal reflex accompanying the pain, an extensive evaluation for other causes should ensue.

Table 22.1 Causes of brief (less than 2 min) unilateral eye pain

Primary headache disorders
Primary stabbing headache (also known as ice pick headache)
SUNCT
SUNA
Paroxysmal hemicrania (indomethacin responsive)
Trigeminal neuralgia: Idiopathic or symptomatic
Nasociliary neuralgia
Supraorbital neuralgia
Occipital neuralgia
Secondary
Demyelination of trigeminal nerve or pathway (younger individuals)
Aneurysms, masses, vascular loop (older individuals) compressing the trigeminal nerve
Trauma
Post-herpetic neuralgia
Infiltrative disorders (neoplastic, sarcoid, Lyme disease)
Giant cell arteritis
Pituitary masses
Cavernous sinus masses
Ocular causes
Dry eyes

Table 22.2 ICHD3 beta Criteria for classic trigeminal neuralgia

A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 min
2. Severe intensity
3. Electric shock-like, shooting, stabbing, or sharp in quality
4. Precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit
E. Not better accounted for by another diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Trigeminal neuralgia can be (1) idiopathic; (2) classical, caused by a vessel compressing the nerve root exit zone (look for vascular loops sitting on the 5th nerve exit zone on older individuals); or (3) secondary, caused by another structural cause. The most common causes of trigeminal neuralgia are demyelinating lesions associated with multiple sclerosis in younger people; in fact, 7% of patients with MS can have a trigeminal neuralgia. Sometimes, these can be bilateral. There can be more ominous causes of trigeminal neuralgia such as tumors, aneurysms or infiltrating lesions.

Trigeminal neuralgia can also occur in conjunction with Cluster headache (sometimes called cluster tic) or with paroxysmal hemicranias (paroxysmal hemicranias tic) which makes the diagnosis unclear.

Evaluation for trigeminal neuralgia starts with appropriate imaging. MR with gadolinium and dedicated protocols targeted at the trigeminal nerve work best to find structural lesions, since routine MR may not show a lesion. Newer imaging techniques such as CISS imaging are also very helpful.

Medical treatment of trigeminal neuralgia is usually anti-epileptic therapy. Agents include carbamazepine 100–1200 mg in three divided doses (usually starting at 200 mg) daily and oxcarbazepine (600–1800 mg in divided doses). Gabapentin has been recommended at doses between 100 and 900 mg three times daily. Other anti-epileptics include phenytoin (starting at 50 mg three times daily titrating to 300–400 mg at night) and lamotrigine (starting with 25 mg every other day and slowly advancing to 200–400 mg). Lamotrigine added to low dose carbamazepine was shown to be effective in the elderly. Other medications to consider include baclofen and onabotulinum toxin which has been successful in some small series.

Surgical treatment for trigeminal neuralgia depends on the person's ability to undergo surgery and the cause. Microvascular decompression is for those who are surgical candidates with success reported to be 70% pain free in 10 years after surgery. For individuals who fail medical therapy and cannot tolerate surgery, there are several peripheral denervation treatments with lidocaine or alcohol injection, and also destructive procedures percutaneously including: destructive lesioning procedures using radiofrequency rhizotomy, glycerol rhizotomy, and sterotactic radiosurgery. One complication of these destructive procedures is anesthesia dolorosa—which can cause severe pain while the area is also numb. This is very difficult to treat.

Ophthalmic Perspective: Dr. Lee

The history alone is so strong for trigeminal neuralgia – older woman with seconds of unilateral severe pain with a trigger. The trigger is the strongest argument that you have the right diagnosis. It is expected that the eye exam is completely normal or should not explain the pain. Sometimes, a patient may note sudden sharp pain lasting a moment occurring once a month or less frequently. They do not have a trigger and this is likely ice pick headache (Case 24). MRI is recommended since up to 10% can have a tumor instead of a vascular loop pressing on the nerve. If you are not comfortable treating this, then you can refer the patient to primary care, facial pain clinic, neurologist, or a neurosurgeon.

If a patient undergoes some type of destructive procedure or microvascular decompression (placing a teflon sponge between the vessel and the nerve), they can develop corneal anesthesia and subsequent keratopathy. In mild cases, I recommend preservative free artificial tears every 1–3 h. In more severe cases, one can develop corneal defects or ulcers, requiring antibiotic ointment 4–8×/day. These patients may require a temporary or permanent tarsorraphy (sewing the lateral third of the eyelids together), if the corneal sensation does not return.

Non-ophthalmic/Non-neurologic Perspective

Trigeminal neuralgia is not rare, and this diagnosis is often made in the primary care office. Characteristic imaging is helpful and anticonvulsant drugs are mainstay treatments. Patients failing medical therapy are frequently sent to neurosurgeons for further consideration of treatment.

Follow Up

An MR scan showed an anterior inferior cerebellar artery (AICA) vascular loop on the right trigeminal nerve (See Fig. 22.1). The patient was tried first on carbamazepine, but she never took it because when she read about the side effects, she decided not take it. She was then placed on gabapentin 300 mg three times daily, but this made her too sleepy. So she tried carbamazepine 200 mg twice daily, and this along with gabapentin 900 mg at night controlled her pain. About 1 year later, she continued only the gabapentin and used carbamazepine for flare ups. She was last seen this year (age 81) with another flare not completely controlled by medication. She will be considering gamma knife for intractable trigeminal neuralgia. She was not thought to be a good surgical candidate for decompression and she did not want a glycerol injection. *Final diagnosis: trigeminal neuralgia*.

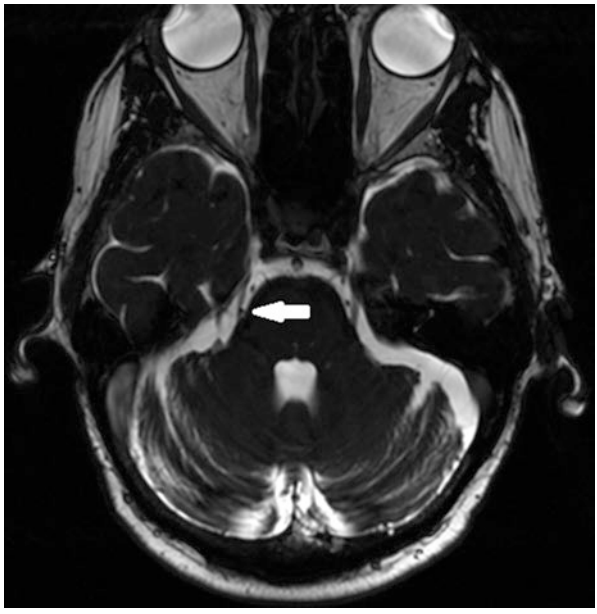

Fig. 22.1 MR scan showing vascular compression at the right 5th nerve root exit zone (*arrow*)

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Case 23

History of Present Illness

A 34-year-old woman with a history of herpes simplex infection in her left eye 15 years ago presented with a 5-year history of severe, throbbing, intermittent, retrobulbar left eye pain lasting hours. There is a constant pain of 2.5/10 with intermittent worsening to 7/10 occurring approximately 5 times per week and increasing in intensity and frequency. There are no triggers and some improvement with ibuprofen and tramadol. The pain is occasionally associated with photophobia, but no phonophobia or nausea. She denies redness, eyelid edema, skin rash, blurred vision, and tearing. There is no pain with eye movement or palpation. She was placed on antivirals orally and topically, but this did not help with the pain.

Past medical and ocular history Degenerative cervical disease Hypothyroidism Depression	*Past surgical history* Cervical fusion 2006, 2008
	Family history None
Medications Famcyclovir Levothyroxine Venlafaxine Tramadol PRN Ibuprofen PRN	*Review of systems* Sinus pressure Eczema Easy bruising Intermittent numbness and tingling of arms and legs
Social history 1 pack per day smoker × 20 years Cashier Former alcoholic	

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_23

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/60
Pupils Equal, briskly reactive, no afferent pupillary defect
Intraocular pressure Right eye: 22 mmHg Left eye: 23 mmHg
External exam Normal, no edema, no redness, no herpetic lesions No tenderness to palpation
Eye motility/alignment Normal
Slit lamp examination Meibomian gland dysfunction × 4 lids Inactive, disciform scar centrally left eye Trace punctate keratopathy both eyes White and quiet conjunctiva No iritis
Visual field Normal
Fundus examination Normal
Neurologic examination Corneal sensation reduced left eye Facial sensation is normal Significant tenderness, left greater occipital nerve—Pressure here reproduces eye pain No numbness or tenderness of the scalp

Discussion

Ophthalmic Perspective: Dr. Lee

The red herring here is the history of herpes simplex infection in the same eye as the severe throbbing eye pain. It seems logical that would cause the pain, and in fact, this patient was sent to a cornea specialist before coming to me. However, the exam here does not comport with active infection or inflammation. The eye is white and quiet without anterior chamber inflammation. The description of the pain compared to the relatively unremarkable eye exam would argue that this is not an ocular cause. I think the ophthalmologist could consider pressing on the supraorbital nerve, infraorbital nerve, trochlea (Fig. 8.1) and greater occipital nerve (GON). Alternatively, the ophthalmologist could tell the patient that this is not an eye issue but a headache one and send her to a neurologist. One could tell her that a lot of headaches are perceived in the eye region because of the referred pain from the trigeminal nerve.

The GON sits medial and inferior to the occipital protuberance. Take care not to press too hard, because you can hurt just about anyone with firm pressure. When

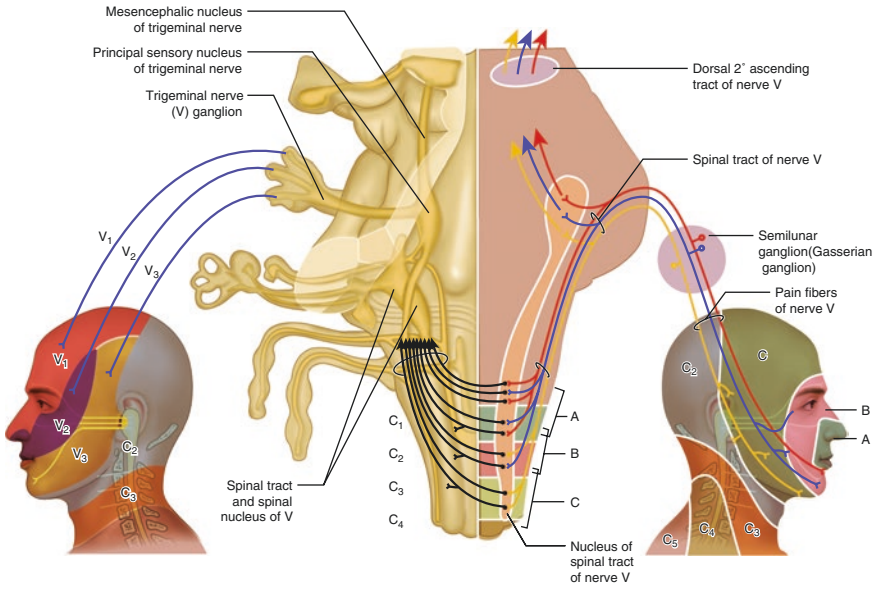

Fig. 23.1 Anatomical cartoon depicts the spinal portion of the trigeminal nerve that sits near the C2 root. Inflammation of the GON likely leads to irritation of the trigeminal nerve causing the perception of pain in the V1 distribution. The left side of the figure demonstrates the traditional three divisional anatomic pattern of sensation (V1, V2, V3). The right side shows the somatotopic and functional, "onion skin" arrangement of the spinal tract nucleus. The rostral part of the nucleus, denoted by the letter A, corresponds in the perioral region. More caudally in the spinal tract nucleus corresponds to the more lateral portions of the face (letters B and C)

the patient says it reproduces the eye pain, then that cinches the diagnosis in my mind. If there is significant tenderness without radiation, I still consider the diagnosis but am less convinced. Why would this cause eye pain? The GON (C2) ganglion sits in the upper spinal cord adjacent to the spinal nucleus of CN V. Irritation and inflammation of the GON can cause irritation and firing of V1 (Fig. 23.1). We often suspect cervicogenic headache when the pain resolves with a GON block.

Neurologic Perspective: Dr. Digre

Cervicogenic headache is somewhat of a lumping term—it usually refers to headaches associated with abnormalities of the neck. This patient really has many reasons for eye pain. First, I am not sure if she also has underlying migraine (see Case 19). Sometimes when pain is accompanied by photophobia, I also ask about other features of migraine including throbbing pain, worsening pain with activity. Recall the definition of probable migraine can be made with moderate to severe pain,

worsening with activity, and unilateral pain in the absence of nausea and or vomiting and both photo and phonophobia. Interestingly, some cervicogenic headache can have migraine features.

The second differential diagnosis is medication overuse headache (MOH) or rebound headache (see Case 20). She is taking tramadol and ibuprofen. We are not told how much, but when individuals take ibuprofen or other non-steroidal anti-inflammatories more than 15 days each month, or combination analgesics more than 10 days each month, the individual is in danger of MOH. The pain of migraine is worsened by overusing medications. So carefully educating patients about over using medications is important. MOH is not rare and is seen in 1–2% of the general population and up to 50% in headache centers. To treat MOH, a withdrawal of the pain medications should ensue and one should work on preventive strategies—medications to prevent the pain and keep her from needing so many acute medications. Even in this patient in whom we think there is cervicogenic headache, medication overuse headache can occur.

The third differential diagnosis is post-herpetic neuralgia which we discuss in Case 38. Post-herpetic neuralgia can occur after a bout of zoster or herpes simplex; however, individuals who are prone to pain like having migraines often have these symptoms more frequently and severely. Also, neuralgia is more continuous and this is more episodic.

A final thought about another diagnosis is occipital neuralgia—which has more shooting pains and usually does not last as long as this headache. But it too can be helped with an occipital nerve block.

Cervicogenic headache is not rare and it is a somewhat of controversial topic since it refers to a headache that comes from the spine. It is generally caused by disorders of the cervical spine from bone, disc, or other soft tissue changes. The ICHD 3 beta criteria are in Table 23.1. The diagnosis is fairly common occurring in 0.4–2.5% of the general population and in up to 20% of patients with chronic headache. In this patient we know that she has imaging evidence of cervical disease, which by the way is really common. 50% of women and men have some signs of cervical degenerative disease by the age of 50. We know that palpation of the greater occipital nerve created her pain but we do not know if range of motion was reduced (frequently seen in cervicogenic headache) and we do not know if her pain would resolve with a nerve block. If it responds to a nerve block, then she meets criteria for cervicogenic headache.

There are also secondary causes of cervicogenic headache including C1-2 arthropathy. It occurs in 5% of individuals in their sixth decade and 18% in the ninth decade. Three-quarters are women and the location is usually unilateral and individuals report crackling noises in the neck. CT scan of the neck can show condylar C1 arthritis or an open mouth skull X-ray and demonstrate this arthritis; this form of arthritis severely limits range of motion and is frequently seen in rheumatoid arthritis. The pain will start occipitally and radiate to the eye. If very severe, surgery is sometimes offered, but C1-2 arthropathy should be evaluated and treated by a neurosurgeon trained in this condition. This patient is likely too young for C1-2 arthropathy. In general, imaging is not required unless there are neurologic signs on examination.

Table 23.1 ICHD 3 beta classification diagnostic classification of cervicogenic headache

A. Any headache fulfilling criterion C
B. Clinical, laboratory, and/or imaging evidence of a disorder in the cervical spine known to cause headache
C. Evidence of at least two of the following:
1. Headache developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
2. Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
3. Cervical range of motion is reduced and headache is made significant worse by provocative maneuvers
4. Headache is abolished following diagnostic blockade of cervical structure or its nerve supply
D. Not better accounted for by another ICHD 3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Treatment is divided into conservative therapy—which is mainly focused on physical therapy which has been shown to be helpful in elderly patients. Trigger point injections may also be helpful and muscle relaxants can be used. Surgical treatments are considered when there is a cervical spine disorder that is causing neurologic deficits—usually not for pain alone.

Non-ophthalmic/Non-neurologic Perspective

Cervicogenic headache is often a vicious cycle where the neck muscles tighten up and compress the GON. The nerve becomes inflamed, which leads to tightening of the neck muscles. If one can break the cycle, this can improve the pain. Most patients with cervicogenic headache do not want a "shot in the back of the head" at the first visit. We often prescribe a muscle relaxant such as metaxolone (Skelaxin) 800 mg 3 times daily along with NSAIDs for 3–5 days. Other medications that are useful include: cyclobenzaprine (Flexeril) 10 mg at night and up to 3 times daily or tizanidine (Zanaflex) 4–8 mg at night. Other interventions include a soft cervical collar to put the head in a neutral position and avoid neck guarding and stretching of the GON. Soft collars however can sometimes worsen symptoms so this is not a long range strategy as it can cause worsening range of motion. One could suggest neck massage or neck physical therapy (PT), which involves massage, strengthening, and stretching. Occasionally, a muscle massager device such as Theracane along with warm towels can make cervicogenic headaches better. Many neurologists, pain specialists, radiologists, and spine surgeons would be willing to give a GON block. In some cases, cervical facet injections by a radiologist or pain specialist may be necessary. Rarely, a patient may undergo greater occipital neurectomy or radiofrequency ablation for pain relief. This is generally done by a pain specialist.

If you were interested in doing an occipital nerve block yourself, you have to use at least a 25-gauge needle because the triamcinolone has a particulate that can clog smaller needles. A 1.5- to 2-in. needle is preferable since some patients have a lot of adipose tissue. The needle is advanced to bone over the area of greatest pain. Be sure to withdraw before injecting since the greater occipital artery is adjacent to the nerve. Generally, if the patient enjoys improvement by half on the pain scale, the chances are high that they will have a good response to the block. In some cases, repeat injections may be necessary.

Follow-Up

The patient underwent a greater occipital nerve block using 1 mL triamcinolone 40 mg/mL and 1 mL 2% lidocaine without epinephrine mixed together into a 3 mL syringe using a 22-gauge 2-in. needle. Five minutes later, the patient's pain went from 4/10 to 0/10. The patient was pain-free at one-month follow-up and did not return afterward. While an occipital nerve block is very helpful in making the diagnosis of cervicogenic headache, this block also works to treat occipital neuralgia and even migraine; so it is not a diagnostic test. *Final diagnosis: cervicogenic headache*.

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Case 24

History of Present Illness

A 45-year-old woman has a personal and family history of migraine. Her migraines started at age 12, and they have been fairly predictable around her menstrual period. They occur about once each month and are controlled with sumatriptan taken at the onset of the migraine. Sometimes she requires promethazine for nausea and a migraine that does not otherwise respond.

She comes in for evaluation of a new pain that used to occur once each year, but now these are occurring around her left eye—as a brief stabbing pain. Some days she can have 1–6 of these. They can also occur anywhere around her head (and posteriorly) as well, but she is most worried because she has had a few around her eye. The attack lasts less than 1–2 s and has no associated tearing, redness of the eye or rhinorrhea. Her eye lids never droops. They do not last long enough to take anything. What should she do?

Past medical and ocular history Myopia	*Past surgical history* Tonsillectomy
Medications Multiple vitamins Sumatriptan prn Promethazine prn	*Family history* Migraine in mother and sister
Social history Married 2 children; no smoking or alcohol	*Review of systems* Negative

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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils 4 mm light BE and 6 mm darkness BE
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective—Dr. Digre

This patient has a history of migraine and now has more frequent brief, short, sharp stabbing pains mainly around her eye, but importantly they occur elsewhere in her head as well. The causes of short stabbing pains (less than 10 s) are a pretty short list—see Table 24.1. Of these, idiopathic stabbing headache (aka ice-pick headache or pain, "jabs and jolts," short-lived headache syndrome, "needle in the eye syndrome") is the most common and frequent. See Table 24.2 for diagnostic criteria. It occurs more frequently in individuals with migraine than those without migraine. In addition, it is more frequent in women (just as migraine is more frequent in women). The frequency can be daily, weekly, monthly, or yearly. Raskin et al. found the severity is usually high in 90% and the quality to be most like ice pick or needle/nail like and most frequently a single isolated jab, but could occur more frequently. Furthermore, the location was, in order of frequency, most commonly temporal followed by orbital/supraorbital then parietal. While the location is the same regularly in less than one-third, it frequently changes locations and can even rarely occur bilaterally.

There are other causes of brief, lancinating pains that are other primary headache disorders. Many of these will have historical features that will give you a clue—for example, headaches only occurring at night (hypnic headache), cold stimulus headache (ice cream headache), exertion, and sexual activity. Brief headaches with autonomic features are discussed elsewhere (Case 28).

Table 24.1 Causes of short eye pain (less than 10 s)

Cause	Length	Location	Other features	Treatment
Primary, without autonomic symptoms				
Idiopathic stabbing HA	Less than 5–10 s	Anywhere in the head	Often seen in individuals with migraine	Non-steroidal, indomethacin
Hypnic headache	Can last 5–15 min; sometimes up to 3 h	Orbital frontal	Older individuals; "alarm clock headache"	Caffeine before bedtime; lithium, melatonin;
Cold stimulus headache (ice cream headache)	Lasting 30 s to less than 5 min	Anywhere—but frontal, temporal most common	Precipitated by eating/drinking something cold	Avoid cold precipitants; indomethacin
Coital headache	5 min–24 h	Anywhere	Acute at onset of orgasm in men more frequently than women; must rule out secondary cause	Pretreat with propranolol, indomethacin
Exertional headache	5 min–24 h	Anywhere	Occurs at peak of exertion	Propranolol, indomethacin
Cough headache	1–30 s	Anywhere, often vertex; often bilateral	Occurs with upper respiratory infection; look for structural lesions since this can be presentation of secondary headache	Indomethacin and other non-steroidals
Primary with autonomic symptoms (conjunctival injection, eyelid edema, lacrimation, nasal congestion, ptosis, or rhinnorrhea)				
SUNCT, SUNA	2–10 s	Unilateral brief with or without conjunctival injection; other autonomic symptoms present	Seen most frequently in men; must image to rule out secondary pathology	Treatment is difficult—sometimes lamotrigine
Episodic Hemicrania	1–30 min	Unilateral and associated with autonomic symptoms	Seen more frequently in women; can be episodic or chronic	Indomethacin responsive (150 mg or less)
Hemicrania continua	While the continuous pain is side locked, there can be jabbing pains on top of these	Unilateral with autonomic symptoms	More frequent in women	Indomethacin responsive

(continued)

Table 24.1 (continued)

Cause	Length	Location	Other features	Treatment
Cluster headache	Usually lasts 20 min to 1–2 h	Always with autonomic symptoms	More frequent in men	Verapamil, lithium, topiramate and many others tried (see cluster chapter)
Secondary brief stabbing headaches Chiari, posterior fossa lesions, pituitary lesions, herpes zoster, stroke, venous thrombosis, multiple sclerosis (Chua et al.)				
Trigeminal neuralgia	Can be seconds	Usually nose, eye, chin	Volleys of pain often precipitated by touching a certain area	Anti-convulsants
Chiari malformations	Can be brief	May be accompanied by downbeat nystagmus, ataxia, sensory changes	Be careful to not be fooled by intracranial hypotension	Depending on severity, treat symptomatically with amitriptyline if severe, refer for surgery
Posterior fossa lesions	Usually ipsilateral	Episodic and may be accompanied by other neurological symptoms (ataxia)	Needs further imaging	Treat underlying disorder
Giant cell arteritis	Usually underlying continuous headache	Usually seen in individuals over 65	Check ESR and CRP in older individuals	Biopsy temporal artery and treat with prednisone
Convexity meningioma	Can be brief and have a continuous pain as well	Ipsilateral to the meningioma	Often older individuals	Surgical removal of tumor

Table 24.2 Idiopathic stabbing headache criteria by ICHD 3 beta

Diagnostic criteria:

(A) Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D

(B) Each stab lasts for up to a few seconds

(C) Stabs recur with irregular frequency, from one to many per day

(D) No cranial autonomic symptoms

(E) Not better accounted for by another ICHD-3 diagnosis

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Idiopathic stabbing headaches can also occur in children. There is no sex preference, and almost any age has been reported. The children may not have migraine, but they may have a family history of migraine as well as migraine-like conditions—motion sickness, episodic vertigo, and abdominal pains. While indomethacin is used in adults and has been tried in children, acetaminophen was also reported to be successful.

We should not forget that secondary headaches can present also with stabbing pain; however, frequently these may have other neurologic findings, or may be associated with a side-locked pain (the stabbing only occurs in one region). Trigeminal neuralgia can also be confused with episodic stabbing headache.

In someone with typical migraine such as our patient, I think she has episodic stabbing headache and simple reassurance can be enough. If the spells are too frequent, I would try indomethacin 25 mg three times daily with meals or 75 mg SR. Other Cox-2 inhibitors such as non-steroidals (celecoxib; naproxen), melatonin, calcium channel blockers, onabotulinum toxin, and gabapentin have been tried.

Ophthalmic Perspective—Dr. Lee

This type of patient definitely will show up in the ophthalmology office. There really is not an eye disease that causes this. Of course, bad corneal disease can give stabbing pain but it is usually much more persistent and frequent. I usually do not scan these individuals. I also ask them if they think it is worth it to take a medicine every day (with side effects) for pain that lasts moments occurring once a month or once a week or however often they have it. Almost all say no. In my experience, this does not become significantly more frequent in the vast majority of people. I do not typically schedule a follow-up unless it changes. I do not believe that the ophthalmologist needs to refer this patient.

Non-ophthalmic/Non-neurologic Perspective

Episodic stabbing headache is not rare and primary care providers will no doubt run into it. The keys to the correct diagnosis are (1) the pain is brief, often *not side locked* and roams around the head, (2) the patient usually has underlying migraine, (3) there are NO autonomic symptoms with episodic stabbing headache, (4) reassurance is frequently the only treatment needed but if it is disabling to the patient, then consider a non-steroidal or indomethacin.

Follow-up

We diagnosed idiopathic stabbing headache since her examination was completely normal. We reassured her that there was no other cause. We offered her indomethacin treatment 25 mg three times daily, but she preferred to not take the medication. She continued treating her monthly migraine headaches. *Final diagnosis: idiopathic stabbing headache*.

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Case 25

History of Present Illness

A healthy 55-year-old man went to see a neurologist for headaches around his eyes. He has a family history of migraine in his paternal grandmother and aunt. He was never car sick as a child. He has had occasional headaches around his eyes that he has attributed to sinus headache since he was 20. They occurred infrequently but especially after drinking red wine. Over the last 10 years he has had steadily worsening sinus headaches unresponsive to acupuncture and sinus medications. He was referred to the neurologist. The pain is behind his eyes, in his forehead and over both cheeks. He has minimal light sensitivity and sound sensitivity but denies nausea or vomiting. The only change that he noticed is that they are getting more frequent—at least weekly and sometimes 2–3 days in a week. When the pain is severe, he thinks he has more nasal stuffiness. He has taken ibuprofen with some success although the efficacy seems to be waning. He wants to know if he should have sinus surgery.

Past medical and ocular history Prostate cancer diagnosed age 54 with normal PSA since Myopic and wears contact lenses	*Past surgical history* Prostatectomy
Medications Occasional flonase Ibuprofen	*Family history* Migraine in a paternal grandmother and two paternal aunts
Social history Married and successful in business	*Review of systems* Per HPI

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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal and no RAPD
Intraocular pressure Right eye: 14 mmHg Left eye: 14 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective—Dr. Digre

I wish I had a dollar for everyone I see that thinks they have sinus headaches—I would be very well off! Sinus headache, contrary to advertising and public belief, is less common than you think. The ICHD 3 beta classifies sinus headache as either acute rhinosinusitis or chronic recurring rhinosinusitis (see Table 25.1). These criteria require evidence of either acute or chronic inflammation and infection either by endoscopy or by imaging. Most individuals end up with normal imaging or minor sinus thickening.

True sinus headaches do not keep recurring every week or month. They also have an abnormal examination. The American Academy of Otolaryngology: Head and Neck Surgery have developed criteria for rhinosinusitis (see Table 25.2). Otolaryngologists point out that sinus headaches from chronic rhinosinusitis do not typically have photo and phonophobia and nausea and vomiting such as what is seen in migraine. The headache more clearly mimics tension-type headache including changes in pressure, nasal congestion, rhinorrhea, and an abnormal ENT examination. Other characteristics include morning worsening with improvement as the day goes on. Furthermore, they point out that the imaging of the sinuses must depict inflammation (Fig. 25.1) in true sinus headache. However, imaging may show sinus thickening in about 30% of scans in even normal non-headache individuals—so imaging alone is insufficient to make the diagnosis. Individuals with more than two bouts of true sinus headache in a year should be worked up for an immune deficiency.

Table 25.1 ICHD 3beta: Acute and Chronic Rhinosinusitis

(A) Clinical, nasal endoscopic and/or imaging evidence of acute (or chronic or past infection) rhinosinusitis
(B) Must have evidence demonstrated by at least two of the following
1. Headache developed in temporal relation to the onset of the rhinosinusitis
2. Either or both:
(a) Headache significantly worsened in parallel with worsening of the rhinosinusitis
(b) Headache has improved or resolved in parallel with improvement in or resolution of the rhinosinusitis
3. Headache is exacerbated by pressure applied over the paranasal sinuses
4. In the case of unilateral rhinosinusitis, headache is localized ipsilateral
(C) Not better accounted for by another diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 25.2 American Academy of Otolaryngology; Head and Neck Surgery

Major criteria
Purulence on examination of the nasal cavity
Face pain/pressure
Nasal blockage or obstruction
Fever (acute sinusitis only)
Anosmia/hypo-osmia
Nasal discharge
Discolored post-nasal drainage
Minor criteria
Headache
Bad breath
Fatigue
Dental pain
Cough
Ear pain or pressure
Fever (non-acute)

Adapted from Houser and Levine, Current Pain and Headache Reports 2008, 12:45–49

Acute frontal sinusitis often causes pain in the medial side of the orbit, maxillary sinusitis causes pain in the cheek and teeth, whereas acute ethmoid sinusitis causes pain at the bridge of the nose or behind the eyes, and sphenoid sinusitis causes pain to the top of the head or whole head.

Otolaryngologists know that the most likely diagnosis is migraine when someone presents with "sinus headache." In fact, studies have shown that among people who think they have sinus headaches, 90% have migraine instead. Why would this be? Well, first the sinuses are innervated by the same trigeminal system that is operant in migraine. Second, nasal congestion, tearing, and rhinorrhea are frequently also seen with migraine.

There are many controversies about sinus headache—especially in discussing mucosal "contact points," septum deviation, enlarged turbinates, and nasal

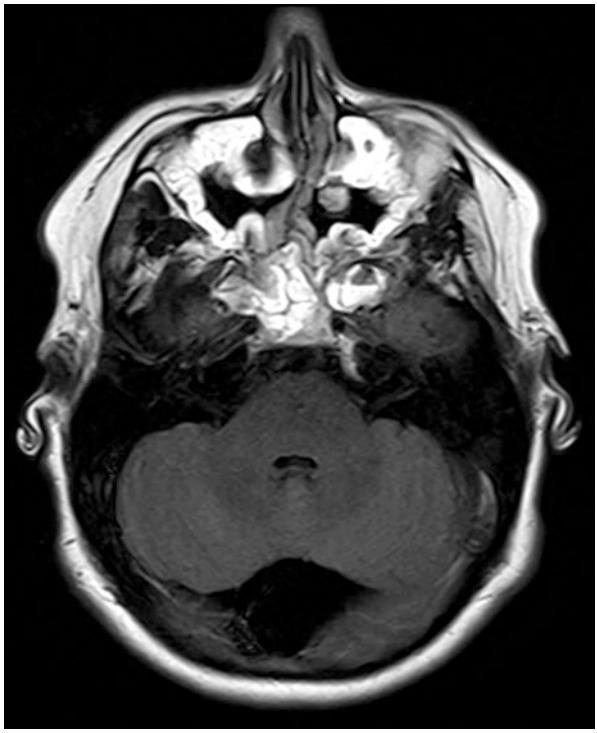

Fig. 25.1 Axial T1 MR scan of chronic sinus disease of the maxillary and sphenoid sinus in a patient with true sinus headache (not the Patient herein)

obstruction. This confusion increases in children who often have viral-mediated rhinitis and headaches. These diagnoses then lead to many unnecessary surgeries.

Make the correct diagnosis here—sinus headache is RARE-less than 4% of all headaches. There are criteria to make the diagnosis. Treatment with nasal decongestants most of the time are treating migraine. Think migraine first when someone complains of sinus headache.

Ophthalmic Perspective—Dr. Lee

I very much agree with Dr. Digre. In fact, I do not send patients with eye pain to otolaryngology, and our otolaryngologists are not interested in seeing headache presumed from sinus disease unless they have clear evidence of sinusitis on imaging. However, to some hammers everything looks like a nail and patients may have repeated sinus surgeries to help their "sinus headache." Postoperatively, they feel better but that is because their migraine resolved. When the migraine returns, the patient undergoes another sinus surgery.

Non-ophthalmic/Non-neurologic Perspective

Sinus disease is such a common symptom coming to a primary care provider. When can you diagnose true sinus headache? First, think migraine—since most individuals who think they have sinus headache will have migraine. If the person meets criteria for sinusitis, treatment with antibiotics may be appropriate. If patients are chronic, they deserve imaging and possible referral to an ENT.

Follow-up

He received a diagnosis of migraine and treated his headaches with sumatriptan which worked far better than all of the previous nasal decongestants and ibuprofen. *Final diagnosis: Migraine masquerading as Sinus headache*.

For Further Study

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Case 26

History of Present Illness

This 63-year-old employed nuclear facility engineer presented with hissing in his ears, multiple transient paresthesias, and a dull headache pressure over his head and eyes. The pressure feeling feels like a band around his head. He has a history of migraine with aura in the past occurring only once each year and migraine without aura 1–2 times each year. Paresthesias occur around his tongue and various parts of his face. He also developed neck pain, vertigo, and dizziness, which was intermittent. He has associated sound sensitivity, but no light sensitivity. The only time he feels at all nauseated with his pressure headaches is when he has a bout of dizziness. Getting out for a walk sometimes helps, but he develops back pain if he walks too much. He sleeps with white noise only, and otherwise, he has insomnia. Extensive imaging was normal.

Past medical and ocular history Diabetes for 5 years Hypertension Hyperlipidemia Asthma Sleep apnea (cannot tolerate CPAP) History of multiple injuries due to motor cycle riding	*Past surgical history* Knee surgery Elbow fracture surgery Vein stripping Parotid gland tumor removal (benign) *Family history* Migraine, blood clots in mother; migraine in brother, sister and son Seizures, father
Medications Diazepam 5 mg prn dizziness Flonase prn Aspirin, acetaminophen caffeine prn (takes about one time each week) Ibuprofen prn	*Review of systems* *Fatigue* Ear pressure, hearing loss left ear Back pain, joint pain, neck pain Dizziness off and on insomnia
Social history Married Not working 7 years due to symptoms No smoking; no alcohol	

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Examination

Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal and reactive to light
Color vision (HRR) Not tested
Stereo vision Not tested
Intraocular pressure Not tested
External exam Normal
Eye alignment Normal
Slit lamp examination Reported to be normal by his ophthalmologist
Visual field Normal
Fundus examination Normal
Neurologic examination Change in sensation around left facial surgical scar. Normal corneal nerve reflex; normal neurological examination except for hearing decrease on the left. Mild loss of vibratory sensation in the feet but deep tendon reflexes normal
Migraine disability inventory score (MIDAS) 0 but he has had 90 days of headache in the last 3 months about grade 5

Discussion

Neurologic Perspective—Dr. Digre

This man has a dull daily headache around his eyes. He has no nausea except with vertigo. He has sound sensitivity but no light sensitivity and activity may help his headache. He meets criteria for *chronic* tension-type headache—occurring more than 15 days each month and having only sound sensitivity. He also has intermittent migraine, and in my experience, almost everyone that I see with tension-type headache has underlying migraine or a history of migraine (as in this man). See the ICHD3 beta criteria for tension-type headache (Table 26.1).

The key features of this kind of headache (rarely associated with eye pain alone) include: bilateral, mild to moderate (never really severe), pain associated with no vomiting and minimal if any nausea, only light or sound sensitivity (never both), and it gets better with activity. While this is thought to be one of the most common causes of headache occurring up to 80% of the population at anyone time, it is the headache least likely to make it to a doctor's office—it usually is not severe. In this

Table 26.1 Chronic tension-type headache by ICHD 3 Beta criteria

(A) Headache occurring on greater 15 days per month on average for >3 months (180 days per year), fulfilling criteria B–D
(B) Lasting hours to days, or unremitting
(C) At least two of the following four characteristics:
1. Bilateral location
2. Pressing or tightening (non-pulsating) quality
3. Mild or moderate intensity
4. Not aggravated by routine physical activity suchas walking or climbing stairs
(D) Both of the following:
1. No more than one of photophobia, phonophobiaor mild nausea
2. Neither moderate or severe nausea nor vomiting
(E) Not better explained by another ICHD3 beta diagnosis

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Table 26.2 Migraine Inventory Disability Assessment Score (MIDAS)

How many days in the last 3 months was your productivity reduced because of headache?
How many days in the last 3 months was your productivity reduced by half because of headache?
How many days in the last 3 months did you not do household work because of your headache?
How many days in the last 3 months was your productivity doing household work reduced because of your headache?
How many days in the last 3 months did you miss family or social occasions because of headache?
Total score
Scores: 0–5 little or no disability
6–10 mild disability
11–20 moderate disability
>21 severe disability
On how many days in the last 3 months did you have a headache
On a scale of 0–10 average how painful were these headaches?

From: Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migrainedisability: The migraine disability assessment (MIDAS) questionnaire. Headache. 2001;41:854–861

man's case his MIDAS (Migraine Inventory Disability Assessment Score) score is 0—meaning the pain has very little impact on his daily life but really is present every day (hence 90 days with headache grade 5) (Table 26.2).

He also has many other symptoms that in my mind are probably related to his migraine tendency including dizziness. His diabetes is associated with early mild peripheral neuropathy and often diabetics can have peculiar roving paresthesias such as his. Since his examination is essentially normal and there are no red flags about his headache, tension-type headache is his predominant headache.

Ophthalmic Perspective—Dr. Lee

This dull ache around the eyes could be consistent with dry eye syndrome (Case 1), and I would check whether he has punctate corneal changes. I would also ask this patient if his pain is worse with prolonged reading, which might be suggestive of "eyestrain" and its differential diagnosis (Case 4). Sometimes tension-type headache can be improved with heat, cold, or massage, or taking a walk (activity). Stretching exercises for the neck and jaw may be helpful. Assessing posture and ergonomics can also lead to headache improvement.

Non-ophthalmic/Non-neurologic Perspective

Tension-type headache is a common complaint in a primary care's office, although it infrequently comes into the office because it is usually not severe. The greatest diagnostic error that occurs in this population is that tension-type headache is OVER diagnosed when the diagnosis is migraine. Be sure to ask—does the patient have light AND sound sensitivity—automatically in the migraine camp. If there is nausea and/or vomiting—the diagnosis is migraine. One of my favorite questions in separating migraine from tension-type headache is what happens with activity—tension-type headache frequently resolves or improves whereas migraine worsens. The reason that I think this is important is that there are many more medication prescribed for migraine and migraine causes disability. The MIDAS score is helpful in this regard—to check on how headaches interfere with someone's life.

Follow-up

While I would not have imaged this man in the first place, he had been previously imaged and I reviewed the imaging and it was (no surprise) normal. This man had been on nortriptyline, which helped but caused him to have difficulty urinating; gabapentin did not help; amitriptyline caused him to sleep for a long time. Cyclobenzaprine had helped his back spasm. We tried him on tizanidine (4 mg) as a mild muscle relaxant but he could not tolerate this. We retried cyclobenzaprine since he tolerated this in the past for his back but he noticed no change in his headache. Finally, we put him on desipramine because it has fewer cholinergic side effects and is in the same family (tricyclic antidepressants) as amitriptyline which is most frequently used in tension-type headache. Acutely, tension-type headache may

respond to aspirin, acetaminophen, ibuprofen, naproxen, diclofenac, and ketoprofen (all Class I evidence). Preventively, amitriptyline 10 mg at night is the evidence-based choice increasing as necessary to 40–60 mg at night. Other preventives include mirtazapine, venlafaxine, and clomipramine. *Final diagnosis: chronic tension-type headache*.

For Further Study

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Case 27

History of Present Illness

A 49-year-old man noted intermittent episodes of severe bilateral eye pain for 1 year. The pain is throbbing and pounding, occurs daily, and lasts approximately 90 min. He denies photopsias, nausea, or vomiting but endorses photophobia. He denies tearing eye redness, or nasal stuffiness. He denies any triggers or pain with eye movement. His past ocular history includes a diagnosis of optic neuropathy LE 20 years ago. Over time, his visual acuity dropped 14 years ago to 20/50 LE and 5 years ago was 20/200 LE. Brain and orbit MRI 20 years ago was normal. He experiences daily episodes of transient vision loss (TVL) LE for the past 20 years, lasting 2 min at a time. The TVL does not coincide with the eye pain.

Past medical and ocular history Diabetes mellitus × 8 years Hypothyroidism	*Past surgical history* None
Medications Dorzolamide-Timolol BE Brimonidine BE Travoprost BE	*Family history* Father—hypertension, cataracts
Social history Unemployed 1–2 drinks a day No tobacco	*Review of systems* Seasonal allergies Intermittent numbness in both hands lasting less than a minute

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_27

Examination
Acuity with correction Right eye: 20/20 Left eye: Hand motions
Pupils Equal in size, round, sluggish LE with RAPD LE
Intraocular pressure Right eye: 12 mmHg Left eye: 15 mmHg
External exam Normal, no proptosis, no ptosis
Eye motility and alignment Normal
Slit lamp examination Normal, deep anterior chamber Open angles to gonioscopy
Visual field Normal RE
Fundus examination 0.4 CDR RE with normal rim 0.7 CDR LE with 2+ pallor of rim
Neurologic examination Normal facial sensation and strength

Discussion

Ophthalmic Perspective—Dr. Lee

The story is fairly unusual. This patient has had daily transient monocular blindness in his LE since he was 29 years old lasting 2 min at a time and is otherwise healthy. This equates to more than 7000 stereotypic episodes of TVL. I would say that this is idiopathic vs. nonorganic and is unrelated to his eye pain. He also has an idiopathic optic neuropathy, which is slowly progressive over 20 years. It is not consistent with glaucoma given the pallor of the optic nerve and the vision being so poor with so much nerve left. He has only had one MRI during this time and I would repeat it. The pain began in the last year, and I would think they are unrelated. I cannot think of a process other than tumor that would affect one optic nerve for 20 years, but the pain would be unusual for a tumor. I do not think that bloodwork would be helpful if the MRI is normal. If it shows enhancement, then I might consider sarcoid, syphilis, lupus, Lyme, and NMO, but this presentation would be rarer than hen's teeth.

As an ophthalmologist, I think we can palpate his lacrimal gland, infraorbital nerve, trochlea, supraorbital nerve, and greater occipital nerve. These are often "hidden" causes of eye pain (see Cases 8 and 23). If the MRI is negative, then I would ask about analgesic overuse and be inclined to send the patient for a headache evaluation.

Neurologic Perspective—Dr. Digre

Wow, this is a tough case even for a neuro-ophthalmologist and headache specialist! First the intermittent transient visual loss is very peculiar. We are not told what the pattern of visual loss is or how he describes it but it lasts only 2 min and has occurred for years with slow damage to the optic nerve. Are these repeated vascular events? This could happen with vasospasm and be a migraine like phenomenon or if he cannot describe it, it is unlikely to be carotid artery-related. At least it is not associated with the pain! The pain that this man has is also peculiar. He has elements of migraine (throbbing and photophobia) but no nausea; we are not told if it worsens with exertion. Also the pain is rather short—90 min which is short for migraine. It has no other trigeminal autonomic cephalgias (Case 28) features either (tearing, rhinorrhea, eye lid edema, etc.) so it is not likely to be hemicranias continua or paroxysmal hemicrania. It is too long for episodic stabbing headache (see Case 24 for a list of short lasting headaches) and it is bilateral so that rules out typical trigeminal neuralgia—and the pain does not really sound neuralgiform since it is not in a single nerve distribution like the trigeminal nerve. Trigeminal neuralgia is more severe and rarely affects the forehead (more commonly the nasal area) and is more brief and frequent. Supraorbital neuralgia is caused sometimes from compression or irritation of the supra-orbital nerve(s) (see Fig. 8.1). There is a headache syndrome called external compression headache which causes bilateral forehead pain, but it is usually caused by wearing a hat or something around the head. Swimmer's headache is seen from swimmers using goggles across the forehead. Diver's headache also is in the forehead but he is not diving or even swimming when he gets these pains. Nummular headache is also a consideration—this is a focal, unilateral headache of unclear etiology that is the size and shape of a large coin—his is bilateral across the whole forehead, but this is a consideration. This kind of pain takes very careful examination of the patient and his imaging to be sure we are not missing anything.

Non-ophthalmic/Non-neurologic Perspective

It certainly is possible that the TVL and slowly progressive optic neuropathy were related to each other since they were in the same eye and began around the same time. It is just very unusual for the two symptoms to run together. The TVL did not change but the vision slowly worsened in the LE. Not sure we could make up a reasonable, common etiology. Slowly progressive vision loss often mandates an MRI. This is a patient that would probably end up best with a neuro-ophthalmologist. The vision loss plus headache plus TVL might worry most ophthalmologists and neurologists.

Table 27.1 Supraorbital neuralgia (from ICHD 2, 2004—not listed in ICHD 3 beta)

Diagnostic criteria
(A) Paroxysmal or constant pain in the region of the supraorbital notch and medial aspect of the forehead in the area supplied by the supraorbital nerve
(B) Tenderness over the nerve in the supraorbital notch
(C) Pain is abolished by local anesthetic blockade or ablation of the supraorbital nerve

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Follow-up

Palpation over the supraorbital nerves reproduced the patient's pain. He was on gabapentin 300 mg daily, so his dose was increased to 300 mg Three times daily. He did not enjoy benefit from this and felt fatigued with the higher dosage. MRI brain and orbit with contrast was unremarkable. The optic nerve appeared normal on the scan. He was diagnosed with idiopathic optic neuropathy and unrelated supraorbital neuralgia. The patient was given 1 mL of triamcinolone 40 mg/mL to both supraorbital nerves and enjoyed complete resolution of his pain within a week. The transient vision loss persisted.

Supraorbital neuralgia is more of an inflammation of a branch of the trigeminal nerve. In contrast, trigeminal neuralgia is typically due to compression of the trigeminal nerve with subsequent demyelination and faulty transmission. For refractory symptoms, other treatment modalities include gabapentin, capsaicin cream, surgical decompression, or resection.

Dr. Digre's comments: This is not completely typical of supraorbital neuralgia since in large series the pain is usually shorter less than 15 min, unilateral, pressing, stabbing, and burning. It is often a consequence of trauma, but non-traumatic cases do occur. Migraine features like this man are less common with this headache type and when reported were reported in individuals with a previous migraine history. I cannot argue with the complete resolution of the pain with supraorbital nerve blocks and that the pain was reproduced by tapping on that area. Interestingly, the supraorbital neuralgia which occurred in the ICHD 2 (2004) (see Table 27.1 for criteria for the condition) does not appear in the ICDH 3 beta. He meets all of the criteria for this condition. Treatment of supraorbital neuralgia has centered around nonsteroidal anti-inflammatory, gabapentin such was tried in this man, pregabalin, and amitriptyline. Nerve stimulators, acupuncture, and radiofrequency ablation as well as surgical decompression have all been tried for this pain. This reinforces the need to palpate the nerve areas in anyone with eye pain or headache! *Final Diagnosis: supraorbital neuralgi. Idiopathic optic atrophy and transient vision loss*.

For Further Study

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Case 28

History of Present Illness

A 29-year-old man presented with intermittent severe eye pain and redness. The pain starts abruptly in the left eye and is a pressure, stabbing, severe, and throbbing pain. He thinks his vision is blurred somewhat during the attack and he does not know if his eyelid droops. He often presses on the eye when it is at its worst. He endorses tearing in the left eye, and rhinorrhea. He has photophobia, nausea, and has vomited once. The pain can last 30–50 min and afterward he has a lingering ache for at least 30 min. He denies any facial numbness. The attacks started 3 weeks ago, but recently he is getting these pains three times daily, and almost every night he is awakened by the pain. He gets very restless with these attacks and has to pace around the room. The pain is interfering with his work and life. He wonders if there is something wrong with his eye that is causing this pain. He has tried ibuprofen without success for the pain.

Past medical and ocular history History of a bicycle accident and "wrenched" back afterward 6 months ago Normal eye examination before college	*Review of systems* Trouble with sleeping due to pain
Medications Ibuprofen prn	*Social history* Works as a teacher Single, engaged to be married Smokes ½ pack of cigarettes/day Drinks beer on weekend but recently quit due to the eye pain
Past surgical history Tonsillectomy	*Family history* Sister and mother have migraine

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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils 4 mm right, 3 mm left in light 8 mm right, 6 mm left in darkness Possible dilation lag on the left No RAPD
Intraocular pressure Right eye: 16 mmHg Left eye: 16 mmHg
External exam 2 mm ptosis left
Extraocular motility Full
Eye alignment Normal
Slit lamp examination Normal tear film No meibomian gland dysfunction
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective—Dr. Digre

This young man has what sounds like cluster headache—a primary headache disorder. Cluster headache belongs to a classification of headache called the trigeminal autonomic cephalgias (TAC). The symptoms of TACs include eye pain, with lacrimation, rhinorrhea, ptosis, and possible Horner's syndrome. The tearing, redness, and nasal symptoms occur only during the headache phase, *but the ptosis and miosis can become permanent*. The international classification of headache disorders (ICHD 3 beta) has criteria for cluster (Table 28.1). He has some risk factors for the development of cluster: his age (usually between 20–40), sex (male is three times more likely than female), and drinking/smoking. His attack length is right for cluster (15 min to 3 h) and the accompanying symptoms are consistent as well (tearing, rhinorrhea, conjunctival injection). Some of the attacks awaken him from sleep, and attacks cause him to pace or be restless—both typical cluster features. Migraine patients, on the other hand, often want to remain still. He has nausea and

Table 28.1 ICHD 3 beta criteria for cluster headache

(A) At least 5 headache attacks fulfilling criteria B–D
(B) Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min (when untreated)
(C) Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
(a) Conjunctival injection and/or lacrimation
(b) Nasal congestion and/or rhinorrhea
(c) Eyelid edema
(d) Forehead and facial sweating
(e) Forehead and facial flushing
(f) Sensation of fullness in the ear
(g) Miosis and/or ptosis
2. A sense of restlessness or agitation
(D) Attacks have a frequency between 1 every other day and 8 per day for more than half of the time when the disorder is active
(E) Not better accounted for by another ICHD-3 diagnosis

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photophobia (more typical migraine features), which occur frequently with cluster attacks. In cluster, the photophobia is frequently unilateral. However, typical cluster headache can simulate a more sinister diagnosis such as carotid artery dissection, tumors in the cavernous sinus, and pituitary tumors.

The first priority is to make the correct diagnosis. Cluster headache and other TACs *all require imaging when first making the diagnosis*, since so many pathologies can mimic cluster headache and the other TACs. Since the patient has a possible Horner syndrome, MR imaging and MR angiography (or CT angiography) should be done to look for compressive lesions or carotid dissection along the oculosympathetic pathway. If studies are negative, the patient can be diagnosed and treated for cluster headache. Our patient's imaging was completely normal.

Cluster occurs daily often at the exact same time each day as seen in our patient. It is typically episodic—meaning there is a remission that can lasts weeks, months, or years between the next group of attacks. It is frequently seasonal, occurring in the spring and fall. Less frequently, cluster can also be chronic—meaning there is no break from the cluster and these individuals can be severely affected. Our patient is in the midst of his first attack, so his diagnosis would be episodic cluster.

Treatment for cluster headache can be divided into two parts. First, preventive therapy is frequently needed; these would be medications taken daily to prevent attacks from occurring. Typical preventives include verapamil (240–480 mg), anticonvulsants like topiramate (50–200 mg), or antidepressants such as lithium (300–900 mg). A burst of steroids prednisone (20–60 mg) at the onset will frequently halt attacks. Acute therapy would also include oxygen 5–10 L/min for 10–15 min.

Table 28.2 ICHD 3 beta Diagnostic Criteria for paroxysmal hemicrania

(A)	At least 20 attacks fulfilling criteria B–E
(B)	Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 min
(C)	At least one of the following symptoms or signs, ipsilateral to the pain:
	1. Conjunctival injection and/or lacrimation
	2. Nasal congestion and/or rhinorrhea
	3. Eyelid edema
	4. Forehead and facial sweating
	5. Forehead and facial flushing
	6. Sensation of fullness in the ear
	7. Miosis and/or ptosis
(D)	Attacks have a frequency above 5 per day for more than half of the time
(E)	Attacks are prevented absolutely by therapeutic doses of indomethacin
(F)	Not better accounted for by another ICHD-3 diagnosis

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Sumatriptan injectable or nasal spray and zolmitriptan nasal spray have clear evidence of benefit. Cluster attacks, in general, do not respond to typical analgesic therapy. Finally, patients should be warned to quit smoking and drinking alcohol during cluster attack periods.

There are many other types of trigeminal autonomic cephalgias—and the way to recognize them is by the gender of the individual and the length of the attack. These are ALL unilateral and can be severe. These ALL can sound like cluster and you can be a hero or "shero" if you get this right. Paroxysmal hemicrania is a shorter version of cluster, more common in women and usually not very long (usually less than 30 min). Individuals have to have at least one autonomic feature including facial flushing and ear fullness. See Table 28.2. One of the keys to the diagnosis and treatment is that it responds absolutely to indomethacin in doses of 75–150 mg. There are two forms: episodic which occurs in bouts of 7 days up to a year with some pain-free times in between and the worse version, chronic paroxysmal hemicrania, occuring for over a year.

Another is short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and the variety without conjunctival injection and tearing (SUNA). See Table 28.3. This headache is really brief—lasting seconds and also accompanied by an autonomic symptom. It is more frequently seen in men and individuals have hundreds of these in a day—they are REALLY frequent. SUNCT usually is accompanied by really prominent tearing and redness of the conjunctivae in the ipsilateral eye. SUNA does not have the red eye. This headache does not respond to the usual medications—some have reported success with lamotrigine.

Table 28.3 ICHD 3 beta Short Unilateral Neuralgiform headache attacks with Conjunctival Injection and Tearing

Diagnostic criteria:

(A) At least 20 attacks fulfilling criteria B–D

(B) Moderate or severe unilateral head pain, with orbital,supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs, series of stabs or in a saw tooth pattern

(C) At least one of the following cranial autonomicsymptoms or signs, ipsilateral to the pain:

1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead and facial sweating
5. Forehead and facial flushing
6. Sensation of fullness in the ear
7. Miosis and/or ptosis

(D) Attacks have a frequency of at least one a day for more than half of the time when the disorder is active

(E) Not better accounted for by another ICHD-3 diagnosis

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Table 28.4 ICHD 3 beta Hemicrania Continuaa

(A) Unilateral headache fulfilling criteria B–D

(B) Present for >3 months, with exacerbations of moderateor greater intensity

(C) Either or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache:
   (a) Conjunctival injection and/or lacrimation
   (b) Nasal congestion and/or rhinorrhea
   (c) Eyelid edema
   (d) Forehead and facial sweating
   (e) Forehead and facial flushing
   (f) Sensation of fullness in the ear
   (g) Miosis and/or ptosis
2. A sense of restlessness or agitation, or aggravation of the pain by movement

(D) Responds absolutely to therapeutic doses of indomethacin

(E) Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Hemicrania continua is a continuous, side-locked headache most frequently seen in women. The pain is unilateral with episodic stabbing worsening. It is also associated with autonomic features. See Table 28.4. It characteristically responds absolutely to indomethacin 75–150 mg a day. See Table 28.5 for comparisons between the TACs.

Table 28.5 Differentiating the trigeminal autonomic cephalgias from migraine

Feature	Cluster	Paroxysmal hemicrania	SUNCT	Hemicrania continua	Migraine
Sex M:F	3:1	1:3	6–8:1	1:2	1:2–3
Attack duration	Usually less than 2 h	2–30 min	6–250 s	Days—with exacerbations over minutes	Hours to days
Number of attacks	1–8	1–40	1/day to 30/h	Usually continuous with episodic stabbing	Usually one attack at a time
Autonomic features	Frequent	Frequent	Conjunctival injection and tearing	At least one	None or occasionally one
Nocturnal awakening	Frequent	Occasional	–	Occasional	Infrequent
Restless during headache	Definitely	Yes	Brief	Yes	NONE—wants to rest/sleep
Indomethacin effect	Rarely helpful	Absolute	None	Absolute	Rarely helpful

Ophthalmic Perspective—Dr. Lee

The patient's story could comport with intermittent angle closure glaucoma. These patients have intermittent unilateral eye pain, nausea/vomiting, ipsilateral blurred vision, and tearing. The episodes are extremely variable lasting minutes to hours. Patients with intermittent angle closure tend to remain still. The blurring is typically significant, where the patient would not be able to function. The ophthalmologist may want to investigate for a narrow anterior chamber or compression gonioscopy (Case 5).

There is also the concern that this represents the knee-jerk reaction to "PAINFUL HORNER SYNDROME" that has been drilled into our heads-carotid dissection. When your knee jerks and you get the MRI/MRA neck, you might miss the diagnosis of cluster, but you would not miss the dissection. Certainly, if you are in doubt, pharmacologic testing could be considered and is covered in Case 17. I have also noticed that many ophthalmologists have a tendency to over-diagnose cluster headache, which is fairly rare. I think it is important to keep in mind that cluster cannot go beyond 3 h and should happen daily for several days.

Non-ophthalmic/Non-neurologic Perspective

Cluster headaches are excruciating, unilateral, and side-locked. The patient is often rocking back and forth if sitting or pacing around. As stated earlier, this should last 15–180 min, and if the duration falls outside of this window, you should not

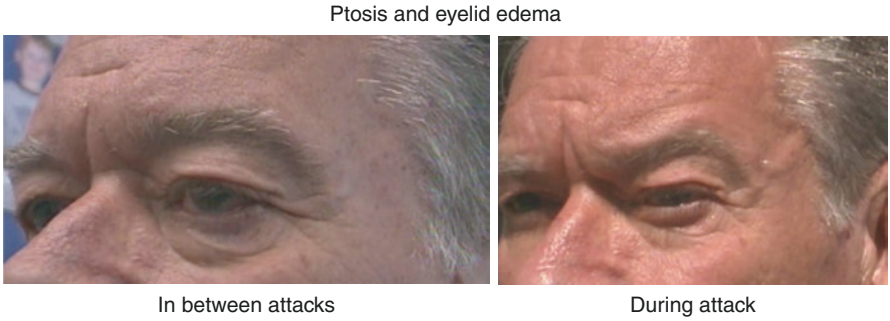

Fig. 28.1 Patient with cluster headache demonstrates normal appearance between attacks (L) and eyelid edema, ptosis, and enlargement of the temporal veins during an attack (R)

diagnose cluster headache. Most of the time the patient will come to see you between episodes, and so a careful history is required focusing on the autonomic symptoms red eye, tearing, nasal stuffiness, rhinorrhea, or eyelid edema or enlargement of temporal vessels (Fig. 28.1) and the stereotypic timing.

If there is some question about Horner syndrome (ipsilateral ptosis and miosis), a neuro-ophthalmology consult could be obtained. If cluster headaches are not responding to conventional therapy, consider referral to a neurologist or headache specialist.

Follow-up

This patient was very happy to hear a diagnosis and even happier to get on treatment. We prescribed prednisone for 2 weeks at a higher dose (40 mg) then tapered him slowly off the prednisone over 2 weeks, while initiating verapamil 80 mg three times daily as a preventive regimen. We did have to increase the dose to 240 mg twice daily to prevent break through clusters. We also gave him an oxygen concentrator and prescription for facial mask. We initiated Sumatriptan 4 mg injectable for attacks that did not respond to oxygen. After 4 months he became headache-free, and was able to successfully taper off verapamil. His Horner's syndrome did not resolve, which is typical of TAC. *Final diagnosis: Trigeminal autonomic cephalgia—cluster headache.*

For Further Study

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Case 29

History of Present Illness

Five months ago, a 66-year-old man with no previous headache history developed pain behind both eyes while running. Since then, he has noted that the pain occurs every time he coughs, sneezes, or picks up something heavy. It intermittently occurs when he bends his head below his waist, strains on the toilet, or clears his throat. It can occur if he gets up from his chair or goes up the stairs too quickly, but if he goes slowly it does not happen. If he does not Valsalva, then it would not happen. He describes it as a pressure pain, rating 5–6 out of 10, and lasting only seconds. He has been getting chiropractic manipulation of his neck and he thinks this is helping. He had a CT and an MRA brain done, which were read as normal. He denies other visual symptoms and migraine accompaniments. He denies any change to his appearance.

Past medical and ocular history Hypothyroidism Seasonal allergies Irritable bowel syndrome Atrial fibrillation	*Past surgical history* Inguinal hernia repair 15 years ago
Medications Levothryoxine Fish oil capsules Multivitamin Flucatisone nasal spray Olapatadine Aspirin	*Family history* Father—irritable bowel syndrome Mother—stroke, heart disease, macular degeneration 2 brothers—hypertension
Social history Former smoker none for 27 years 2–3 drinks, 2–3 times per week No drug use Married	*Review of systems* Post nasal drip Knee and hip pain Mild scalp tenderness No weight loss, jaw claudication, malaise

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal, brisk, no afferent pupillary defect
Intraocular pressure Right eye: 18 mmHg Left eye: 24 mmHg
External exam No swelling, normal temporal arteries, no tenderness to palpation of trochlea, supraorbital or infraorbital foramina
Eye alignment Normal
Slit lamp examination Normal, no cells, deep anterior chamber
Visual field Normal
Fundus examination Epiretinal membrane RE, single microaneurysm LE
Neurologic examination Normal

Discussion

Ophthalmic Perspective—Dr. Lee

At first glance, it seems like he is describing headaches brought on by movement, which might make one think of migraine (Case 19), which is often made worse with movement. However, he is older to have a first migraine, migraines do not last seconds, and he denies other symptoms that accompany migraine. Low intracranial pressure can lead to headaches when a patient is sitting or standing but resolve with lying down. Usually, the headache persists while the patient is upright and that is not what he is describing. Pain lasting seconds might be consistent with neuropathic pain. Classically, neuropathic pain is described as electric shock like, but he describes an ache. He notes that chiropractic manipulation has made him better, so I would palpate over his greater occipital nerve (Case 23). It may be a red herring. He notes mild scalp tenderness, but no other symptoms of GCA (Case 32). I might consider a sed rate and CRP, if I felt that his story were strong enough after talking to him. If the values were markedly elevated, then I would pursue a temporal artery biopsy. If they were normal or mildly elevated, then I would probably observe from that perspective. If they were markedly high, then I would start prednisone and pursue a temporal artery biopsy. His eye pressure is elevated, but not to the degree that this would cause pain. Also, angle closure glaucoma (Case 5) would not be bilateral and simultaneous and would last for longer periods of time.

Boiling it down, he really sounds like it is more commonly associated with effort or Valsalva. There is an entity known as cough headache. This can be a benign phenomenon or relate to an Arnold Chiari malformation (Fig. 29.1), posterior fossa lesions, or aneurysms. Typically, these lesions would give more significant headache

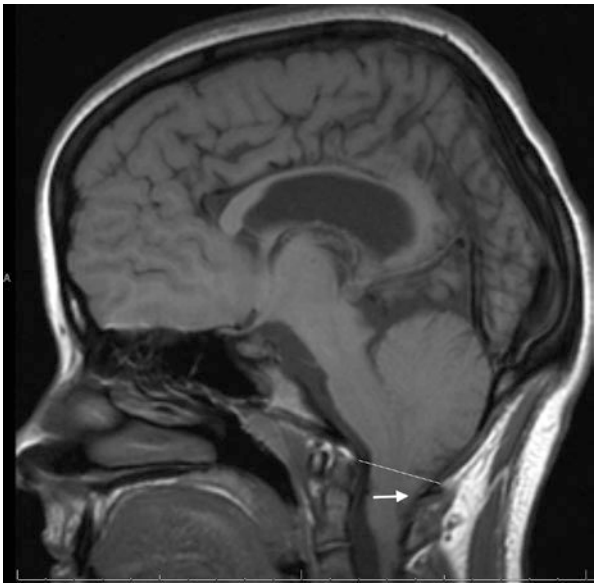

Fig. 29.1 Sagittal T1 MRI showing significant tonsillar herniation. Note the line signifying the foramen magnum. The tonsils (*arrow*) are well below this level consistent with an Arnold Chiari malformation

symptoms—worse pain, longer durations. I would look to see if his imaging shows any issues. If he has a lesion, then I would consider referral to neurosurgery.

Neurologic Perspective—Dr. Digre

This is a short headache brought on by cough or straining in an older individual with presumably NO previous headache disorder. This is a headache to pay attention to. Traction on the dura can cause these new headaches. The headaches are brief—too short for many different headache types—maybe like ice pick headache or SUNCT (this SUNCT while brief has conjunctival injection and tearing, Case 28). See Table 24.1 where we go through the differential diagnosis of short headaches.

One of the prominent features of this headache is that it is precipitated by coughing or Valsalva maneuver. There is a primary headache disorder (meaning there is no other cause to it) called Primary Cough Headache! It is sometimes also known as Valsalva maneuver headache (see Table 29.1). While primary cough headache is a rare headache disorder it can localize around the eyes. It is most often bilateral and sometimes posteriorly and interestingly this headache hits people over 40 or 50.

However, there is caution with cough headache. Look for a secondary cause! The one diagnosis you do not want to miss with cough headache is a Chiari malformation since up to 40% of individuals presenting with cough headache can have this diagnosis. Other posterior fossa lesions like tumors should be ruled out. So this guy deserves an MR not a CT scan to look at the cranial cervical junction. In addition, be careful not to miss intracranial hypotension (Case 31) that can look a lot like a Chiari 1. Other causes of a cough headache include pinealoma, basilar impression, subdural hematoma, brain tumor, midbrain cyst, and pituitary tumor. Treatment of these secondary or symptomatic cough headaches is dictated by the underlying pathology.

Table 29.1 ICHD-3 beta Primary Cough Headache

Diagnostic criteria:
(A) At least two headache episodes fulfilling criteria BD
(B) Brought on by and occurring only in association with coughing, straining, and/or other Valsalva maneuver
(C) Sudden onset
(D) Lasting between 1 s and 2 h
(E) Not better accounted for by another ICHD-3 diagnosis

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Treatment of primary cough headache has been indomethacin—sometimes in higher doses. Acetazolamide, amitriptyline, naproxen, and propranolol have been reported to be helpful in some.

Non-ophthalmic/Non-neurologic Perspective

This is an uncommon cause of headache, but requires a careful history. The patient should have an MRI and MRA to evaluate for Chiari malformations, posterior fossa lesions, or aneurysm. We would recommend giving contrast, since one can also look for thickening and enhancement of the dura mater seen in spontaneous intracranial hypotension.

Follow-up

I did not have his scans, and so I called radiology where he had it done and asked them to look at the source images for an Arnold Chiari malformation or other posterior fossa lesions. There were none present. Therefore, this clinical presentation would be consistent with primary cough headache (formerly known as benign cough headache). This entity often lasts seconds at a time, is more common in men, and does not occur under the age of 40 years. His description is a little different in that most patients describe sharp pain. It is associated with a normal MRI and mild symptoms. It may benefit from the use of indomethacin or acetazolamide, but the patient was not interested. This often spontaneously resolves over the course of several years. The patient was given reassurance and will follow-up with his primary eye doctor regarding the epiretinal membrane, elevated eye pressure, and single microaneurysm in the LE. *Final diagnosis: Primary cough headache*.

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Case 30

History of Present Illness

A 52-year-old cardiology nurse has a history of a father with headaches and she really had rare periodic headaches that were always easily treated with ibuprofen. She was rear ended on the freeway by a truck going about 35–40 mph. No air bags were deployed, she struck her head but did not lose consciousness, and did not go to the hospital although emergency medical services were called. The next day she went to instacare for a headache, neck pain, and eye pain. She was given ibuprofen and sent home. She developed light sensitivity and missed work for a week. Her primary care physician ordered an MR of the brain and cervical spine about 2 weeks later and aside from some disc degeneration and one white spot on the brain, the imaging was normal. She saw a neurosurgeon who treated her with 6 days of steroids, but there was no effect on her eye pain. The headache became less frequent, but the eye pain persisted. The pain is in both eyes left more than right and when the headache occurs, the right eye pain intensifies. Her left eye pain severity fluctuates as well. Currently, her worst headache occurs when the eye pain is severe—it feels like a brick on the forehead and a band around the eyes. She has light and sound sensitivity and when it is severe, she has nausea. These occur every 2 weeks and she lies down. She has moderate headaches about 4 days each week lasting 2–8 h. The eye pain is bilateral left more than right, sometimes she has watering in her both eyes, and sometimes her eyes look red. Her neck is always sore. She feels her processing speed is reduced and speech sometimes slurs.

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_30

Past medical and ocular history Basal cell cancer	*Past surgical history* History of basal cell cancer removed by Moh's surgery
Medications Vitamins C, D Norethindrone Ibuprofen, hydrocodone PRN	*Family history* Glaucoma Macular degeneration
Social history Married, works as a nurse No smoking or alcohol use	*Review of systems* Per HPI

Examination

Acuity with correction Right eye: 20/20 Left eye: 20/20-1
Pupils 3 mm OU in light; 4 mm OU in darkness; no RAPD
Intraocular pressure Right eye: 14 mmHg Left eye: 13 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination Mild meibomian gland dysfunction; trace nuclear sclerosis OU
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective—Dr. Digre

The phenotype of this patient's worst headache is migraine (moderate to severe, light and sound sensitivity with nausea and worsening with activity). While she had periodic headaches before, after her whiplash and motor vehicle accident, she now has developed migraine-like headaches, which are considered post-traumatic. Headaches are very common after trauma to the head and neck. In fact, 90% of persons with traumatic brain injury will have headache. There are two flavors of post-traumatic headache—acute (occurring right after the injury) and persistent (occurring for over 3 months after the injury). While most of the time headaches and symptoms will resolve, many continue to have complaints after 3 months (about

20%). These headaches and eye pain can occur after moderate to severe trauma or mild trauma such as in this case. Furthermore, the headache can be attributed to whiplash along with traumatic brain injury. Headaches may be seen as an isolated symptom, but often there are other symptoms like difficulty concentrating, depression, dizziness, fatigue, depression and anxiety, insomnia, and irritability. In this case, she had both a blow to the head without loss of consciousness and whiplash (a sudden acceleration/deceleration) with movement of head either in flexion or extension.

The risk factors for the development of post-traumatic headache include: female gender, and history of previous traumatic brain injury. The phenotype of the headache is often chronic tension type (Case 26) in the majority, and mixed tension-type and migraine-like headaches—such as seen in our patient. The most common cause of post-traumatic headache is motor vehicle accidents, but falls, sports and recreational injuries and assaults are causative.

Post-concussive symptoms are not rare and fall into four types including sleep disturbance, cognitive changes, emotional issues, and somatic complaints like fatigue. She has developed, according to the ICHD 3beta, a persistent headache after mild head trauma (see Table 30.1) and persistent headache attributed to whiplash (see Table 30.2).

In addition, she developed eye pain right after the injury. This pain may have a couple of sources—first, as we have seen in cervicogenic headache (Case 29) eye pain can occur probably related to the anatomy of the nucleus caudalis of the trigeminal system into the upper cervical cord.

She also has dry eyes which will compound the pain problems. Her Schirmer's were 1 mm in both eyes. Dry eyes may have been a pre-morbid condition but dry eye symptoms can occur after trauma too. In addition, chronic pain disorders have

Table 30.1 ICHD 3 beta criteria for Persistent Headache attributed to mild head injury

Headache fulfilling the following:

1. Associated with NONE of the following
   (a) Loss of consciousness for over 30 min
   (b) Glasgow coma scale less than 13
   (c) Post-traumatic amnesia lasting over 24 h
   (d) Altered level of awareness for over 24 h
   (e) Imaging evidence of traumatic head injury such as hemorrhage or contusion
2. Associated immediately following the head injury one or more of the following:
   (a) Transient confusion, disorientation, or impaired consciousness
   (b) Loss of memory for events immediately before or after the head injury
   (c) Two or more of the following symptoms: nausea, vomiting, visual disturbance, dizziness and or vertigo, impaired memory or concentration
3. Headache for over 3 months after the injury to the head
4. Not accounted for by another diagnosis

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Table 30.2 ICHD 3 beta criteria for Persistent headache after Whiplash

A headache for over 3 months caused by whiplash
Criteria:
(A) Any headache that fulfills criteria C and D
(B) Whiplash associated with neck pain and/or headache has occurred
(C) Headache developed within 7 days after whiplash
(D) Headache persists for more than 3 months after whiplash
(E) No better accounted for by another diagnosis

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also been associated with dry eye symptoms. Certainly, aggressively treating this problem will help her eye pain.

Treatment of whiplash and post-traumatic-associated pains has focused on education—explaining what happened, avoiding immobilization of the neck, encouraging normal neck movements, and getting back to work. Physiotherapy in some cases may be helpful, but was not found to be cost-effective. Further, evaluate for medication overuse—since many individuals receive narcotic medication at the time of the accident that can further exacerbate headaches (Case 20). Treat the headache based on the phenotype (e.g., migraine-specific medications can be helpful in migraine-like pains like tricyclics, beta blockers, and anticonvulsants). Treat psychological symptoms and also treat insomnia, depression, and anxiety. Risk factors for poor outcome include: severe pain, headache at the time of injury, older age, lower educational level, no seatbelt use, low back pain, pre-injury neck pain, high pain catastrophizing, and female sex. There has long been a controversy about whether post-traumatic headaches are non-organic or present because of compensation or legal issues. In general, while there are certainly cases of malingering, most individuals want to get back to work like our patient.

Ophthalmic Perspective—Dr. Lee

Frankly, I was unaware of dry eye developing after head trauma, but I believe it since I know one of the authors of that citation well. We discuss the treatment for dry eye in Chap. 1. Two other common disturbances that occur following trauma are convergence insufficiency (Case 4) and photophobia (Case 21). Some other findings that might occur include nystagmus, binocular diplopia, or visual loss. Nystagmus and visual loss are not related to eye pain. There is a nonorganic kind of fluttering eye movements called voluntary flutter. Usually patients cannot maintain it for more than 1 min and there is characteristic fluttering of the eyelids. Visual loss can also be nonorganic. This should be evaluated with optical coherence tomography of the nerve fiber layer (RNFL) and the macula at least 3 months after the injury. Commotio will show thinning of the outer nuclear layer or disruption of the ellipsoid. Optic neuropathy will show thinner RNFL and ganglion cell layer. Binocular diplopia

from a traumatic fourth nerve palsy can result in eyestrain and neck pain. The eyestrain occurs by trying to fuse the two images together causes strain on the eyes. The neck pain relates to patients with fourth nerve palsies typically tilt their head to one side to improve the double vision. Convergence spasm is typically nonorganic and manifests as an esotropia with miosis upon attempted abduction.

Non-ophthalmic/Non-neurologic Perspective

Post-traumatic headache and whiplash are common complaints in the primary care office. It is clear that education, appropriate preventive medications for the phenotype of the headache is helpful. Be aware that the eye pain may be related to dry eyes in addition to cervical spasm or trauma.

Follow-up

We educated her on her headache and dry eye diagnoses. We started her on tizanidine 4 mg at night or sleep and also headache prevention and treated her dry eyes aggressively with preservative free artificial tears. We suggested she take isometheptene/acetaminophen combination (Midrin) for her migraine headaches. She continued working and was doing well. *Final diagnosis: post-traumatic eye pain*.

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Case 31

History of Present Illness

A 32-year-old body builder and car salesman lifted weights every morning. He had no previous headache or eye problems. One day while at work in his usual routine, he developed a relatively acute, severe headache with pressure behind his eyes. He noticed if he would lie down, it would abate, but within minutes of standing up, he had a severe headache and the pressure feeling behind his eyes would begin. He also complains of neck pain. He has minimal light sensitivity and mild sound sensitivity—and some muffling to his hearing, but no nausea. The pain does worsen with activity—and he stopped lifting weights. He tried to sleep it off, but when it did not resolve after 2 weeks, he began missing work and was referred for further evaluation. Recently, he has noted fleeting diplopia—which is side by side, and only present in the distance—and not all of the time.

Past medical and ocular history History of MVA at age 18—no loss of consciousness	*Past surgical history* None
Medications None	*Family history* Non-contributory
Social history Married; used to smoke but quit years ago. Drinks socially on occasion	*Review of systems* Since the headache started he has been trying to sleep more

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_31

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal and no RAPD
Intraocular pressure Right eye: 14 mmHg Left eye: 14 mmHg
External exam Normal
Eye alignment He has a mild comitant esophoria of 4–8 diopters on right and left lateral gaze
Slit lamp examination Normal
Visual field Normal to confrontation
Fundus examination Normal
Neurologic examination Normal

Discussion

Neurologic Perspective—Dr. Digre

This is a new onset of a daily headache in someone who has not had headaches in the past—he requires further work up and questioning. While this could be "new daily persistent headache"—a diagnosis of a headache starting one day and never going away, the real clue in this case is the positional nature of his headache. Anytime there are positional headaches, one has to consider a low cerebrospinal fluid volume or low intracranial pressure. The most common cause is after a lumbar puncture, but these positional headaches can start spontaneously at any time. Eye pain does occur with these headaches as well, but is often a dull ache—and not the primary complaint. Other things can cause a positional headache too. Individuals who have had a Chiari malformation surgery, a large dural sac, colloid cyst of the third ventricle, post-coital headache, cardiac cephalgia (eye pain and headache with upright position and exertion, relieved by rest), and postural orthostatic tachycardia syndrome (POTS) (usually seen in young women with striking tachycardia after standing up for a while) can have positional headaches. These headaches are commonly mis-diagnosed as tension-type headache. The diplopia is not rare—probably coming from tugging on the sixth cranial nerve as the brain stem slumps downward toward the foramen magnum.

While trauma is obviously a risk factor for developing these headaches, sports such as golf and weight lifting, coughing from a upper respiratory infection, chiropractor

Table 31.1 ICHD 3 beta: Intracranial hypotension

Description: Orthostatic headache caused by low cerebrospinal fluid (CSF) pressure of spontaneous origin. It is usually accompanied by neck stiffness and subjective hearing symptoms. It remits after normalization of CSF pressure
Diagnostic criteria:
(A) Any headache fulfilling criterion C
(B) Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
(C) Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
(D) Not better accounted for by another ICHD-3 diagnosis

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manipulation, fishing and even yoga have been reported with its development. Even minor trauma like sitting on a 4-wheeler can induce it in certain individuals. It is thought that people with connective tissue problems like Marfan's and Ehlers Danlos syndromes are more susceptible.

The diagnosis is usually made by history and with imaging (Table 31.1). MRI shows a sagging brain including cerebellar tonsillar herniation, optic nerve and chiasmal downward displacement, and striking meningeal enhancement. The diffuse meningeal enhancement seen on MRI, reported just over 10 years ago, has become one of the key diagnostic imaging features. Since meningeal enhancement alone, however, can be a sign of other conditions causing headache (meningitis, meningeal carcinomatosis, neurosarcoidosis, subarachnoid hemorrhage), look for other findings. The other clear feature is the descent of the brain and brain stem, including: cerebellar tonsillar herniation, reduced size of the pre-pontine cistern, inferior descent of the optic chiasm, and descent of the iter (or the aqueduct opening). Ventricular size is on the smaller size in some and reverts to normal after normalization of pressure. Enlargement of the pituitary gland has also been shown. Engorgement of the venous plexus and spinal veins also occurs.

In this disorder, the spinal fluid pressure is not invariably low. Less than 50% of individuals in many had pressures of less than 40 mm CSF—and many are normal—so reliance on pressure alone is inadequate. There can be lymphocytic pleocytosis and increased CSF protein (up to a 1000 mg/dL in some cases). Once the diagnosis has been made—treatment with a blind blood patch is often recommended since many individuals will have complete resolutions of their symptoms.

However, if that fails, then looking for the leak is the next step and this is sometimes tricky. The first imaging test can be high-resolution MRI, and rarely a leak can be found. A CT myelogram is usually recommended, from the base of the skull through the lumbar sacral regions. MR gadolinium myelogram has also been recommended.

Often medical treatment with IV fluids, corticosteroids, and IV caffeine has been successful in treating the headache. Most frequently a directed blood patch is required. The cause of the headache is more likely to be related to the volume and not the pressure. Many complications of untreated intracranial hypovolemia or hypotension occur including: subdural hematomas, stroke, central herniation syndrome with stupor and coma.

Ophthalmic Perspective—Dr. Lee

I think it is important to note that the diplopia is not positional in intracranial hypotension—meaning the double vision does not vary as quickly as the headache. Additionally, not all patients have double vision or a sixth nerve palsy. So, if the patient merely has eye pain or headache, then the diagnosis is really predicated on the history of positional headache. Unless of course, you have an MRI and this shows the dural thickening and enhancement, then the diagnosis may be suggested by the radiologist.

Orbital varices can cause proptosis that varies with head position or Valsalva, but these are not typically painful. Patients with autonomic dysfunction and pre-syncope may develop transient bilateral visual loss with standing. Associated symptoms can include lightheadedness, photopsias, and ataxia. Headache would be very unusual in this circumstance. Patients with Arnold Chiari malformations could develop headache with Valsalva or cough (Case 29), but this should be easily distinguishable from the positional headache of low ICP.

When confronted with this diagnosis, it is best to send the patient for a blood patch or to neurology to identify a leak using the imaging tools Dr. Digre mentioned. These patients most often have a leak from the area of a spinal root.

Non-ophthalmic/Non-neurologic Perspective

These positional headaches can occur in the primary care provider office and the history is not always straight forward. I have had patients come to my clinic—and when I walk in the room they are lying on the floor or on the examining table because they are more comfortable. This is a great clue to this disorder. The new headache is really a tip off too—and always asking about positional changes helps to make this diagnosis. Sometimes if the pain has been present for a long time, ask about what the pain was like at the very onset of the new daily persistent headache; after a long period of time, the positional aspect of this pain can go away.

If the patient has diplopia—have them look at the end of the room at a target and see if by cross covering their eyes you pick up an eso deviation (i.e., the eye moves from in to out) and especially look for an eso in right and left gaze. Also check for downbeating nystagmus because this can occur with this type of headache and eye pain.

Follow-up

Imaging showed classic signs of intracranial hypovolemia with slumping of the posterior fossa and tonsillar herniation, enlarged pituitary gland, axial images showed compression of the midbrain, and smooth dural enhancement (see Fig. 31.1).

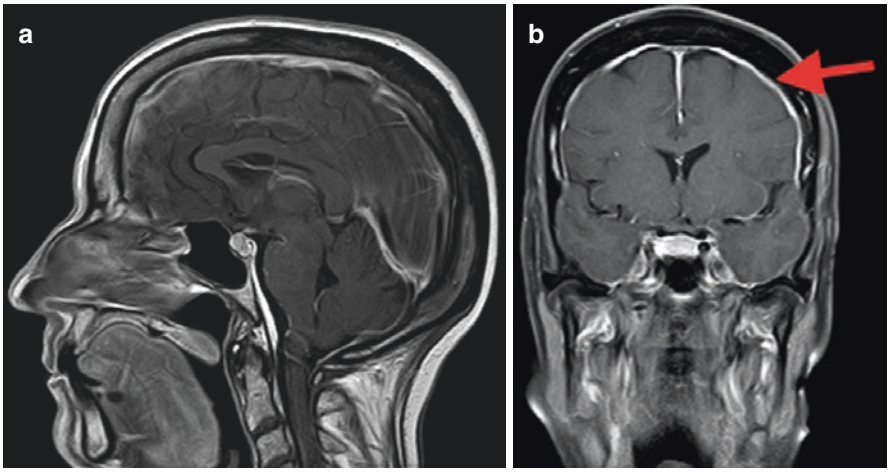

Fig. 31.1 (**a**) Sagittal T1 MR scan showing tonsillar descent, dilated superior sagittal sinus and enlarged pituitary; (**b**) coronal postgadolinium T1 shows marked thickening and enhancement of the dura (*arrow*)

We did a blind blood patch with good relief of the headache and eye pain, but since he still had intermittent pain, we repeated the blood patch with a larger volume and the symptoms resolved. We recommended that he hold off on weight lifting for about 3–6 months so that he did not have a recurrence. *Final diagnosis: spontaneous intracranial hypotension.*

For Further Study

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Case 32

History of Present Illness

A 70-year-old white man began having sharp pains around the left eye a few days after lumbar spine surgery 4 months ago. He notes that the eye and temple area are tender to palpation. The pain is constantly a 3 of 10 but increases to 10/10 for hours at a time. He denies nausea, vomiting, phonophobia, and photophobia. He denies a personal or family history of migraine. He was diagnosed with migraine and was treated with sumatriptan, diphenhydramine, ketorolac, and prochlorperazine. He was then given prednisone 40 mg daily for 10 days and his headache resolved completely and then returned when the steroids were finished. He was then begun on indomethacin 25 mg three times daily without benefit.

Past medical and ocular history Hypertension Seasonal allergies Heart block	*Past surgical history* Appendectomy as a child Knee surgery 2012 Cataract surgery 2013 Pacemaker
Medications Aspirin Fish oil Vitamin D Loratadine Lisinopril Indomethacin	*Family history* No pertinent history
Social history Retired social worker Former smoker Occasional alcohol	*Review of systems* Postnasal drip Chronic cough Pain with chewing Easy bruising Bilateral knee pain Constipation No weight loss, anorexia, malaise

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_32

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal, brisk, no afferent pupillary defect
Intraocular pressure Right eye: 12 mmHg Left eye: 13 mmHg
External exam Tenderness of left temple Dermatochalasis of both upper lids No proptosis
Eye alignment and motility Normal, notes left eye pain with movement
Slit lamp examination Normal except intraocular lenses
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective—Dr. Lee

Generally speaking, new headache/eye pain in a 70-year-old is unusual. New migraine in a septuagenarian without migraine accompaniments would be a diagnosis of exclusion. Additionally, he did not respond to the migraine cocktail. Interestingly, his eye pain resolved with steroid use, which suggests inflammation, infection, or edema. The eyes are white and quiet, but he has pain with eye movement. One consideration would be a myositis of the extraocular muscles. Malignancies are not uncommon in this age group and steroids can improve pain/headache from cerebral edema. Infections can invade from the paranasal sinuses and also respond to steroids transiently. I think a CT orbit with and without contrast would be reasonable (the patient has a pacemaker precluding an MRI) to evaluate for eye muscle enlargement, paranasal sinus involvement, abscess, and mass.

His review of systems also shows pain with chewing. It is critical to find out more information about this in patients older than 50 years because this could represent giant cell arteritis (GCA). Patients with true jaw claudication experience pain similar to what patients with leg claudication do. The pain begins after prolonged chewing, worsens as the chewing progresses, and improves over the course of minutes after the chewing has stopped. Pain with opening the jaw (temporomandibular joint disease), initially biting down (cracked tooth, tooth disease), or that stops immediately when chewing desists (tooth disease) are not consistent with jaw claudication. If he

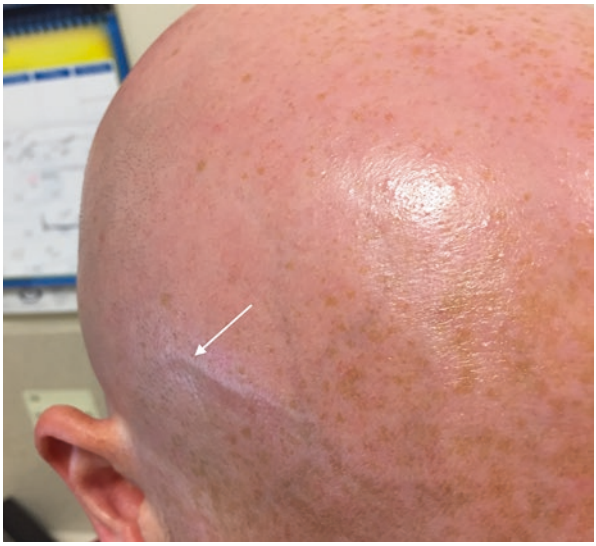

Fig. 32.1 External photograph shows an enlarged temporal artery. Palpation may show a reduced pulse or tenderness

endorses true jaw claudication, my suspicion goes up for GCA and he buys himself a temporal artery biopsy. If he does not, then I would check ESR and CRP. A high ESR is age divided by 2 in a man and age divided by 2 + 5 in a woman. Be careful because 20% of patients with GCA may have no systemic symptoms or a normal ESR. A high CRP is over the normal limits of the testing laboratory. Make sure you pay attention to the units since some labs report in mg/L and others in mg/dL, which is an order of 10 off. So a CRP of 4 could be really high or really normal! I would palpate his temporal arteries to look for tenderness or pulselessness. Is it enlarged or ropy (Fig. 32.1)? If the suspicion for GCA is high, then I would start oral prednisone and get a temporal artery biopsy of at least 2 cm in length right away. He has been on prednisone for 10 days recently. Generally, the results are not falsely negative if the patient has been on prednisone less than 10–14 days.

Neurologic Perspective—Dr. Digre

First, this man has NEVER had migraine history—a new headache in anyone over 40 is a cause for great concern. Normally, we would get an MR scan on any new headache like this, but of course the pacemaker makes this more difficult. CT imaging would be a first step. Second, the review of systems lists jaw pain with chewing—one of the most sensitive questions for giant cell arteritis. In fact in many series of positive temporal artery biopsies, jaw claudication is the most common symptom. I would say ANYONE with a headache over the age of 65—that should be one of your go-to questions. If we look at the ICHD 3 beta criteria (Table 32.1) for giant cell arteritis—this guy has it: he has scalp tenderness AND jaw claudication. He also had a response to his headache with steroids! So I am betting on a positive biopsy.

Table 32.1 ICHD3 beta criteria for giant cell arteritis headache

Diagnostic criteria:
(A) Giant cell arteritis (GCA) has been diagnosed
(B) Must have Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical or biological signs of onset of GCA, or has led to the diagnosis of GCA
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with worsening of GCA
(b) Headache has significantly improved or resolved within 3 days of high-dose steroid treatment
3. Headache is associated with scalp tenderness and/or jaw claudication

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

I am with Dr. Lee—he needs a ESR and CRP and a temporal artery biopsy. There is some intriguing work being done on using ultrasound or MR imaging, but this is not good enough yet for diagnosis. In my practice, I see many individuals diagnosed with GCA without a biopsy. I think this is one disorder that you have to get a right diagnosis—and sometimes you have to do both sides if you are suspicious. You do not want to put older individuals on medications that can cause side effects like steroids without a good solid diagnosis. Finally, headache is very common with GCA (about 75%) of the time—and only a quarter are actually in the temple. Eye pain occurs around 10% of the time—so keep this one in your differential of eye pain in older individuals!

Non-ophthalmic/Non-neurologic Perspective

A GCA review of systems includes asking about pain with chewing, weight loss, anorexia, malaise, scalp tenderness, fevers, and shoulder or hip arthralgias. Jaw claudication is by far the most specific symptom. Checking ESR and CRP in anyone over 65 with a new headache is reasonable. If they are elevated, then starting prednisone and ordering a temporal artery biopsy is reasonable. In my experience, if the headache does not improve on high-dose prednisone, then it is less likely to be GCA related.

Follow-up

The patient underwent an unremarkable CT brain and orbit. The ESR was 45 mm/h and the CRP was 0.8 mg/dL (normal < 0.5 mg/dL). The patient was placed on prednisone 40 mg daily and underwent a left temporal artery biopsy, which was positive. The patient remained on prednisone and aspirin and was referred to rheumatology. He was very interested in a steroid sparing agent and inquired about tocilizumab (FDA-approved for GCA on 5/22/17). *Final Diagnosis: Giant cell arteritis, temporal arteritis*.

For Further Study

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Case 33

History of Present Illness

A 39-year-old completely healthy woman presented to the emergency room. Four days before she defecated and suffered an "explosion" of pain in her head and behind her eyes. She had throbbing pain and nausea. She was first seen at an outside hospital and diagnosed with probable migraine. A head CT was negative and she did not have a lumbar puncture. She was discharged and the pain gradually decreased over the next 2 days and she was able to return to work. Then 4 days later she again experienced another explosion in her head. She had mild photophobia. She has a history of previous migraine. She does not recall any sympathomimetic use.

Past medical and ocular history Moderate obesity Two pregnancies delivered by cesarean section	*Past surgical history* None
Medications Occasional codeine for headaches	*Family history* Cerebral aneurysm in a great aunt
Social history Married with two children; no smoking, alcohol use	*Review of systems* No prodromal illness

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_33

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal and no RAPD
Intraocular pressure Right eye: 14 mmHg Left eye: 14 mmHg
External exam Unremarkable
Eye alignment Normal
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal Blood pressure 116/75

Discussion

Neurologic Perspective—Dr. Digre

The sudden onset of the worst headache of one's life is sometimes called a "Thunderclap Headache"—and it usually makes every provider sit up and pay attention—since this is the typical headache of an ominous headache like a sub-arachnoid hemorrhage. Indeed 70% of subarachoid hemorrhages from an aneurysm will present this way. The key feature of these headaches are the pain develops in less than 1 min and it is very severe—usually resulting in going to an emergency room. There is often photophobia and phonophobia as well as nausea and vomiting.

There are both primary and secondary thunderclap headaches. The definition of a primary thunderclap headache by the ICHD 3 beta is that NO other cause is found (see Table 33.1). This primary headache can be caused by cough (Case 29) or sexual intercourse (sometimes called orgasmic headache). However, before making the diagnosis, secondary causes must be evaluated. There are many serious causes of a thunderclap headache besides sub-arachnoid hemorrhage. See Table 33.2 for a list of primary and secondary causes of thunderclap headache. Looking for a secondary cause for thunderclap is essential and headaches must be thoroughly evaluated with imaging of the brain (usually a CT) and vessel imaging—CTA or MRA. In addition, a lumbar puncture must be done to look for sub-arachnoid hemorrhage. Most of the time, many of the causes will be seen on CT or MR scan.

In this case, the CT scan was initially normal, and the severe headache recurred 4 days later. This pattern of the *recurrent thunderclap headache* repetitively recurring

Table 33.1 Diagnostic criteria for Primary thunderclap headache (by ICHD3 beta)

(A) Severe head pain fulfilling criteria B and C
(B) Abrupt onset, reaching maximum intensity in <1 min
(C) Lasting for more than 5 min
(D) Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 33.2 Causes of thunderclap headache

Primary thunderclap headache:
Benign Exertional headache
Cough headache
Exertional headache
Orgasmic headache
Secondary thunderclap headache:
Vascular causes:
Subarachnoid hemorrhage from an aneurysm other non-aneurysmal subarachnoid hemorrhage causes:
Vertebral dissection
Cavernous angioma
Vasculitis
Amyloid angiopathy
Reversible vasoconstriction syndrome
Cerebrovenous sinus thrombosis
Intracerebral hemorrhage
Arterial dissection
Posterior reversible encephalopathy syndrome (PRES)
Reversible cerebral vasoconstriction syndrome (RCVS)
Pregnancy (usually post-partum)—and pregnancy complications
Migraine
Medications associated with RCVS:
Illicit drugs (like cocaine, marijuana, lysergic acid diethylamide LSD, amphetamines, ecstasy)
Sympathomimetic drugs (epinephrine, pseudoephedrine, diet pills)
Triptans (e.g. Sumatriptan,
Ergotamines
Bromocriptine
Serotoninergic drugs (e.g. sertraline, fluoxetine)
Immunosuppressant (cyclophosphamide, Tacrolimus, interferon alpha)
Blood products: (intravenous immunoglobulin IVIG, blood transfusion)
Others: Nicotine patches, oral contraceptives, ginseng, licorice, indomethacin
Swimming and bathing
Altitude
Tumors
Pituitary apoplexy
Colloid cyst of the third ventricle
Intracranial hypotension
Acute sinusitis—barotrauma

is typical of reversible cerebral vasoconstriction syndrome (RCVS). RCVS occurs usually in middle aged women, although all ages and sex occurs. These headaches may be triggered by simple every day activities such as bathing, swimming, or coughing. Frequently, the CT scan is initially normal. Most of these cases are misdiagnosed as migraine as in our case. Vessel imaging early on can be negative, and looking for risk factors in the history for the diagnosis is a good idea. The vessel imaging can look a lot like vasculitis, but a vasculitis workup is usually negative and the CSF in RCVS is usually near normal. Even more vexing is that vessel imaging can be initially normal and repeated vessel imaging should be performed, if there are repeated bouts or one of the risk factors. Making the correct diagnosis is often difficult. First, ruling out a sub-arachnoid hemorrhage with a CT scan and also LP is often done. In RCVS sometimes there can be small hemorrhages, but there is no aneurysm on angiography. Treatment of RCVS is directed usually to the use of calcium channel blockers such as verapamil or nimodipine treatment. Steroids may worsen the condition but have been used on occasion. Occasionally blood pressure may be elevated and may require treatment. While the outcome is usually excellent, complications can occur including hemorrhage, seizures, and stroke-like symptoms if not stroke. We really do not understand the cause of these reversible constrictions—and some have suggested abnormal vascular receptor sensitivity.

Ophthalmic Perspective—Dr. Lee

These patients have the "worst headache of their life" and the pain is very sudden onset. For the most part these patients will not present to the ophthalmologist and one of our ilk may never see a patient with RCVS. However, I do have some thoughts for the differential of the patient with sudden severe eye pain and headache. Besides an aneurysm, pituitary apoplexy can cause abrupt and severe headache and also cause ophthalmic findings. Usually this occurs in the setting of a previously present (but often not known about) pituitary adenoma. A bleed into the tumor or an infarction in the tumor leads to sudden expansion. The pituitary gland sits below the chiasm and between the two cavernous sinuses. If the tumor expands superiorly, then the patient can develop vision loss in one or both eyes. If it expands laterally, then it may cause a unilateral or bilateral third, fourth, and/or sixth nerve palsy. Since the pain is sudden onset, the patient should get a scan no matter what and imaging will typically show a bleed into a large sellar mass. The biggest thing is to scan patients with sudden and horrible headache.

Non-ophthalmic/Non-neurologic Perspective

Thunderclap headache is a type of eye/head pain that all primary care physicians should know about. While primary headache (benign, primary thunderclap headache) is the most common, these headaches require an extensive evaluation of imaging, lumbar puncture, and vessel imaging. Look out for RCVS since this one can be caused by many medications often used in general internal medicine and primary care.

Follow-up

The CT scan was normal; Lumbar puncture: protein 38, glucose 61, 0 WBC, 60 RBC, normal opening pressure. She had an MR scan which was normal. She was admitted and a re-read of the CT showed a very small subarachnoid hemorrhage on the left parietal region. She underwent an angiogram which showed diffuse segmental narrowing of her arteries in the MCA and PCA distribution (Fig. 33.1). There was no evidence of an aneurysm. Initially, she was thought to have a vasculitis, but all laboratory studies were negative. A trial of prednisone was initiated, and her headache subsided once again. She was diagnosed with RCVS or benign reversible angiopathy (see Table 33.3). She was placed on verapamil with improvement of her headache. She continued verapamil and baby aspirin without recurrence of her thunderclap headache. *Final Diagnosis: thunderclap headache due to Reversible Vasoconstriction Syndrome*.

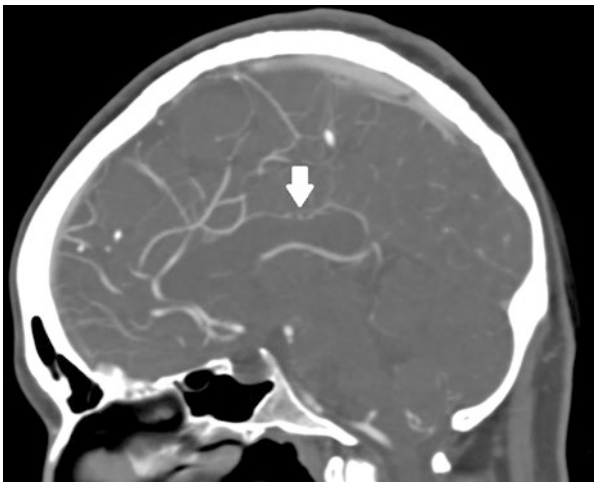

Fig. 33.1 Sagittal CTA source image shows arteriolar "beading" (*arrow*) consistent with RCVS. With thanks to Jennifer Majersik and Adam DeHavenon for this case

Table 33.3 Diagnostic criteria for the diagnosis of reversible vasoconstriction syndrome (RCVS)

(A)	Any new headache fulfilling criterion C
(B)	Reversible cerebral vasoconstriction syndrome (RCVS) has been diagnosed
(C)	Evidence of causation demonstrated by at least one of the following:
	1. Headache, with or without focal deficits and/or seizures, has led to angiography (with "strings and beads" appearance) and diagnosis of RCVS
	2. Headache has either or both of the following characteristics:
	(a) Recurrent during 1 month, and with thunderclap onset
	(b) Triggered by sexual activity, exertion, Valsalva maneuvers, emotion, bathing and/or showering
	3. No new significant headache occurs >1 month after onset
(D)	Not better accounted for by another ICHD-3 diagnosis, and aneurysmal subarachnoid hemorrhage has been excluded by appropriate investigations

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

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Part IV
Neurologic Disorders Causing Eye Pain: Abnormal Eye or Neurologic Exam

Case 34

History of Present Illness

A 19-year-old Pakistani student studying statistics at a local university was transferred for work up for unexplained fevers and headaches. He developed neck pain radiating to both eyes and fever off and on for 2–3 weeks. He was seen in the emergency room and a lumbar puncture showed 162 white cells with 81% lymphocytes. A protein was 82 mg/dl (15–45 mg/dl) and glucose was 36 mg/dl (50–80 mg/dl). He was treated with ceftriaxone and underwent a complete work up for bacterial meningitis and viral meningitis (including EBV, enterovirus, HIV, VZV, Rocky Mountain spotted fever, Brucella, West Nile virus, eastern and western equine encephalitis). His chest X-ray and abdominal CT were negative. He had a seizure and when he awakened, he complained that he could not see. He was transferred to our hospital with headaches, severe eye pain, and photophobia.

Past medical and ocular history None	*Past surgical history* None
Medications Normally none	*Family history* None known
Social history Statistic student at a university Originally from Pakistan	*Review of systems* Fevers and myalgias

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_34

Examination
Acuity with correction Right eye: Bare LP Left eye: Bare LP No Optokinetic Drum response
Pupils 4 mm BE in light; 6 mm in darkness No discernable RAPD but very sluggishly reactive pupils
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg
External exam Very slight ptosis left eye
Eye alignment and motility Bilateral esotropia by Krimsky; unable to look completely laterally
Slit lamp examination Normal
Visual field None appreciated
Fundus examination Very slight pallor diffusely in both eyes
Neurologic examination Somewhat lethargic; neck stiffness; cranial nerves otherwise normal. Decreased leg strength and unable to stand. Deep tendon reflexes present but reduced
VEP Not-recordable

Discussion

Neurologic Perspective—Dr. Digre

This man had a new persistent headache that did not stop, and while one might think of new daily persistent headache, the patient has decreased vision, bilateral sixth nerve palsies in the face of headaches, light sensitivity, neck pain, fevers, and an abnormal CSF. This kind of presentation smacks of infection in an otherwise healthy guy. And it really sounds like a kind of meningitis. Headache caused by meningitis while not common occurs in 1–2% of patients presenting to an emergency room for headache. It should not be surprising that meningitis can cause eye pain and/or headache since the meninges are also supplied by the first division of the trigeminal nerve. The pain is usually bilateral and of course may involve the entire head; neck pain can be present since there is meningeal inflammation around the nerve roots. In bacterial meningitis, the headache can progress rapidly to the worst headache of a person's life, or in chronic meningitis or aseptic meningitis, the pain may be insidious and gradually develop. Photophobia, phonophobia, nausea, and vomiting may accompany the headache, making differentiating the pain from migraine difficult. The most important thing is to get a history—and hearing about a new headache, fever, and neck stiffness tips you off to the diagnosis of meningitis.

Our patient's initial evaluation was completely negative, and the outside hospital rightly started antibacterial agents, but the CSF findings are really what we would

consider an aseptic meningitis—since there are only a moderate number of white cells and only somewhat low glucose. The differential diagnosis includes infections such as herpes simplex virus type 2, herpesvirus type 6, varicella-zoster virus (VZV), enterovirus, Epstein-Barr virus, arbovirus, mycoplasma pneumonia, Borrelia burgdorferi (Lyme), Treponema pallidum (syphilis) cryptococcus neofomans, tuberculosis, and coccidiomycosis. Viral meningitis occurs more frequently in children or young adults and frequently in the spring or fall.

There are also non-infectious etiologies of aseptic meningitis including sarcoidsis, leptomeningeal carcinomatosis, Behcet's disease and even medications (trimethoprim sulfamethoxazole, sulfasalazine, intravenous gamma globulin (IVIG), and some of the monoclonal antibodies). There is even a recurrent form of aseptic meningitis not precipitated by drugs called Mollaret's meningitis—which can present with recurrent chronic headache. Tuberculous meningitis is one of the most difficult to diagnose since it often has an insidious onset. It is one of the most common causes of meningitis worldwide. It is not associated with pulmonary tuberculosis in over half of the cases. Because it causes intense inflammation and thick purulent exudate that has a predilection to the base of the brain, cranial neuropathies are common. Complications include hydrocephalus and brain ischemia from a vasculitis of the blood vessels. Cranial nerve palsies can be present in meningitis with sixth nerve involvement being most likely. Optic neuropathy can occur in tuberculosis due to an arachnoiditis of the optic nerve and chiasm from inflammation of the basal meninges.

The work-up of the cerebrospinal fluid in aseptic meningitis includes: viral cultures, PCR for enterovirus, HSV2, HHV6, VZV, EBV, HIV1 RNA, Virus-specific IgM antibody, India ink and fungal culture, Cryptococcal antigen, Coccidiomycosis immitis complement fixation, Histoplasma polysaccharide antigen, VDRL, FTA-ABS, and anti-Borrelia Burgdorferi antibodies. For tuberculosis diagnosis ordering a PCR for M tuberculosis is very specific, but can be lower in sensitivity. Other tests include chest X-ray, or intradermal tuberculin skin test, Quantifreron gold testing, and neuro-imaging.

Treatment of the meningitis really depends on the diagnosis since antivirals are frequently given for some of the viral meningitides, and steroids for sarcoidosis and Behcet's. Tuberculous meningitis is usually treated with Isoniazid, pyrazinamide, Rifampin, Streptomycin, and ethambutol. Steroid treatment of tuberculous meningitis is begun if the patient has hydrocephalus, or other signs of vasculitis, and the World Health Organization does recommend corticosteroids to reduce death and disability. The level of consciousness often determines the prognosis—meaning that if treatment is started before the person becomes comatose, then the outcome is good.

Ophthalmic Perspective—Dr. Lee

This patient could have visited the ophthalmologist first with bilateral eye pain and neck pain instead of the ER. The presence of fevers along with the neck pain may have prompted neuroimaging or a referral to the ER. It depends on how well the ophthalmologist takes a history or the patient complains of stiff neck. Let us suppose that the patient had no visual complaints and the eye exam were normal.

Studies show that getting neuroimaging with a normal eye exam and eye pain is low yield. Since he did not go to the ophthalmologist before his visual loss, we do not know if he had eye findings that may have tipped us off. The patient did not have visual complaints or double vision prior to his seizure. He may have had subacute acuity, color vision loss, or visual field loss that could have been picked up as an optic neuropathy. The optic nerve pallor, if present, may have prompted neuroimaging, which would have identified the leptomeningeal enhancement.

Besides ophthalmoplegia and optic atrophy, there were no other eye findings present on this patient's examination. However, there are some other things to consider ophthalmologically speaking in meningitis. The most common infectious causes of simultaneous ocular and meningeal infections include cat scratch, syphilis, tuberculosis, and Lyme. Cat scratch may show a neuroretinitis and uveitis. Syphilis, Lyme, and TB can cause just about any inflammatory lesion of the eye including iritis, vitritis, retinal or choroidal lesions, and orbital inflammation (same with sarcoid!). Fungal infections may present with an endophthalmitis picture or varying degrees of chorioretinal whitening. Papilledema from increased intracranial pressure may occur from Lyme, Cryptococcus, carcinomatous meningitis, viral meningitides, or Brucellosis among others. In some cases, patients may present with predominantly ocular findings but may have meningeal signs and symptoms that lead to the diagnosis.

Non-ophthalmic/Non-neurologic Perspective

The triad of headache, fever, and stiff neck should ring a bell for meningitis in all primary care providers and emergency room specialists. The usual work up is to get the history to see if it can be determined what type of meningitis. When someone is really acutely ill, suspect bacterial meningitis. Often starting antibacterials and then getting imaging (usually CT) is the immediate work-up. Examination of the cerebrospinal fluid is essential. Opening pressure is often elevated in meningitis. If there is a major increased in white cells, particularly polymorphonuclear cells and a low glucose—think bacterial meningitis. If there is elevated mononuclear cells and low glucose think about mycobacterial, fungal, syphilis, and carcinomatous meningitis. If there are atypical lymphocytes think about viral meningitis. Treatment of acute bacterial meningitis includes Vancomycin 15 mg/kg IV every 6 h and Cefriaxone 2 g every 12 h or Cefotaximine 2 g IV every 8 h. If herpes virus encephalitis/meningitis is suspected consider Acyclovir 10–15 mg every 8 h.

Follow-up

Imaging revealed multiple areas of leptomeningeal enhancement and signal abnormality predominantly about the right temporal lobe, frontal lobe and occipital lobe, without distinct nodularity (Fig. 34.1). These findings were concerning for an

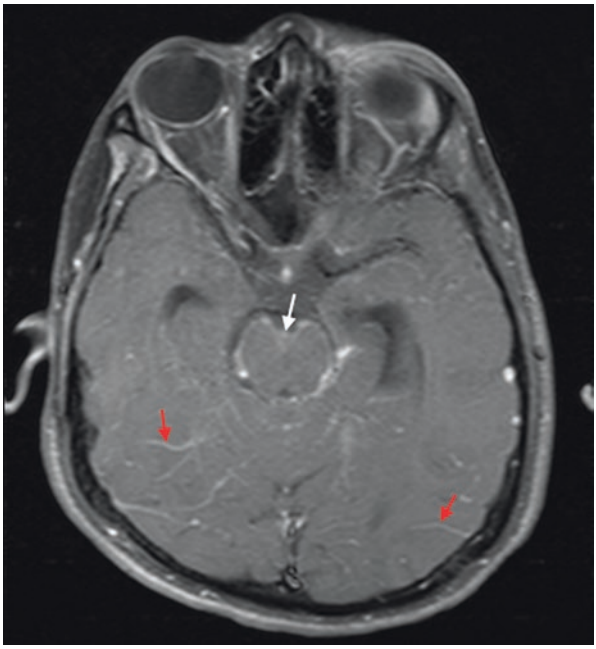

Fig. 34.1 Axial T1 postgadolinium MRI shows leptomeningeal enhancement (*red arrows*) and enhancement in the interpeduncular cistern (*white arrow*)

unusual leptomeningeal infection, neoplastic processes with CSF spread of tumor, lymphoma versus sarcoidosis. Quantiferon Gold TB was positive. AFB culture was positive. A PCR for mycobacterium tuberculosis was positive on CSF. He was begun on rifampin 600 mg each day, ethambutol 1000 mg each day for 2 months, and isoniazid 300 mg each day, pryridoxine 50 mg each day. During the hospitalization, he was also treated with IV solumedrol and then switched to prednisone taper. He was continued on Keppra for seizure protection. The IV antibiotics were discontinued. He was followed for several years and his vision eventually improved to 6/200 OD, 20/500 OS, and 20/300 using both eyes. His pupils remained sluggishly reactive and he had finger counting fields superiorly and hand motions inferiorly. He had visual rehabilitation and was able to finish university. His headaches and eye pain eventually resolved when the meningitis was controlled. *Final diagnosis: tuberculous meningitis*.

For Further Study

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Case 35

History of Present Illness

A 20-year-old male restaurant worker was referred for eye pain associated with visual loss. Two weeks before he was seen he noted the he had some left eye pain with eye movements or rubbing his eye. The eye feels sore, and he has stabbing pains as well. About a week ago, he developed mild blurred vision. He has not noticed any other weakness, numbness, or other symptoms. He does travel and was recently in India.

Past medical and ocular history None	*Past surgical history* None
Medications None	*Family history* Mother with depression Maternal grandfather with cancer
Social history Smokes rare; also rare alcohol Works in a restaurant He is single and travels a lot	*Review of systems* Negative

Examination

Acuity with correction Right eye: 20/20 Left eye: 20/60
Pupils Equal, but with a 1.9 log unit relative afferent pupillary defect on the left
Color vision (HRR plates) 9/9 OD and 4/9 OS
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg
External exam Normal

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Eye alignment Normal
Slit lamp examination Normal
Visual field Dense temporal defect OS (see original and follow-up visual fields, Fig. 35.1)
Fundus examination Normal appearing optic nerves; normal retina
Neurologic examination Normal
OCT Mildly reduced nerve fiber layer inferiorly

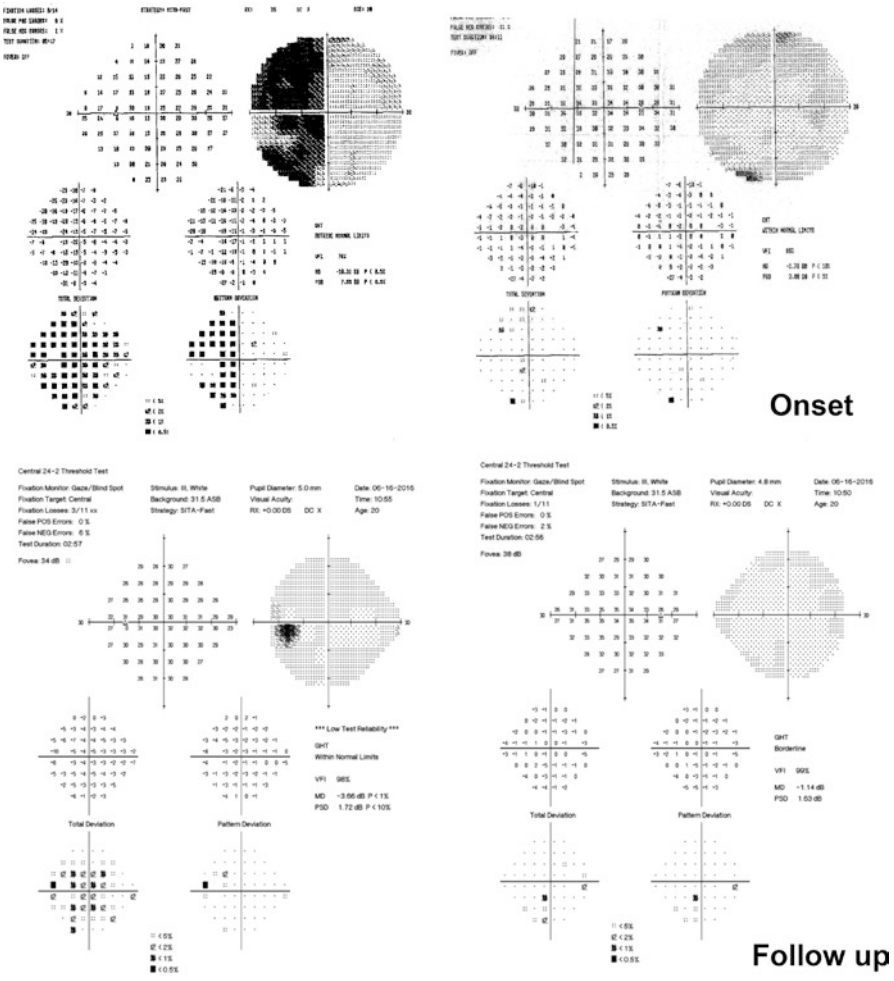

Fig. 35.1 Visual field at onset (*top*) showed a dense temporal defect, which at 3 months (*bottom*) improved greatly

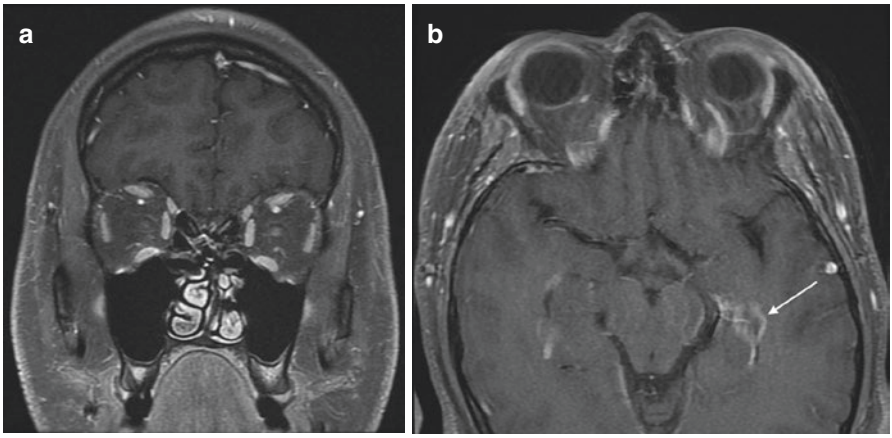

Fig. 35.2 (**a**) Coronal postgadolinium T1 shows subtle enhancement of the left optic nerve. (**b**) There was an enhancing ring-like lesion (*arrow*)

He underwent an MRI showing optic nerve brightness on STIR imaging and also enhancement (Fig. 35.2a) and multiple white matter lesions signal on FLAIR imaging as well as a enhancing ring-like lesion (Fig. 35.2b).

Discussion

Neurologic Perspective—Dr. Digre

Any young (20–45 years old) adult presenting with reduced vision and eye pain (especially with eye movement) is suspicious for optic neuritis. Optic neuritis is most frequently seen with multiple sclerosis. The hallmark signs are reduced vision, the presence of a relative afferent pupillary defect (provided that the visual loss is unilateral), and frequently a normal appearing fundus. The old adage: the patient looks out and sees nothing from the eye, and the examiner sees nothing wrong, holds in optic neuritis. The disc usually appears normal, but in about one-third of cases there may be swelling. The reduction in color vision in the eye with the neuritis is also classic for the diagnosis of optic neuritis. Mimics of optic neuritis exist including neuromyelitis optica, sarcoid optic neuropathy, which may or may not be painful; anterior ischemic optic neuropathy and Leber's hereditary optic neuropathy usually present with disc swelling and are generally not painful.

The eye pain with optic neuritis is mild to moderate. Severe pain, while it can occur, is atypical, especially if it awakens the patient at night. Pain is most common when the orbital optic nerve is involved as in this case. Some believe the eye pain to be related to where the muscles insert in the posterior orbit.

The evaluation of optic neuritis includes imaging—MR scan with gadolinium. In this case the optic nerve enhanced along the entire optic nerve. Sometimes there is

no optic nerve enhancement. The brain imaging is also critical since finding even one lesion on MR increases the likelihood of MS to 75% in 15 years. A lumbar puncture may be helpful. Doing protein, glucose, cells, and oligoclonal bands can be helpful if the presentation is unusual or if there is some concern about the MR appearance such as in this case. We did not do a visually evoked potential since we were sure he had an optic neuropathy.

The Optic Neuritis Treatment Trial taught us that an extensive blood battery is not necessary, unless there are other factors that could be present. In this case our patient had traveled frequently to other countries, most recently India, so we did do a CSF examination. We would consider CBC, ESR, NMO IgG, Quantiferon Gold, RPR, and toxoplasmosis IgG/IgM, and Chest CT. Our biggest concern was possible Tuberculosis because of the travel to India or toxoplasmosis because of the ring-enhancing lesion.

Ophthalmic Perspective—Dr. Lee

I would also be a bit concerned about Cryptococcus given the ring-enhancing lesion and travel to India. This can be assessed on his spinal fluid. It is a rare cause of an infectious optic neuropathy and is much more common in the southern US, South America, and Africa. If it were to come back positive, then I would also assess him for HIV. Patients with long segments of optic nerve enhancement are concerning for neuromyelitis optica. I would ask him about intractable hiccups or vomiting (yes, this is part of the diagnostic criteria for NMO!!). If his vision does not improve like typical optic neuritis, then I would consider imaging his spinal cord for long (> 3 vertebral segments) lesions.

In follow-up, we expect his vision to improve with typical optic neuritis with or without IV steroids. He may develop Uhthoff phenomenon – when he gets hot or exercises, his vision may decline in the affected eye for 20–60 min. This does not cause further damage to the eye and does not represent a recurrence. This can occur with any optic nerve injury but is much more common with optic neuritis. Lastly, in many cases, the optic neuritis may be idiopathic and unrelated to multiple sclerosis. The risk of recurrence is approximately 33%.

Non-ophthalmic/Non-neurologic Perspective

Individuals presenting with eye pain and visual loss in primary care without any finding except for an RAPD should lead the practitioner to consider optic neuritis. If referral to an ophthalmologist, neurologist, or neuro-ophthalmologist cannot occur in a timely fashion, then one may consider ordering an orbital MRI with gadolinium and fat suppression. Patients with optic neuritis have an enhancing optic nerve in over 90% of cases. If the MRI shows white matter lesions consistent with demyelinating disease, then consider referral to neurology to treat for multiple sclerosis.

Follow-up

His workup was negative except for oligoclonal bands in his spinal fluid. After the above studies, we diagnosed him with multiple sclerosis and treated him with intravenous steroids, 1 gram IV for 3 days with a short taper. The treatment of optic neuritis with intravenous steroids has been accepted to hasten recovery of the optic neuritis and perhaps delay for a while the onset of clinically symptomatic multiple sclerosis. It does not improve the visual or visual field outcome. It does help the eye pain in most cases. As is typical for most optic neuritis his vision cleared to 20/20 and his nerve showed pallor in about 6 weeks. He was referred to the neurology service and was placed on glatiramer acetate (Copaxone). They are following his imaging. *Final diagnosis: optic neuritis*.

For Further Study

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Case 36

History of Present Illness

A 28-year-old woman was referred for eye pain and headaches. She had been to the emergency room in 3 different hospitals for headache and eye pain. Each time she was treated with a migraine cocktail without success. She was referred now for a dilated examination to look for papilledema. She had a family history of migraine, and she herself had occasional migraines. However, this headache and eye pain started rather abruptly and she thinks it is different than her migraines. She has some pain with eye movement and a pressure feeling behind her eyes. The headache is holocranial with pain into her neck and between her shoulder blades. She occasionally has a whooshing noise in her head—especially at night when it is quiet.

Past medical and ocular history Hypothyroidism Obesity	*Past surgical history* Tonsillectomy at age 8
Medications Multiple vitamin Synthroid	*Family history* Mother has migraine
Social history She does not smoke or drink	*Review of systems* Trouble sleeping at night

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_36

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Pupils Equal pupils, No Relative afferent pupillary defect
Intraocular pressure Right eye: 15 mmHg Left eye: 15 mmHg
External exam Normal
Eye alignment Normal
Slit lamp examination Normal
Visual field Normal to confrontation; Formal visual fields show enlarged blindspot and scattered defects
Fundus examination Bilateral optic disc swelling
Neurologic examination BMI is 45 Normal neurological

Discussion

Neurologic Perspective—Dr. Digre

This young woman has a change in her headache and has eye pain. What is more, she has been to the emergency room three times for help and no one bothered to look at her optic discs. I have seen this frequently, in fact, if I hear someone has been to the emergency room several times with a headache or eye pain that does not go away, I immediately consider increased intracranial pressure and idiopathic intracranial hypertension (IIH). Neurologists often miss papilledema since they are not comfortable using an ophthalmoscope and they rarely dilate the patient. Another problem is overdiagnosing IIH especially if someone has anomalous optic discs and headache.

Of course with papilledema, one first has to consider other causes of intracranial hypertension and I would order an MRI and MRV or CTV. The MR can be helpful since it may show signs of increased intracranial pressure as well. These include: an empty sella, dilated optic nerve sheaths, flattening of the posterior globe, and often dilated spaces around the foramen ovale as well as Meckel's cave. It also will exclude a mass lesion. The venogram is also critical since individuals with venous thrombosis can present identically to the primary or idiopathic intracranial pressure; the treatment of venous sinus thrombosis is different and therefore important to exclude.

After imaging, a lumbar puncture, measuring the opening pressure is important as well as checking the fluid to be sure there is no evidence of meningitis. The opening pressure is also important to measure correctly—usually in the lateral decubitus

Table 36.1 IIH headache according to the ICHD3 beta

Headache caused by idiopathic intracranial hypertension (IIH), usually accompanied by other symptoms and/or clinical signs of IIH. It remits after normalization of cerebrospinal fluid pressure
Diagnostic criteria:
(A) Any headache fulfilling criterion C
(B) Idiopathic intracranial hypertension (IIH) has been diagnosed, with CSF pressure >250 mm CSF (measured by lumbar puncture performed in the lateral decubitus position, without sedative medications, or by epidural or intraventricular monitoring)
(C) Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to IIH, or led to its discovery
2. Headache is relieved by reducing intracranial hypertension
3. Headache is aggravated in temporal relation to increase in intracranial pressure
(D) Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

position with legs outstretched—being sure to have the patient relaxed and not having a Valsalva maneuver.

Most neurologists do not have the capability of performing visual fields. It is extremely important if someone has papilledema to get a formal visual field. Visual acuity alone is not enough to follow these individuals. We get optic disc photos to follow the papilledema and sometimes OCT is also helpful in order to see if the swelling is decreasing.

To diagnose the headache associated with IIH see the ICHD 3beta (Table 36.1). There are many interesting caveats about diagnosing IIH-related headache. First, when papilledema is not present, can you still call it IIH if the pressure is only mildly elevated? I see many patients with clear migraine and elevated pressures being called IIH. I think IIH without papilledema is not common. I suggest that we do not worship the opening pressure alone. Second, notice in the definition that the headache leads to the discovery of the IIH—such as is in this case. Also, the finding of the headache going away with the lumbar puncture is not 100% either. Many individuals with migraine say that their headaches improve after lumbar puncture.

Treatment of IIH is usually weight loss—and this woman is obese. I recommend five vegetables a day and walking 10,000 steps or swimming as exercise. For some, a dietician is very helpful in setting up a weight loss program. We also use acetazolamide. The recently completed Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) showed that acetazolamide along with weight loss was more efficacious over weight loss alone.

Treating the eye pain and headache in IIH can really be a challenge, since just lowering the pressure alone may not treat the headache and eye pain. The best treatment for the headache is usually acetazolamide and a migraine preventative such as topiramate, amitriptyline (although weight gain can occur with this), or other migraine preventive. This woman also has a history of underlying migraine—individuals with IIH have a higher incidence of migraine (60%)—which is much higher than in the general public (18% of women). The migraine headache can be treated acutely with triptans or other migraine-specific medications.

Ophthalmic Perspective—Dr. Lee

You can titrate the acetazolamide up to 4 g/day according to the IIHTT. If you are not comfortable with that, then perhaps go up to 2.5 g/day (in divided doses). If that does not help the eye or head pain, then I would send the patient to a neurologist to help manage headache but the acuity, field, and nerves need to be monitored by an ophthalmologist.

Generally, I do not advocate for a shunting procedure in patients with severe headache alone. Although uncommon, there is risk to having a shunt, so I typically reserve a shunt for those with moderate to severe visual loss. I have seen patients go to a neurosurgeon for a shunt for the pulse synchronous tinnitus and headache despite my protests.

In some cases, the patient complains of persistent headache despite the papilledema resolving. They insist that this is due to the intracranial pressure being high. Sometimes, I will repeat the lumbar puncture to demonstrate to the patient that the pressure is not high. In other cases, the patient is willing to visit a neurologist to manage headache. I also have several patients who just want to stay on low-dose acetazolamide. I do not have a problem with this, since we know that this was used to treat glaucoma and has a reasonable safety profile over many years of treatment. It also may help some people with migraine.

If a patient becomes pregnant, topiramate is contraindicated. Acetazolamide is category C, but there have been a number of patients who have taken acetazolamide while pregnant. We ask patients on acetazolamide to avoid pregnancy. If they become pregnant, we may discuss stopping the medication for the first trimester or staying on it. Finally, patients with a sulfa antibiotic allergy do not have cross reactivity with sulfa diuretics, but anyone with an allergy to one medication may be allergic to another.

Non-ophthalmic/Non-neurologic Perspective

Finding papilledema can be challenging for the primary care physician too. Dilating the patient with 0.5% tropicamide is helpful in better seeing the optic disc. Recently photographs with a non-mydriatic camera have helped primary care and emergency room physicians see the optic discs better. There are also new phone apps and devices that allow one to take a picture of the fundus.

If papilledema is seen—MR and MRV or CTV is important to order along with a lumbar puncture. A primary care physician may be the best place to assist the patient with weight loss strategies that are known to be helpful along with acetazolamide.

Headache and eye pain with IIH is so common. Over 50% of patients with IIH had previously diagnosed migraine headache. It is also the headache that causes a reduced quality of life. So treating the migraine is really important in the treatment of IIH.

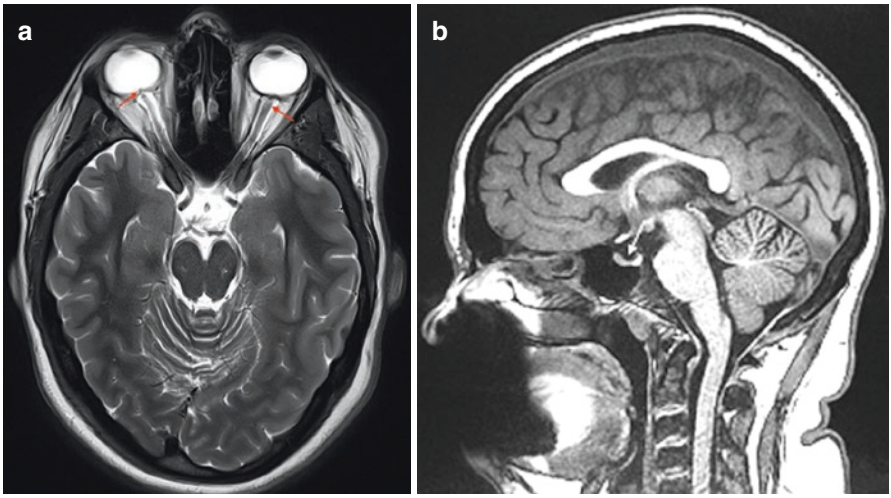

Fig. 36.1 (**a**) Axial T2 MRI shows evidence of increased intracranial pressure including flattened posterior globe and dilated optic nerve sheaths (*arrows*). (**b**) Sagittal T1 MRI shows a partially empty sella (*arrow*)

Follow-up

This woman had a normal MR and MRV except for an empty sella and other findings of intracranial pressure (see Fig. 36.1). We started her on 500 mg acetazolamide twice daily and encouraged weight loss. Her most acute headache improved after the lumbar puncture, and she now is followed with resolution of the papilledema, but her headaches persist. I have kept her on acetazolamide and topiramate. That combination can cause lowered bicarbonate levels, tingling, taste changes, and weight loss, but by and large it is well tolerated. If intolerable, then sodium bicarbonate 1300 mg twice daily can improve these side effects. Another consideration is electrolyte replacement drinks. I follow electrolytes, which so far have been normal. *Final diagnosis: idiopathic intracranial hypertension*.

For Further Study

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Case 37

History of Present Illness

A 51-year-old sheet metal worker developed photophobia and bilateral eye ache 2–3 months ago. The pain is constant, which she describes as 5 out of 10. The pain worsens when she immerses herself in cold water. She states that the pain is localized to the eyes and, overall, is not getting better or worse. Two weeks after the pain began, her right eye became red. She denies tearing, discharge, or foreign body sensation. She denies blurred vision, double vision, or ptosis. She does not wear contact lenses and has been using Visine without improvement in the redness or pain. The redness is worse upon awakening. She has heard a ringing in his left ear for the past month, which is constant.

Past medical and ocular history Steroid-responsive glaucoma (given for pink eye in the past) Wears glasses	*Past surgical history* None
Medications Artificial tears PRN Tetrahydrozoline (Visine) PRN	*Family history* Mother had brain cancer Father had glaucoma but not severe
Social history Works with sheet metal Social drinker Has never smoked	*Review of systems* Per HPI

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_37

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/25
Pupils Equal in size, Round shape, briskly reactive, no APD
Intraocular pressure Right eye: 23 mmHg Left eye: 23 mmHg
External exam No ptosis, 1 mm of proptosis RE, no eyelid edema
Motility and Eye alignment Normal
Slit lamp examination RE: Normal cornea, large tortuous conjunctival vessels, no papillae or follicles. The vessels do not blanch with neosynephrine (see Fig. 37.1a) LE: normal
Visual field Normal
Fundus examination 0.4 CDR RE/0.5 CDR LE Normal
Neurologic examination Normal facial sensation Otherwise unremarkable

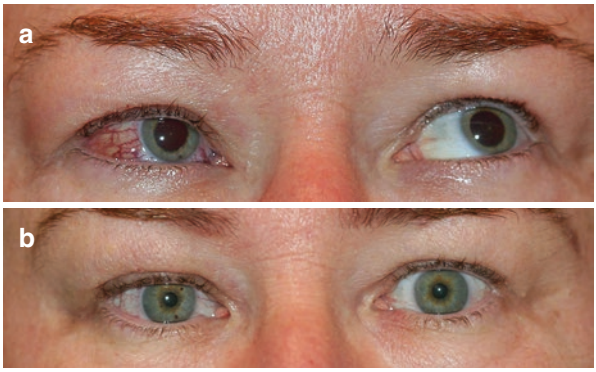

Fig. 37.1 Color photos show a red right eye. (**a**) Notice the corkscrew type vessels typical of dural cavernous fistulas. (**b**) After treatment the redness resolved

Discussion

Ophthalmic Perspective—Dr. Lee

Although her initial complaint was eye pain, I cannot ignore the red eye (I doubt this is a red herring since it is ipsilateral to the pain). I will say that I have no idea why her pain is worse when going under water. This story is not consistent with conjunctivitis since there is no discharge or tearing. Additionally, the 2-month history is

unusual for conjunctivitis (Case 13). Generally, the pain of scleritis gets worse over time. She does not have any other stigmata of inflammation such as conjunctival edema (chemosis), and she describes pain in both eyes but only her right eye is red. Metal workers can get a metallic foreign body in their corneas, but her corneas were clear. An intraocular foreign body typically causes a decline in vision and ipsilateral, unilateral pain. It is not unusual to have 1 mm of relative proptosis in normal individual but this may represent a real orbital finding.

I would like to know more about the ringing in her ear. Is it high-pitched or does sound like rushing water that pulses with his heartbeat pulse synchronous tinnitus (PST)? If you look closely at the redness, there are areas of relative "white" sclera between the big red vessels, which are veins. Note also that these beefy veins start at the limbus (junction of the cornea and conjunctiva). These are characteristic vessels that we would see in a carotid cavernous (C-C) fistula.

C-C fistulas are abnormal connections between the carotid artery and the venous flow in the cavernous sinus. There are two basic kinds of C-C fistula: high-flow and low-flow. High-flow fistulas are usually traumatic and dramatic. The eye looks very proptotic with dramatic eyelid edema, conjunctival edema, and proptosis. Basically, it looks like the eye is popping out of the head, which is not the case here. Low-flow fistulas typically present in elderly women and PST is common. If the venous flow is toward the eye, then the patient gets arterialized conjunctival veins as seen here (if the venous flow is more posterior, then the eye looks white and quiet). Some patients can develop diplopia or facial pain from CN 3,4,5,6 involvement. Occasionally, patients have a defect between cavernous sinuses and can develop bilateral findings despite a unilateral fistula. The diagnosis is supported by a CT or MRI that shows enlargement of the superior ophthalmic vein (SOV) but may require conventional catheter angiography to confirm. I would start with a CT/CTV or an MRI/MRV to evaluate this patient.

Neurologic Perspective—Dr. Digre

I saw a case like this 2 days ago in my clinic, so I know these cases are not rare. First, she is of the right sex and age. Individuals with the indirect fistulas are usually middle or older aged women. The dull ache is really typical of these indirect dural fistulas. I do not understand the worsening of pain with water either—unless cold water could cause cold-induced headache. Sometimes having the patient bend over will make it worse. Morning worsening is definitely a typical headache feature. See the ICHD 3 beta criteria for dural arteriovenous fistula (Table 37.1). The cork-screw like vessels on the conjunctivae either unilaterally or bilaterally are also really typical—and like this lady, they do not blanch or go away with a topical sympathomimetic. The red did not come out with Visine (which has a topical sympathomimetic). The elevated intraocular pressure is also typical—and sometimes the pressure is high enough that it too requires therapy.

When fistulas are posteriorly draining into the petrosal sinuses, you do not see the red eye, but can get facial numbness from trigeminal neuropathy, facial weakness from a seventh nerve palsy, or diplopia from usually a third nerve palsy. The posteriorly draining dural fistulas often cause a painful eye, but there will be no

Table 37.1 ICHD 3 beta criteria for dural arteriovenous fistula

(A) Any new headache fulfilling criterion C
(B) A dural arteriovenous fistula (DAVF) has been diagnosed
(C) Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical signs of DAVF, or has led to the diagnosis of DAVF
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with other symptoms or clinical or radiological signs of growth of the DAVF
(b) Headache has significantly improved after treatment of the DAVF
3. At least one of the following:
(a) Headache is accompanied by pulsatile tinnitus
(b) Headache is accompanied by ophthalmoplegia
(c) Headache is both progressive and worse in the morning and/or during coughing and/or bending over
4. Headache is localized to the site of the DAVF
(D) Not better accounted for by another ICHD-3 diagnosis, and intracerebral hemorrhage and cerebral venous thrombosis have been excluded by appropriate investigations

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

red eye. Risk factors to getting these fistula include: female sex, older individuals, hypertension, and connective tissue disorders.

Besides getting MRI or CT with contrast, orbital color Doppler can be helpful since it may detect the abnormal direction of flow. Occasionally angiography is required to find the fistula since these fistulas can be made up of branches from the internal or external carotid artery. We usually watch and admire if there are few symptoms since 20–50% of these can close spontaneously. Air plane travel, using the opposite hand to intermittently occlude the carotid artery on the side of the fistula—in this case she would use her left hand to occlude her right artery—often will assist in closure. She is not on anti-platelet therapy, but if she were, you could have her stop it. If she chooses to observe, she should have her intraocular pressure followed. Sometimes chemosis can progress and further treatment may be necessary. These procedures include endovascular therapy (most common), direct surgery, and radiotherapy. Rarely, these fistulas can recur.

Non-ophthalmic/Non-neurologic Perspective

Common things being common, history, and exam should help us rule out conjunctivitis and foreign body (see above discussion). Intraocular inflammation is harder to see unless you are facile with a slit lamp. Generally speaking, a 2–3 month history without worsening of pain or vision does not warrant an emergent consultation no matter the cause. This particular kind of red eye is pattern recognition and if PST is present, then the suspicion becomes very high. If you obtained a scan, then you would direct the radiologist to look carefully at the SOV.

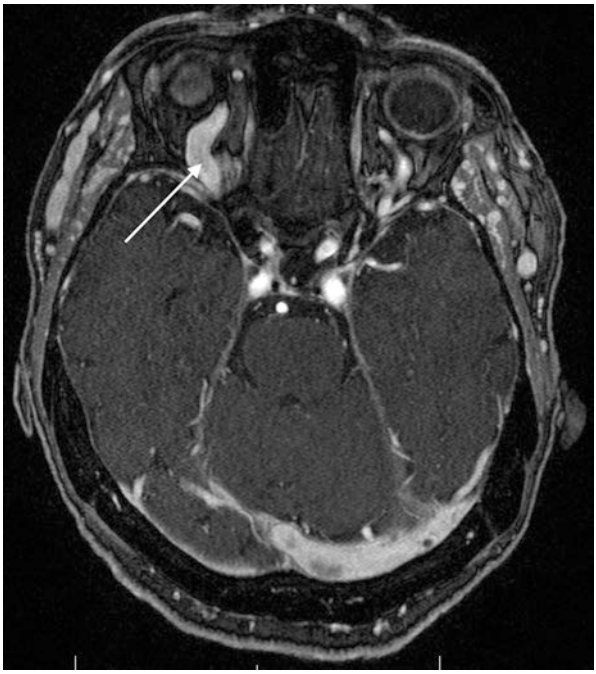

Fig. 37.2 Axial T1 MRI shows a dilated and tortuous right superior ophthalmic vein (*arrow*)

Follow-up

The patient endorsed PST. MRI (Fig. 37.2) and MRV showed enlargement of the right SOV and several atypical flow voids in the right cavernous sinus. Approximately 50% of low-flow fistulas can spontaneously resolve over a year, and observation is reasonable in the absence of a defect or deficiency. Angiography may be required to secure a diagnosis in some individuals and is also used to close fistulas. This patient chose to undergo angiography and coiling. The redness and pain were gone at 6-week follow-up (Fig. 37.1b). *Final diagnosis: Low-flow, Cavernous-carotid fistula (dural cavernous fistula)*.

For Further Study

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Case 38

History of Present Illness

An 86-year-old man had a history of migraine with aura as a young man with infrequent headache. He also had an episode of aura without headache every 2–3 months for the last 20 years. However, about 2 weeks prior to being seen, he developed a severe, incapacitating headache—over his left eye. The pain was boring, not throbbing, and he had no light or sound sensitivity. While it is always there, sometimes the pain worsens 2–3 times in the day, and this can last 3–4 h. He is able to ignore it some of the time, especially if he is busy, but at night it keeps him from sleeping. He tried over the counter ibuprofen and acetaminophen/aspirin/caffeine and he even tried some left over cafergot (caffeine and ergotamine) combination with only modest success. His primary care physician ordered an MR scan which was normal and an ESR which was also normal. He had left over hydrocodone from a previous surgery, and this provided temporary relief.

Past medical and ocular history History of a right facial fracture after a fall 5 years ago Sinus infection 6 months prior to being seen Asthma Basal cell cancer on face Osteroporosis Arthritis Dry eyes	*Past surgical history* Appendectomy years ago Bilateral ptosis surgery Cataract surgery Skin biopsy and basal cell removal *Family history* No history of headache or migraine Father had cancer
Medications Aldendronate 70 Vitamin D Diclofenac 75 Omeprazole 20 Sumatriptan 100 prn Hydrocodone prn Tobradex drops prn Tears prn	*Review of systems* Difficulty sleeping Recent onset of fatigue *Social history* Married Physician Non-smoker, non-drinker

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_38

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/25
Pupils 2 mm BE in light, 4 mm BE in darkness, no RAPD
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg
External exam He had raised papules on his forehead over the left brow into the top of the hairline; he had mild ptosis on the left and thickening of the eye lid on the left (Fig. 38.1)
Eye alignment Normal
Slit lamp examination Chemosis of the sclera (mild) Normal without cell or flare Bilateral PCIOL
Visual field Normal
Fundus examination Normal
Neurologic examination Normal; normal corneal reflex

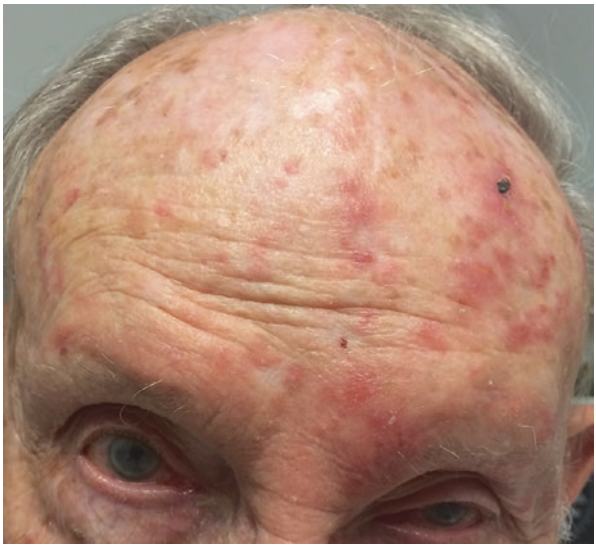

Fig. 38.1 External color photographs show small vesicles in the left V1 frontal nerve distribution and also the mild ptosis on the left

Discussion

Neurologic Perspective—Dr. Digre

The patient really has a new onset of headache over the left eye. While he has been a migraine sufferer in the past, this does not sound like migraine—it has been daily for 3 weeks and sometimes severe and he had no migrainous features (light and sound sensitivity, nausea, or vomiting). A new headache in the elderly of course should makes us think about temporal arteritis. His primary care checked a ESR and CRP and these were normal. Imaging of the brain was appropriate in a new headache in an older person, since he did have a history of sinus infection several months before. The tip off that this was herpes zoster was the rash over the forehead in the distribution of the first division of the trigeminal nerve. The boring pain is typical and the pain is often precedes the rash—leading to an erroneous diagnoses.

Herpes Zoster affects about 30% of the population over a lifetime! This is NOT a rare condition and when it occurs, 10–20% will have Zoster ophthalmicus. The virus is a recurrence of viral particles that live in ganglia throughout the nervous system. The typical headache associated with zoster involving the head includes: pain before the eruption that is completely new for the individual, stabbing pain ipsilateral to the eruption, and the pain interrupts sleep. See the criteria for the acute diagnosis (Table 38.1). Frequently the pain is severe enough, that the individual has visited an emergency room before the diagnosis. The pain is frequently misdiagnosed as migraine, tension-type headache, dry eye, trigeminal neuralgia, and glaucoma.

Risk factors for developing herpes zoster ophthalmicus include age—with older individuals being more susceptible, immune compromise, and pregnancy. An 85-year-old has a 50% chance of having zoster twice in a life time. There is a prodrome before

Table 38.1 ICHD 3 beta criteria: Acute painful trigeminal neuropathy attributed to Herpes Zoster

Diagnostic criteria:
(A) Unilateral head and/or facial pain lasting <3 months and fulfilling criterion C
(B) Either or both of the following:
1. Herpetic eruption has occurred in the territory of a trigeminal nerve branch or branches
2. Varicella zoster virus DNA has been detected in the CSF by polymerase chain reaction
(C) Evidence of causation demonstrated by both of the following:
1. Pain preceded the herpetic eruption by <7 days
2. Pain is located in the distribution of the same trigeminal nerve branch or branches
(D) Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 38.2 ICHD 3 beta: Post-herpetic trigeminal neuropathy

Diagnostic criteria:
(A) Unilateral head and/or facial pain persisting or recurring for <3 months and fulfilling criterion C
(B) History of acute Herpes zoster affecting a trigeminal nerve branch or branches
(C) Evidence of causation demonstrated by both of the following:
1. Pain developed in temporal relation to the acute Herpes zoster
2. Pain is located in the distribution of the same trigeminal nerve branch or branches
(D) Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

the rash appears in many. *In some no rash ever appears*. Herpes Zoster ophthalmicus affects the trigeminal nerve (cranial nerve 5). There are three branches that can be affected. In our patient, the first branch (frontal nerve) was affected. However, when the nasociliary nerve is affected, sinuses, the skin over the nose, both eyelids, conjunctiva, sclera can be affected. The tell-tale rash on the nose, Hutchinson's sign, alerts us to look carefully at the anterior segment and cornea for involvement.

The most frequent complication of herpes zoster ophthalmicus is post-herpetic neuralgia—and this complication occurs in over 50% of older adults such as our patient. Other neurologic complications are less rare, but can be serious including a meningoencephalitis, cranial neuropathy, and even stroke. Systemic complications include pneumonitis (which can be fatal) and hepatitis. Post-herpetic neuralgia is also an unwelcome pain. The acute pain gradually gives way to a deep burning, hypersensitivity, sometimes "crawling" pain with lancinating pains on top of that. The amount of post-herpetic neuralgia can correlate with the severity of involvement. The older the individual, often the worse the neuralgia can be. Suicide risk in the elderly with chronic post-herpetic neuralgia is not rare. See the ICHD 3beta criteria for post-herpetic neuralgia (Table 38.2).

Treatment of acute herpes Zoster ophthalmicus is with valacyclovir (1 g three times daily) or famciclovir (500 mg three times daily) which are similarly effective for 7 days if started within 3 days of the rash. Treatment with the antiviral agents reduces zoster-related pain by half. Famciclovir is often used in individuals with decreased renal clearance. Side effects are few, but can include more headache, nausea, or gastrointestinal side effects.

Gabapentin (slowly escalating doses 300–1200 mg three times daily) given acutely with the antiviral agents may reduce post-herpetic neuralgia. Other treatments such as corticosteroids are not recommended due to side effects (development of diabetes, hypertension, and glaucoma in the older individuals). Treatment of post-herpetic neuralgia includes anticonvulsants like gabapentin (300–1200 mg three times daily), or pregabalin (escalating doses to 300–600 mg each day); these have been shown to be effective in randomized controlled trials. Lidocaine patches and tricyclic antidepressants (e.g. amitriptyline or nortriptyline 25–100 mg at night) have also been shown to be helpful. Opioid analgesics are often used for the acute pain, but have many side effects especially in the elderly.

Ophthalmic Perspective—Dr. Lee

Herpes zoster is most likely here because of the rash that respects the vertical midline. Sometimes the pain precedes the rash and I agree that temporal arteritis is a concern (Case 32) ESR and CRP are about 95–99% sensitive for GCA, so it drops on the differential in this case. Another consideration is that sometimes skin cancers can have a local reoccurrence and travel along the trigeminal nerve. This typically causes pain and numbness. We are not told where the skin cancer was, but it would be important to check facial sensation and inquire about the original location of the basal cell carcinoma. The rash, however, would not be seen in skin cancer recurrence.

I would also point out the importance of checking corneal sensation in HZO. A numb cornea can lead to neurotrophic injury to the cornea along with corneal ulceration and scarring. Patients with a numb cornea should be followed by an ophthalmologist and instructed to seek care if their eye turns red. These patients may need erythromycin ointment.

In some cases of HZO, the eyelid edema can be massive—so severe that the eye is swollen shut. One may need to use retractors or a speculum for a good look at the eye. Cool compresses and erythromycin ointment twice daily are reasonable for conjunctival involvement. Corneal pseudodendrites can be managed with topical ganciclovir three times daily. Topical prednisolone acetate four times daily is used for stromal keratitis with a slow taper over months if no epithelial defect is present. Treatment of uveitis with topical steroids and a cycloplegic agent are reasonable. Some cases of uveitis may be associated with increased IOP and that may require attention. Although HZO can cause a severe infection in the retina causing significant vision loss, this typically is not associated with the skin rash. However, a dilated eye examination is warranted to be sure the retina is not affected.

Non-ophthalmic/Non-neurologic Perspective

Herpes zoster is not a rare problem in primary care. Herpes zoster ophthalmicus is also common. The main things to be concerned about are treating with antivirals as above within 3 days of the rash. Watch the involvement of the eye—and if there is chemosis, redness of the eye, or blurred vision, the patient should see an ophthalmologist. Treatment of post-herpetic neuralgia is very important.

Follow-up

We treated the patient with famciclovir 500 mg three times daily for 7 days. We also started him on gabapentin 100 mg at night, increasing up to 300 mg three times daily. At follow-up he was doing well. We typically keep patients on this for 2–3

months until the sensations and pains have reduced. There are some whose post-herpetic neuralgia require months-years of treatment. *Final diagnosis: herpes zoster ophthalmicus*.

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Case 39

History of Present Illness

An 83-year-old man noted 3–4 months ago that he fell down, hit his head and afterward he could not open his right eye and could not move his right eye. An MRI at that time was read as normal. This has not gotten better or worse as far as he can tell. He has had headache behind his right eye for the past 2 months. The headache is deep, boring, and constant. He rates it at a 6–7/10. Acetaminophen takes the edge off. Nothing seems to make it worse or better. He denies ever having a headache in his life before this. He denies a family history of migraine. He has lost 17# in the past 6 months due to a poor appetite. He had a workup of a normal ESR and CRP and a normal CT angiogram.

Past medical and ocular history Mild dementia Atrial fibrillation Squamous cell and basal carcinomas Hypertension Hyperlipidemia Benign prostatic hypertrophy Gastric reflux Syncope Glaucoma	*Past surgical history* Cataract BE Retinal detachment LE 4 years ago Multiple skin cancers removed *Family history* Unremarkable
Medications Donepezil Finasteride HCTZ Ipratropium Latanoprost Lisinopril Metroprolol Omeprazole Simvastatin Warfarin	*Review of systems* Hearing loss bilaterally Runny nose Poor memory *Social history* Retired from the military 25 years ago Does not smoke 1–2 drinks a day

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_39

Examination
Acuity with correction Right eye: 20/40 Left eye: 20/50
Pupils RE unreactive to light or near, larger than left APD LE
Intraocular pressure Right eye: 11 mmHg Left eye: 14 mmHg
Color vision All correct BE
External exam Complete ptosis RE Scar along right temple Hertel: 20 mm BE
Eye alignmentand motility Exotropic in primary gaze Unable to elevate, adduct, or depress his right eye at all No torsion with attempted downgaze 25% abduction deficit RE LE normal
Slit lamp examination Intraocular lenses BE
Visual field Altitudinal defect RE Significant constriction LE
Fundus examination Cupping LE ≫ RE
Neurologic examination Corneal reflex absent

Discussion

Ophthalmic Perspective—Dr. Lee

This patient has multiple cranial neuropathies. The complete ptosis and complete third nerve palsy are the biggest things here. However, he has a mild abduction deficit in the RE. When a patient has a third nerve palsy, you can determine fourth nerve function by having the patient look up and down. The eye should intort on downgaze if the fourth nerve is functioning properly. He has no torsion of the RE on downgaze. The patient also has facial numbness in the right V1 distribution. So, to summarize, he has right third, fourth, fifth, and sixth nerve dysfunction. These nerves all hang out together in the cavernous sinus.

The patient's ESR and CRP were negative arguing away from giant cell arteritis. I would like to look carefully at his previous MRI. If this does not show an abnormality, then I would likely repeat the scan with thin cuts through the right cavernous sinus. He may have Tolosa Hunt Syndrome (Case 40), but usually that does not

cause facial numbness. In this age group, I would be more concerned about a metastasis. Also consider that patients with skin cancers on the face can develop perineural spread if the margins were not clean with resection. The cancer spreads along the trigeminal nerve and causes numbness and/or pain. It can lead to an optic neuropathy and/or CN III, IV, and VI dysfunction if it makes it to the orbital apex and cavernous sinus. I would also look at V1 to see if it is enlarged or enhancing.

If there is an enhancing lesion in the cavernous sinus, one could consider steroid treatment vs. biopsy. The danger of steroids is that you do not know what you are treating and it may make it harder to identify lymphoma. A biopsy of the cavernous sinus can be fairly invasive at this age. If there is a lesion of V1, then a more anterior orbital biopsy can be considered.

Finally, as an aside, he has an APD in the LE. He has cupping of the optic nerves LE ≫ RE consistent with asymmetric glaucoma. The color vision is normal, which is what you would expect with glaucoma; whereas an optic neuropathy would typically show poor color vision. I do not think the APD is relevant to the other cranial nerve palsies.

Neurologic Perspective—Dr. Digre

Here is another older person with a new headache and an abnormal examination—this is worrisome. While we are told he has had a fall, his imaging is normal so we know he probably does not have a subdural hematoma and since he is awake and alert, he is not herniating—despite his pupil-involving third nerve palsy. He also has numbness in the V1 distribution. One important point is *pain plus numbness equals something bad*! For example the numb chin symptom is usually a sign of underlying malignancy until proven otherwise.

We are told that he has had multiple skin cancers (both basal and squamous) removed. This is an important historical point. Reviewing the previous MR would be my first step—many times focusing the attention of the neuro-radiologist to the area of interest is helpful. In this case, cranial nerves 3, 4, 5, and maybe 6 localizes to the superior orbital fissure and cavernous sinus region. You may need to "run" the nerves with the neuro-radiologist!

In general, perineural spread in skin cancer is through the fifth and seventh cranial nerve since the skin has direct access to these nerves in the face and head. These cancers can track along these nerves centrally via the orbit and superior orbital fissure, foramen rotundum (V2) and foramen ovale (V3) where they gain access to other cranial nerves such as in this case. Squamous cell is slightly more common in perineural invasion than basal cell. Involvement of V or VII carries a worse prognosis.

While skin cancers can have perineural spread so can other tumors like adenocystic carcinoma, lymphoma, and nasopharyngeal carcinomas. The differential diagnosis in most cases other than cancer (for example metastasis) would be sarcoid and infections (like mucormycosis). MR imaging with gadolinium is most important. Treatment depends on the extent of infiltration and radiotherapy is usually what is recommended.

Non-ophthalmic/Non-neurologic Perspective

This patient was presumed to have a right, microvascular third nerve palsy. When it did not improve in 3–4 months, he was sent for further evaluation. If someone had checked facial sensation, then that would indicate that this is not an isolated third. Additionally, his original MRI was described as normal, but maybe it is not. Not everyone is comfortable looking at MRIs by themself, but a phone call to a radiologist asking him/her to take a closer look at the cranial nerves may have yielded a diagnosis.

Follow-up

The MRI (Fig. 39.1) showed enlargement and enhancement of a right V1 branch of the trigeminal nerve and also the right cavernous sinus. Biopsy of the branch showed poorly differentiated adenocarcinoma from a primary lung or gastrointestinal cancer. Full body PET scan showed a hot spot in the colon. Colonoscopy with biopsy was consistent with a colon adenocarcinoma but the immunohistochemical properties did not match! He was diagnosed with an orbital adenocarcinoma of unknown etiology. He underwent cranial radiation and chemotherapy. There was no improvement in his eye movements, but he continues to do well 4 years after diagnosis. *Final diagnosis: Metastatic adenocarcinoma to the cavernous sinus*.

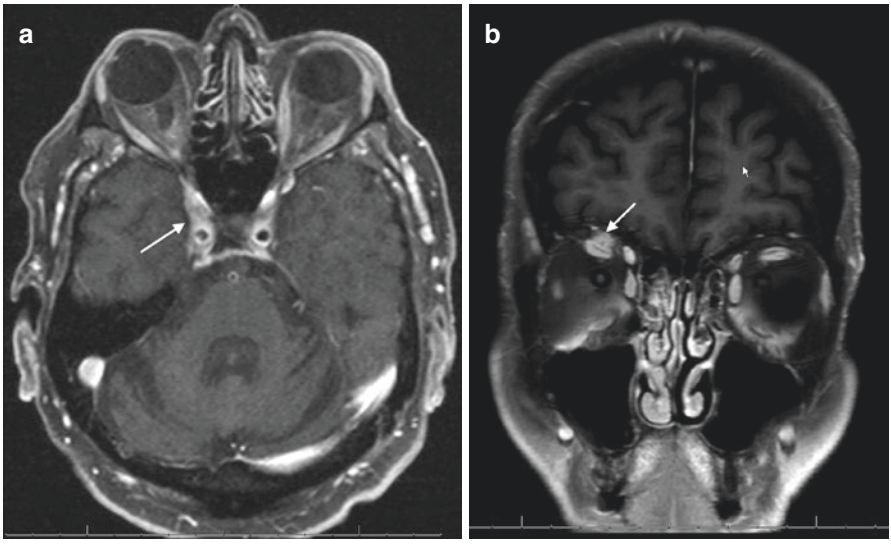

Fig. 39.1 (**a**) Axial MRI shows widening of the right cavernous sinus compared to the left (*arrow*). (**b**) Post-contrast Coronal T1 MRI shows enlargement and enhancement of the supraorbital nerve (*arrow*). Note the displacement of the superior rectus inferiorly

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Case 40

History of Present Illness

A 36-year-old woman with no previous headache history developed a painful right eye 5 weeks ago. The pain is a deep, boring ache (2/10) behind the right eye with sharp, brief pains (5/10) intermittently. There was no tenderness or painful eye movements. She denied photophobia, redness, discharge, vision loss, or double vision. She went to an optometrist who diagnosed her with uveitis and gave her steroid eye drops. One week later she developed diplopia and the records showed she had a right abduction deficit and the uveitis was gone. No further testing was performed. Two weeks after that, the optometrist recorded an exotropia. She states that the diplopia is constant and does not fluctuate over the day. She thinks her vision is blurry RE. She is not a native English speaker, and she is a poor historian.

Past medical and ocular history Endometriosis Ovarian cyst	*Past surgical history* Laparascopic salpingo-oophorectomy
Medications Loratadine Ibuprofen Artificial tears	*Family history* Mother—some kind of eye degeneration, not blind
Social history A nun from Africa visiting for one year No alcohol No tobacco	*Review of systems* Seasonal allergies Trouble sleeping Poor appetite Feels sadness and anxiety

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_40

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/15
Color vision Misses half a plate RE Identifies all plates LE
Pupils In bright light RE 4 mm, LE 3 mm In dim light RE 5 mm, LE 4.5 mm RE is sluggish, LE is brisk, no RAPD
Intraocular pressure Right eye: 20 mmHg Left eye: 18 mmHg
External exam 1.5 mm ptosis RUL 2 mm relative proptosis RE Normal facial sensation and strength
Eye motility and alignment RE: 10% abduction, 10% elevation, 10% adduction, and 50% depression (saccades were slowed) LE: Normal
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal including facial sensation

Discussion

Ophthalmic Perspective—Dr. Lee

I think it unlikely that she had uveitis. We will never know, but it seems unlikely given the lack of photophobia, red eye, and the resolution in just 1 week. Additionally, the pain did not resolve when the "uveitis" did. Instead, the pain was likely the initial symptom of the process picking off her right sixth nerve then her right third and fourth nerves. She describes blurred vision RE. Her acuity is 20/20 RE and she misses half a color plate with the RE but there is no APD. I do not think she has an optic neuropathy at this point, but it could be the earliest manifestation of one. The third, fourth, and sixth nerves run together in the cavernous sinus, the superior orbital fissure, and the posterior orbit. See also Fig. 18.2 for a diagram of the cavernous sinus, orbital fissure, and cranial nerves. The optic nerve meets them in the posterior orbit. In either case, we need to evaluate the back of the orbit into the cavernous sinus, and I would choose an MRI with gadolinium along with fat suppressed imaging. The pain would make myasthenia unlikely. Although she has

proptosis, this would be a very rapid course for thyroid eye disease (TED), which also does not usually cause ptosis. Finally, the saccades were slowed suggesting a neuropathic cause and not a restrictive process like TED (Case 14). There is an entity discussed in Case 43 called ophthalmoplegic migraine but this almost always occurs first under the age of 10. The pain and subacute progression here would suggest an infectious, inflammatory, or neoplastic cause. We can wait for the MRI to come back or order some basic inflammatory and infectious labs such as CBC, ESR, ACE, ANA, Lyme, RPR (I know she is a nun, but I would still order), Serum IgG4, Quantiferon gold (she is from Africa), C-ANCA.

Neurologic Perspective—Dr. Digre

This woman has painful ophthalmoplegia—pain around one eye associated with partial cranial nerve 3, 4, and 6 dysfunction. She is young (less than 40) and has no known malignancy or known infections. There is a huge differential of painful ophthalmoplegia (see Table 40.1). Imaging is the first step since many findings like aneurysm, sinus disease, and tumors maybe seen. This person deserves evaluation

Table 40.1 Differential diagnosis of painful ophthalmoplegia (in part from Kline, Hoyt)

Trauma
Vascular
Carotid cavernous fistula or thrombosis (Case 37)
Aneurysm: intracavernous or internal carotid/posterior cerebral (Case 42)
Diabetic/ischemic third nerve palsy
Carotid dissection
Vasculitis: granulomatosis with polyangiitis (Wegener's) (Case 15)
Giant cell arteritis (Case 32)
Neoplastic
Primary tumors: Pituitary, Meningioma, Neurofibroma, craniopharyngioma, chordoma, and other(Case 41)
Metastases: nasopharyngeal, squamous cell, lymphoma, myeloma, carcinoma (breast, prostate, lung), melanoma
Infections and Inflammation
Bacterial: sinus (Case 25)
Viral: Zoster (Case 38)
Fungal:Mucormycosis, aspergillosis
Spirochete: syphilis, Lyme
Mycobacterial: TB
IgG 4 disease
Orbital pseudotumor (Case 11)
Other
Sarcoid
Ophthalmoplegic Migraine (Case 43)
Tolosa Hunt Syndrome

Table 40.2 ICHD 3 beta Diagnostic criteria for Tolosa Hunt syndrome

(A)	Unilateral headache fulfilling criterion C
(B)	Both of the following:
	1. Granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy
	2. Paresis of one or more of the ipsilateral IIIrd, IVth, and/or VIth cranial nerves
(C)	Evidence of causation demonstrated by both of the following:
	1. Headache has preceded paresis of the IIIrd, IVth, and/or VIth nerves by _2 weeks, or developed with it
	2. Headache is localized around the ipsilateral brow and eye
(D)	Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

as well not only the blood work that Dr. Lee ordered, but also consider a chest X-ray and possibly cerebrospinal fluid evaluation looking for infections. She is from a developing country and tuberculosis is very common. Sometimes, any lesion found needs to be biopsied to rule out secondary causes of painful ophthalmoplegia.

Let us suppose that this work up is largely negative, we are left with the diagnosis of Tolosa Hunt disease. While Tolosa Hunt is usually a diagnosis of exclusion of all of the things listed in Table 40.1, there are criteria to make the diagnosis (see Table 40.2). This condition can present at any age from either gender. Usually pain comes first (like in this case) followed by diplopia. The pain is often really severe—and stabbing, burning, intense boring pain is the usual description. In addition, the pain is around the eye, forehead, or temple. Any of the ocular motor nerves can be involved in addition to the sympathetic and all three divisions of V and rarely the facial nerve or optic nerve is involved. Imaging usually shows enhancement of the cavernous sinus region and this often spreads beyond the sinus into the posterior fossa.

Treatment is usually steroids and one of the real hallmarks of this disease is that steroids really stop the pain. Sometimes as tapering occurs, the pain can recur weeks, months, or years later. The dose for prednisone is variable—in children, it is usually 1 mg/kg/day. In adults, it is usually 60 mg each day and then taper. Other medications considered include methotrexate, infliximab, and rarely radiotherapy.

Non-ophthalmic/Non-neurologic Perspective

Hopefully you can diagnose multiple cranial neuropathies and localize them based on the company they keep. I think a patient like this with diplopia, ptosis, and pain will get an MRI from most physicians. However, I would just comment that you should ask for fat-suppressed images and order contrast when you look

at the orbit. Otherwise, the patient may be getting a second MRI! Given the complexity of the situation, I do not think most primary care providers and neurologists would be comfortable with this patient and this patient should be seen by a neuro-ophthalmologist.

Follow-up

Her MRI showed an enhancing lesion in the right cavernous sinus and right superior orbital fissure (Fig. 40.1). This was not continguous with the paranasal sinuses. Her lab workup was negative, and she was begun on prednisone 1 mg/kg/day for 7 days. She enjoyed complete resolution of her pain and double vision, and repeat MRI was not performed at that time. Two weeks later, she developed recurrent pain. MRI showed no change to the lesion from the first MRI. Another course of prednisone was begun reducing the daily dose by 10 mg every week for 8 weeks with resolution of her pain. A third MRI showed a persistent enhancing lesion with partial interval resolution of the lesion. A neurosurgical biopsy was planned; however the patient

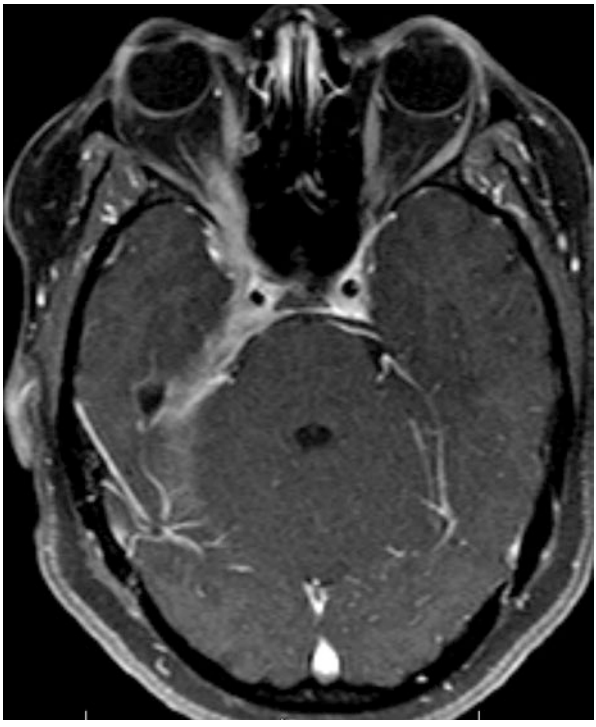

Fig. 40.1 MR (T1, fat desaturated with contrast) Imaging shows enhancement extending from the right superior orbital fissure, through the cavernous sinus along the posterior tentorium of the petrous bone. This is a typical appearance of Tolosa Hunt Syndrome

was found to have an ovarian mass. She remained on 20 mg prednisone for the brain lesion while her ovarian mass underwent biopsy. The mass proved to be benign, and repeat MRI 2 months after the third MRI showed complete resolution of the lesion. She was tapered off steroids and her symptoms did not return. *Final Diagnosis: Tolosa Hunt syndrome*.

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Case 41

History of Present Illness

A 60-year-old right-handed woman presented with bilateral eye pain. While she used to get "stress headaches" off and on earlier in her life, these headaches were dull, bi-frontal and temporal and behind her eyes. She noticed mild light sensitivity. While ibuprofen dulls the headache and eye discomfort now, the headache/eye discomfort continues daily. She thought she was having trouble with her glasses, and saw her optometrist who found a normal exam. The blurring continued and she noticed trouble with both horizontal and vertical diplopia with driving and reading. She has had more fatigue. She saw her optometrist again and had a visual field (Fig. 41.1) and she was referred for further evaluation.

Past medical and ocular history Anemia (mild) Osteoarthritis Hypothyroidism Wears glasses for reading Dry eyes (mild)	*Past surgical history* Tonsilectomy Cesarean section
Medications Ibuprofen 200 mg every 4–6 h prn Levothroxine Artificial tears	*Family history* Daughter—migraine Mother—arthritis, stroke, cancer, thyroid Father—hypertension
Social history Works as a chemist for a mining company Divorced with four children; no smoking but occasional alcohol use	*Review of systems* Per HPI

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_41

Examination
Acuity with correction Right eye: 20/70 Left eye: 20/40
Pupils Equal with a 0.9 log unit RAPD in the right eye
Color vision (HRR) 1/6 OD and 3/6 OS
Stereo vision No fly; 0/3 animals; 0/9 circles
Intraocular pressure Right eye: 12 mmHg Left eye: 12 mmHg
External exam Normal
Eye alignment By Maddox rod she had one prism diopter Left hyper and two prism diopter of exophoria—which was comitant in all directions
Slit lamp examination Normal except for mild bilateral nuclear sclerosis
Visual field To confrontation: finger counting in all quadrants but red desaturations bitemporally. Formal visual fields showed a bitemporal hemianopia (see Fig. 41.1)
Fundus examination Cup to disc ratio 0.8 OD and 0.5 OS
Neurologic examination Normal except for decreased vibration in the right big toe, and mild pronator drift in the right arm

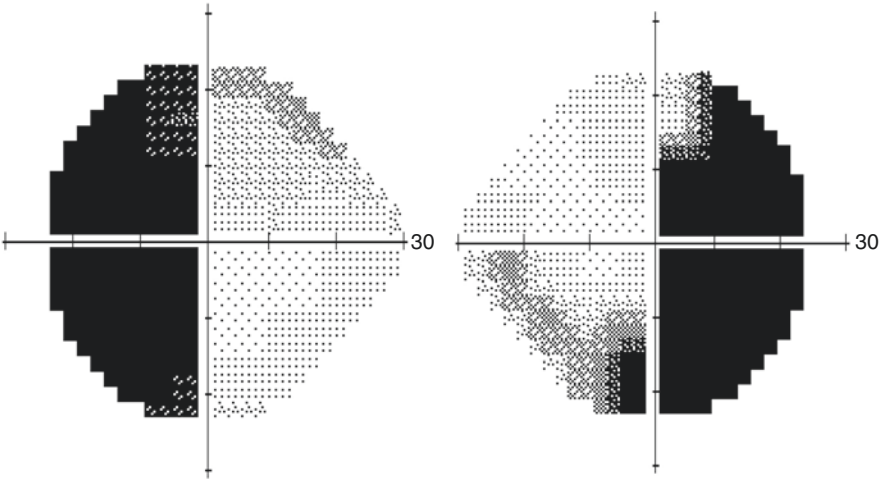

Fig. 41.1 Visual fields show a bitemporal visual field defect

Discussion

Neurologic Perspective—Dr. Digre

There were several clues in the history and examination that the eye pain to point to the correct diagnosis. First, she had blurred vision that was not correctable with refraction and she had reduced color vision testing and a bitemporal hemianopia to confrontation with red colored balls. While she had mild nuclear sclerosis, this could not account for the visual field defect, or the reduced color vision. Second, her complaints of diplopia were associated with very mild abnormalities on Maddox Rod testing and this could be the phenomenon of hemifield slide in which the visual fields nasally can be affected by mild transient slips of a phoria or tropia which can cause variable diplopia. Third, her eye discomfort and bitemporal headache was associated with mild photophobia. Photophobia can be a presenting symptom of a pituitary tumor, and a new headache in an older person should lead to further investigation. So we are suspecting a lesion affecting the chiasm—perhaps a pituitary tumor.

The evaluation for a suspected pituitary tumor should be a dedicated MR of the sella region with sagittal, coronal, and axial views. Blood studies are also helpful to look for underlying endocrinologic findings: thyroid studies (T4 and Thyroid stimulating hormone [TSH], prolactin, growth hormone, Luteinizing hormone, Follicular stimulating hormone, testosterone). In our patient, her hormones were normal. So if this is a tumor, this was a non-secretory pituitary tumor.

Treatment when vision is threatened is either surgical removal often through a transphenoidal approach. If the tumor is not completely removed or if the vision is not correctable, then directed radiation is considered. Often post-operatively, individuals require hormone replacement and are at risk for the development of diabetes insipidus.

One of the dreaded complications of pituitary tumor is pituitary apoplexy or sudden bleed into a pituitary tumor. This is often heralded by a sudden onset of headache/eye pain or visual loss or both.

The cause of the headache and eye pain is probably related to the tentorial innervation (from branches off of V1) to the meninges and blood vessels around the sellar region. While there are no guidelines for the treatment of headache and eye pain related to pituitary tumors, non-steroidal anti-inflammatories such as naproxen 400–600 mg two to three times each day or meloxicam, diclofenac, or ibuprofen can be helpful. Headache and eye pain can worsen post-operatively, not just because of surgical changes, but fat packing that is generally used with the transsphenoidal approach can transiently worsen compression on the tentorial nerves and increase the pain and discomfort. This generally resolves within 1 month and one can uses non-steroidal medication to treat as listed above.

The prognosis is usually good for vision, especially if the optical coherence tomography (OCT) is normal as was the case in this woman. The headache generally resolves after tumor removal.

Ophthalmic Perspective—Dr. Lee

In most cases, we focus on the patient's chief complaint. The patient herein may have significant eye pain and minimize the blurry vision or the double vision, because this may be most concerning to her. Although this case seems straightforward, in an eye office, not all practitioners check color vision and pupils carefully. So, maybe we miss the optic neuropathy. Personally, I believe that anyone with uncorrectable visual acuity ought to undergo formal perimetry. It really tells you whether the patient has true disease or maybe this is something benign like refractive error. It can also help localize vision loss as in this case.

The double vision here is a red herring. The comitant (same in all directions) nature suggests that this is a pre-existing misalignment that is breaking down. However, it might have led a physician to order an MRI and they would have found a chiasmal lesion by "accident."

Non-ophthalmic/Non-neurologic Perspective

A patient complaining of eye pain and blurred vision should have their visual acuity checked in each eye separately. For confrontation visual fields, the patient covers one eye and the examiner shows the patient two red objects in two different locations simultaneously and asks if they appear similar. The examiner can also hold up different fingers in different quadrants and ask the patient to add them. If one finds a reduced visual field in the temporal (toward the ear) hemifield in each eye, this could suggest a chiasmal issue such as a pituitary tumor.

Follow-up

She had an MR scan which showed a large pituitary tumor compressing the right optic nerve (Fig. 41.2). Our patient underwent tumor resection through a transphenoidal approach. Her vision gradually improved. Her headache worsened shortly after surgery for a short while, but later improved. *Final diagnosis: Eye pain secondary to a pituitary adenoma*.

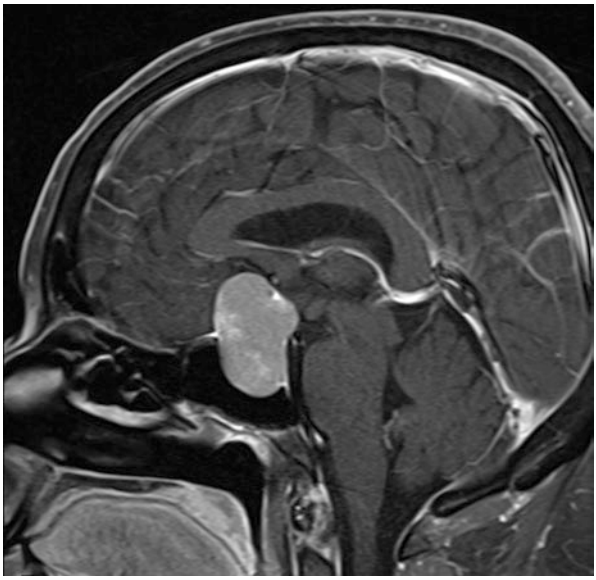

Fig. 41.2 Sagittal MRI shows an enhancing sellar mass extending into the suprasellar space

For Further Study

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Case 42

History of Present Illness

A 75-year-old retired administrative assistant with a history of cataracts and previous corneal erosion many years before was doing well until one day she noticed she had a deep throbbing pain over her right eye and that her eye lid seemed droopy. Within 2 weeks she was seeing double. She remembers a severe headache 2 weeks before. She has a history of migraines all of her life, but recently she was getting more headaches. She is worried, since things seem to be progressing—she was sent for urgent evaluation by her ophthalmologist.

Past medical and ocular history Hypertension Left bundle branch block	*Past surgical history* None
Medications Hydrochlorothiazide 50 Lopressor 50 Potassium 20 Aspirin 625	*Family history* Father and mother heart disease and hypertension
Social history Widowed with three children and now retired	*Review of systems* Dizziness

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
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Examination
Acuity with correction Right eye: 20/50 Left eye: 20/40
Pupils 7.5 mm OD in darkness to 7.0 mm OD light 5.5 mm OS in darkness 4.5 mm OS light Near 7 mm OD and 3 mm OS NO RAPD by reverse technique
Intraocular pressure Right eye: 15 mmHg Left eye: 15 mmHg
External exam 3 mm Ptosis OD
Eye alignment Limited elevation and adduction-3 and depression-2. Good abduction (see Fig. 42.1); she has 25 diopters of right exotropia and eight diopters of hypotropia
Slit lamp examination Conjunctiva 1 + injection OU; 1 + nuclear sclerosis OD, and 1 + posterior subcapsular cataract OD
Visual field Normal
Fundus examination Normal
Neurologic examination Aside from eye findings she was normal

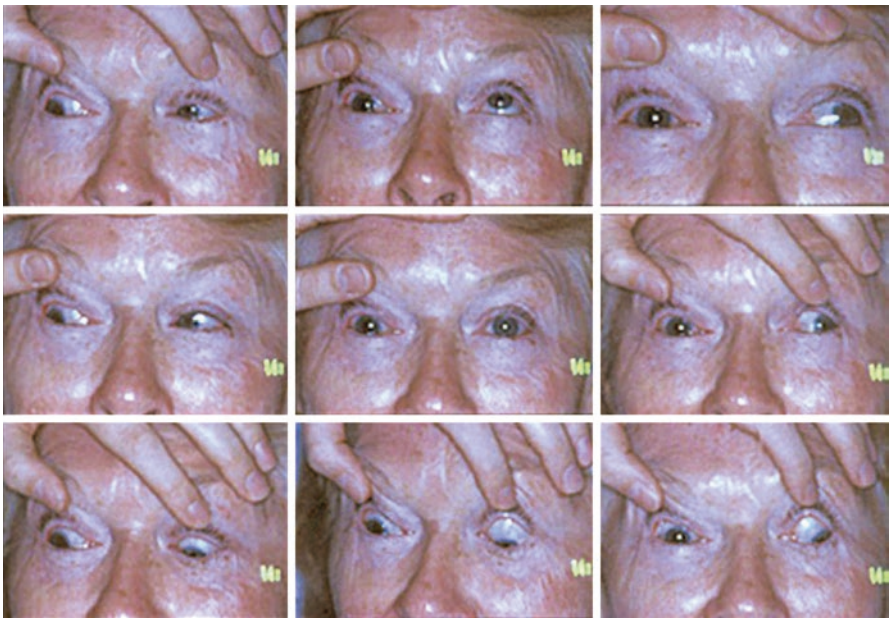

Fig. 42.1 These were her cardinal positions of gaze. Note, that we had to raise her lid to get these photos. The findings were typical for a pupil involving, third nerve palsy

Discussion

Neurologic Perspective—Dr. Digre

When a person over 60 starts having new headaches, diplopia, and ptosis—you have to pay attention! First, she had a previous headache 2 weeks ago, and you have to find out what happened with that. Also careful query about other constitutional symptoms (fatigue, pain with chewing her food)—looking for giant cell arteritis. The ptosis and diplopia could be a symptom of ocular myasthenia, but there is pain—and that is not myasthenia. The new pain with ptosis, a slightly larger pupil on the right, and a pattern of a third nerve palsy is really disturbing.

In evaluation, the first step would be emergent imaging—MR scan and MRA to rule out a mass lesion or aneurysm as well as ESR and CRP (since a painful third could also be giant cell arteritis) (Case 32).

Aneurysms—especially posterior communicating (PComm) aneurysm compressing the third nerve are one of the most feared causes of a new onset headache and a third nerve palsy especially with pupil involvement such as is in this case. Failure to diagnose correctly can lead to a deadly outcome. Sometimes the symptoms are vague and not easy to diagnose, and sometimes the symptoms are sudden onset of a severe headache related to a sub-arachnoid hemorrhage. A sentinel headache, like the headache she had 2 weeks before can be a warning of an aneurysm. When thinking of thunderclap headache (Case 33), it is worth remembering that aneurysm is one of the feared causes along with reversible vasoconstriction syndrome, arterial dissection, and venous thrombosis among others. The sentinel headache can occur without evidence of a bleed. Headaches commonly occur with both ruptured and non-ruptured aneurysm. The ICHD 3beta criteria for headache with saccular aneurysm are in Table 42.1.

Table 42.1 Headache attributed to unruptured saccular aneurysm

Diagnostic criteria:
(A) Any new headache fulfilling criterion C
(B) An unruptured saccular aneurysm has been diagnosed
(C) Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in close temporal relation to other symptoms and/or clinical signs of unruptured saccular aneurysm, or has led to its diagnosis
2. Either or both of the following:
(a) Headache has significantly worsened in parallel with other symptoms or clinical or radiological signs of growth of the saccular aneurysm
(b) Headache has resolved after treatment of the saccular aneurysm
3. Either or both of the following:
(a) Headache has sudden or thunderclap onset
(b) Headache is associated with a painful IIIrd nerve palsy
(D) Not better accounted for by another ICHD-3 diagnosis, and intracranial hemorrhage and reversible cerebral vasoconstriction syndrome have been excluded by appropriate investigations

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia.* 2013;33:629-808

While aneurysms may lie dormant for years and never rupture, risk factors for rupture of aneurysms include: female sex (check), age (check), hypertension (check) aneurysm size (over 7 mm), and location. The most common symptom of an unruptured aneurysm is headache, sometimes stroke like symptoms, and cranial neuropathy. The most common symptom of a ruptured aneurysm is sudden onset of headache with nausea and photophobia (symptoms of dural irritation), followed by change in mental status and possibly abnormal neurological examination.

Third nerve palsy (TNP) is the most common cranial neuropathy seen with an aneurysm followed by other cranial nerve palsies such as a fourth, sixth, fifth (first and second division). The pain involved in this TNP comes from small first division twigs innervating the third nerve—so eye pain occurs in association with the third nerve compression from aneurysm in over a quarter of the cases.

Some of the causes of misdiagnosis include: diagnosing a primary headache (thunderclap or migraine), diagnosing stroke (if there are neurological deficits), diagnosing meningitis or infection if there is fever, or microvascular cranial neuropathy (Case 18).

Evaluation should proceed with imaging: CT to look for acute blood and CTA for an aneurysm or MR (acutely blood may not show up) and MRA. When an aneurysm is detected, the size is very important, since as the size increases so does the risk of hemorrhage. For example, aneurysms in the anterior circulation less than 6–7 mm are considered incidental and often not treated since the risk of bleeding is so rare. Whereas larger ones or ones found in the posterior circulation have a greater risk of bleeding.

Occasionally, digital subtraction angiography is needed to adequately define the aneurysm before clipping. However, when an aneurysm is *symptomatic* like in our case, it will require emergent treatment—with either clipping or coiling.

What happens to the pain and to the TNP after treatment? Guresir et al found that clipping brought greater resolution to the TNP than coiling (complete improvement 55% compared to 32% and partial improvement 92% vs 74%). Others have found 90% improve no matter what the treatment. The pain generally resolves after treatment, but I have seen post-clipping pain continue—usually behind the eye or on the ipsilateral side of the head. Anti-inflammatories or anticonvulsants such as gabapentin can be very helpful.

Ophthalmic Perspective—Dr. Lee

The rule of thumb is that a TNP is an aneurysm until proven otherwise. Sometimes, as Dr. Digre points out, the TNP can be very subtle. In any patient with ptosis, I look to see if there is anisocoria. If a bigger pupil is on the same side as ptosis, then I am concerned about a TNP. If it is smaller on the same side of ptosis, then I am worried about Horner syndrome (Case 17). If the patient with ptosis does not complain of double vision, I have the patient look up to see if I observe limited elevation and I ask the patient if they see double in upgaze. Generally, patients with diplopia only in upgaze do not notice it, because we do not look up that often in daily life. In many ophthalmic practices, a technician checks eye movements and pupils then dilates

the patient, so it is critical to instruct your staff about this scenario. Lastly, I would not be concerned if the patient has isolated ptosis (without anisocoria or ophthalmoplegia) or has an isolated large pupil. However, if the eye movements are consistent with a partial TNP then it is important to rule out aneurysm.

There was a super interesting and scary paper about underdiagnosis of PComm aneurysms causing TNP. It turns out that patients underwent good CTA or MRA, which showed the aneurysm but the aneurysms were missed. The reason…either a neuroradiology-trained radiologist did not read the film or the request did not include language about a TNP. So, if you are going to get a scan, make sure that you include a history of TNP and evaluate for PComm aneurysm. If the scan is normal, then call the radiologist to make sure they are neuroradiology trained and comfortable ruling an aneurysm out.

Non-ophthalmic/Non-neurologic Perspective

The lesson here is an older person with a new onset headache deserves immediate attention especially if there are any findings of neurological involvement. Besides listening to the history, examining the cranial nerves carefully and looking at the pupil in this case was key. Often, an isolated dilated pupil is NOT an emergency, but any hint of ptosis or diplopia should trigger an emergent CT and/or MR imaging.

Follow-up

She had an emergent CT which was negative, but an MR and MRA and digital subtraction angiogram (Fig. 42.2) showed a posterior communicating artery aneurysm that was clipped by neurosurgery. She did very well and is currently alive in her 90s.

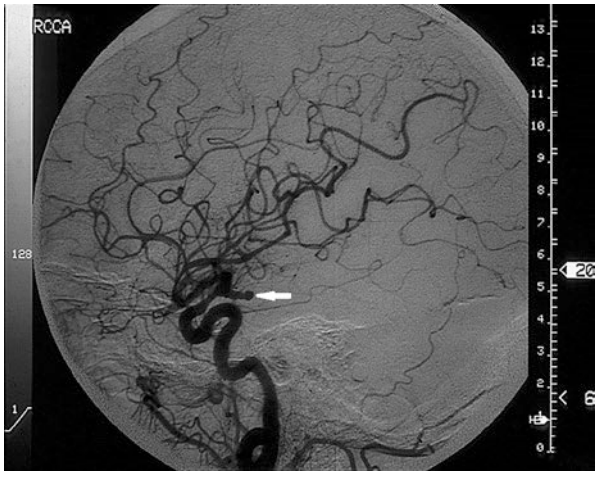

Fig. 42.2 Right internal carotid angiogram shows the PComm aneurysm (*arrow*)

She still has residual right hypertropia which appears to be stable. Her headaches completely resolved. *Final diagnosis: Posterior Communicating aneurysm causing 3NP*.

For Further Study

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Case 43

History of Present Illness

A 6-year-old girl developed a severe unilateral, throbbing headache upon awakening 3 weeks ago. She experienced nausea, vomiting, photophobia and lay in bed. The headache resolved after several hours, but she experienced persistent left eye pain, which she described as sharp. One week later, her left upper eyelid drooped. It was constant and unassociated with vision loss, ptosis, or worsening pain. One week later, she developed diplopia and went to the emergency department (ED). Brain MRI at that time was read as normal. The father notes that her left pupil has been larger "as different as a dime and a quarter."

Past medical and ocular history Born at 39 weeks with normal pregnancy and delivery Achieved normal milestones No ocular or medical history	*Past surgical history* None
Medications None	*Family history* Mother—sick headaches starting in college
Social history Kindergartener, both parents at home, one older sibling. No pets Denies alcohol, tobacco, and street drugs	*Review of systems* No fever, chills, or night sweats Some moderate malaise No neck stiffness No weight loss Feels well

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_43

Examination
Acuity with correction Right eye: 20/20 Left eye: 20/20
Color vision Normal BE
Pupils Pharmacologically dilated by referring ophthalmologist Notes reflect left pupil was larger
Intraocular pressure Right eye: Globe soft to palpation Left eye: Globe soft to palpation
External exam RE appears normal 2.5 mm ptosis LUL No proptosis or enophthalmos
Eye motility and alignment RE was normal LE showed normal abduction and intorsion on downgaze LE 50% adduction, 50% elevation, and 75% depression
Slit lamp examination Normal
Visual field Normal
Fundus examination Normal
Neurologic examination Normal facial sensation and strength Normal neurologic exam besides left CN 3

Discussion

Ophthalmic Perspective—Dr. Lee

Historically, the patient had what sounds to be her first migraine headache 3 weeks ago and suffered persistent LE pain. While she is on the young side, migraine can happen in that age group. Later, however, she develops a slowly progressive, pupil-involving, left third nerve palsy (3NP). We really do not need to ask about myasthenic symptoms, because myasthenia does not cause pain nor affect the pupil. It appears neurologically isolated with intact cranial nerves 2 (normal acuity and color vision), 4 (intorsion with downgaze), 5 (normal facial sensation), 6 (normal abduction), and 7 (normal facial strength). Thyroid eye disease does not cause ptosis. It usually does not occur in this age group or present this acutely. There are also no obvious orbital signs suggesting thyroid eye disease.

We are always worried about aneurysm in a patient with a pupil-involving 3NP. This patient is young for aneurysm, but we do not want to miss it especially since CTA and MRA are noninvasive and apt to find essentially all aneurysms big enough to cause 3NP.

There is a phenomenon known as ophthalmoplegic migraine (recently renamed recurrent painful ophthalmoplegic neuropathy) that usually presents before age 10. Often the child experiences a migrainous headache followed by a third nerve palsy (it can be a sixth or a fourth nerve palsy too). Although the headache resolves within hours, the nerve palsy resolves spontaneously over several weeks. Brain MRI almost always shows enhancement of the third nerve at the root exit zone (This suggests that this is not really migraine). So, I would like to look at the MRI from the ED. If the MRI were not performed with gadolinium, then I would send her for an MRI/MRA brain with gadolinium letting the radiologist know that she has a left 3NP and please evaluate for posterior communicating artery aneurysm. If the original MRI were done well and did not show enhancement, then I would talk to the radiologist and the parents about CTA vs. MRA. Some institutions have better results with one vs. the other but CTA has radiation (which we worry about giving in children).

Neurologic Perspective—Dr. Digre

This child has a family history of migraine and we do not know if she was a colicky baby, but colic can portend migraine as the child gets older. She has a headache 3 weeks before that really sounds like migraine, and the mother obviously knew she had a migraine and sent her to bed to sleep the migraine off. However, the pain persisted and she had sequential ptosis and diplopia and now her examination looks like a pupil involving third nerve palsy. We have to consider the differential diagnosis of a painful third nerve palsy in childhood (see Table 43.1).

Imaging apparently was negative—or at least no gross abnormality was identified. Recurrent ophthalmoplegic neuropathy is a likely diagnosis here. However, according to the ICHD 3 beta criteria (see Table 43.2), the child should have at least three attacks to be called recurrent ophthalmoplegic neuropathy (formerly known as

Table 43.1 Causes of third nerve palsy in childhood

Congenital
Trauma
Tumor
Vascular (aneurysm)
Meningitis
Idiopathic (including ophthalmoplegic migraine)

Table 43.2 ICHD 3 beta diagnosis of Recurrent painful ophthalmoplegic neuropathy (ophthalmoplegic migraine; ophthalmoplegic neuropathy)

(A)	At least two attacks fulfilling criterion B
(B)	Unilateral headache accompanied by ipsilateral paresis of one, two or all three ocular motor nerves
(C)	Orbital, parasellar, or posterior fossa lesion has been excluded by appropriate investigation
(D)	Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808

Table 43.3 Causes of a painful third nerve palsy

Vascular causes
Ischemia
Aneurysm
Pituitary apoplexy
Fistula (cavernous)
Inflammation
Giant cell arteritis
Tolosa Hunt Syndrome
Infection
Meningitis
Tumor
Pituitary tumor
Pituitary apoplexy
Demyelination
Multiple sclerosis
Other
Ophthalmoplegic migraine or recurrent ophthalmoplegic neuropathy
Herniation

ophthalmoplegic migraine). In general, this is seen more frequently in girls at around age 4–10. However, it has been reported in individuals over 50. Pain is often orbital or periorbital and the pain most frequently occurs before the onset of the cranial neuropathy and the headache often goes away before the third nerve palsy resolves. The pain may have some migraine symptoms like nausea, and vomiting, photophobia but about 1/3 do not. The third nerve is most frequently involved—rarely the sixth alone or combined with CN 3. The majority of individuals will have typical migraine in between third nerve attacks. The pupil is most often partially or completely involved. The spinal fluid is usually normal. The cause of the recurrent neuropathy is unknown but some think it is a recurrent demyelinating event. Treatment of the neuropathy is usually waiting, treat the pain with non-steroidal anti-inflammatories, but some have suggested steroid therapy. Third nerve palsies are always tricky especially when they are painful (Table 43.3).

Non-ophthalmic/Non-neurologic Perspective

If you are comfortable diagnosing a 3NP, then you could consider ordering an MRI/MRA with contrast. It is critical that you talk to the radiologist about the diagnosis of a 3NP and get a reading the same day because of the risk of aneurysm. It is also MUCH better to use a radiologist with neuroradiology fellowship training.

Follow-up

I reviewed the MRI personally. It was done with gadolinium and was not read by a neuroradiologist. The scan showed avid enhancement in the area of the left third nerve exit zone consistent with recurrent ophthalmoplegic neuropathy or ophthalmoplegic migraine (Fig. 43.1). Because the migraine headache occurred 1–2 weeks before the 3NP and the patient noted moderate malaise, a lumbar puncture was also performed to evaluate cell count, protein, glucose, cytology, and Lyme. The spinal fluid was normal. The patient's 3NP resolved over the next 4 weeks. The patient's parents were warned that it is not unusual for this to recur over the patient's lifetime. *Final diagnosis: Ophthalmoplegic migraine (Probable recurrent painful ophthalmoplegic neuropathy).*

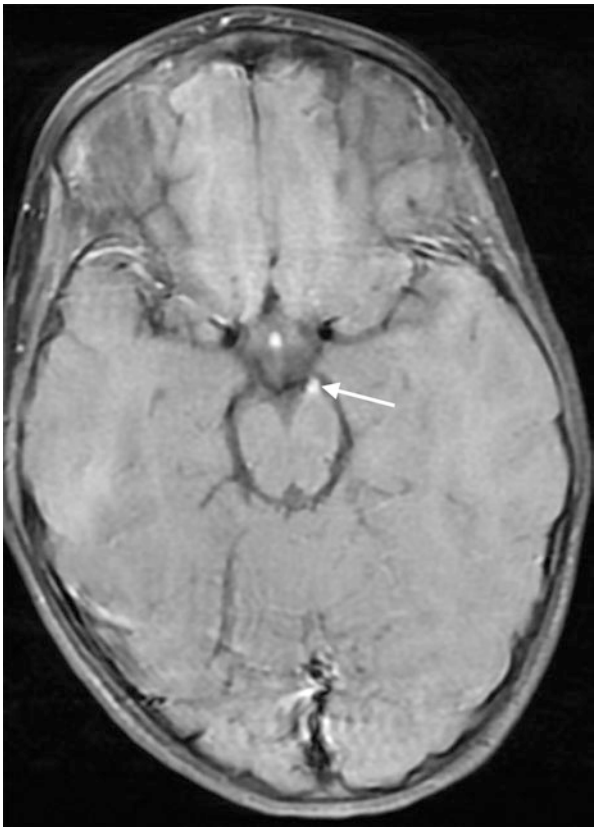

Fig. 43.1 Axial T1 postgadolinium MRI shows the typical bright signal at the left third nerve (*arrow*) exit zone between the cerebral peduncles

For Further Study

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Appendix A

List of Tables

Case	Page	Diagnosis	Table
1	3	Dry eye syndrome	None
2	9	Corneal erosions	None
3	15	Post LASIK pain	None
4	21	"Eye strain"	None
5	27	Intermittent angle closure glaucoma	5: Drugs causing angle closure glaucoma
6	33	Blepharospasm	None
7	39	Chalazion	None
8	43	Trochleitis	8: Diagnostic criteria for trochleitis
9	49	Lacrimal gland tumor	None
10	53	Posterior scleritis	10: Diagnostic criteria for headaches attributable to ocular inflammatory disorder
11	61	Idiopathic orbital inflammatory syndrome	11: Causes of orbital inflammation/proptosis and eye pain
12	69	Uveitis	12: Uveitis and meningitis syndromes
13	75	Conjunctivitis	13: Differential diagnosis of a red eye
14	81	Thyroid eye disease	14: Clinical activity score for thyroid eye disease
15	87	Orbital mass	None
16	93	Ocular ischemic syndrome	None
17	99	Horner syndrome	17: Paratrigeminal oculosympathetic syndrome (Raeder's syndrome)
18	105	Microvascular cranial nerve palsy	None
19	113	Migraine	19.1: Diagnostic criteria for migraine without aura 19.2: Diagnostic criteria for migraine with aura 19.3: Diagnostic criteria for typical aura without headache 19.4: Diagnostic criteria for chronic migraine

(continued)

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Case	Page	Diagnosis	Table
20	119	Medication overuse headache	20.1: Risk factors that lead to chronic migraine 20.2: Diagnostic criteria for medication overuse headache
21	125	Photophobia	None
22	131	Trigeminal neuralgia	22.1: Causes of brief (less than 2 min) unilateral eye pain 22.2: Diagnostic criteria for classic trigeminal neuralgia
23	137	Cervicogenic headache	23: Diagnostic classification of cervicogenic headache
24	143	Ice pick headache	24.1: Causes of short eye pain (less than 10 seconds) 24.2: Diagnostic criteria for idiopathic stabbing headache
25	149	Sinus disease	25.1: Diagnostic criteria for acute and chronic rhinosinusitis 25.2: Diagnostic criteria for acute and chronic rhinosinusitis
26	155	Tension-type headache	26.1: Diagnostic criteria for chronic tension-type headache 26.2: Migraine Inventory Disability Assessment Score (MIDAS)
27	161	Supraorbital neuralgia	27: Diagnostic criteria for supraorbital neuralgia
28	165	Trigeminal autonomic cephalgia	28.1: Diagnostic criteria for cluster headache 28.2: Diagnostic criteria for paroxysmal hemicrania 28.3: Diagnostic criteria for SUNCT 28.4: Diagnostic criteria for hemicrania continua 28.5: Differentiating the trigeminal autonomic cephalgias from migraine
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Appendix C

Obtaining a History and Doing an Exam for Eye Pain

Taking an Eye Pain History

In many cases of eye pain and headache, no physical findings exist. This means that the diagnosis depends almost completely on the history. Remembering to cover the five elements of the history can prove extremely helpful. These include the **family history, life history, attack history**, the **medical and psychiatric history**, and the **medication and drug history**.

The family history helps us understand if there is a genetic predisposition to headache or chronic pain. The strongest familial association occurs with migraine and tension-type headaches and other pain disorders like fibromyalgia. Occasionally cluster headache can run in families. Headaches/eye pain beginning at an older age without a family history may raise concern for a secondary headache. A strong family history of aneurysm may direct one to rule out aneurysm. Family history of autoimmune disorders may suggest an inflammatory cause of pain as the first manifestation of a new autoimmune disorder in the patient.

The **life history** helps determine if this represents new or changed headache over time. New chronic daily headache or a significant change in attack characteristics should raise a red flag for a secondary headache especially in an older individual.

The heart of the history for eye pain is the **attack history** which focuses on the quality, frequency, duration, modifying factors, and accompanying features. What does the pain feel like? Is it sharp, scratching, shooting, stabbing, pounding, aching, or throbbing? Is it constant or intermittent? If it is intermittent, then how often does it occur? How many times a day, week, month, or year? How long does it last and what was the time course? Is it seconds, minutes, hours, or days? An apoplectic pain raises concern for a secondary cause (aneurysm or secondary thunderclap headache; Cases 33 and 42). What makes it better or worse? Sometimes patients will tell you that touching the face (trigeminal neuralgia; Case 22), moving the eye, sunlight, or sitting upright (Spontaneous intracranial hypotension; Case 31) might worsen the

pain. It might improve with exercise (Tension-type headache; Case 26) or lying in a dark room or pressing on the back of the neck (Cervical spasm; Case 23). As we all know, pain is unique to each patient and one patient's throbbing may be another patient's aching. However, if one can elicit a classic history for an eye pain or headache disorder, a diagnosis may be determined. Accompanying features to inquire about include migraine symptoms (nausea, vomiting, photophobia, phonophobia, and osmophobia (migraine; Case 19)), autonomic symptoms (epiphora, conjunctival injection, ptosis, miosis, sweating, and nasal stuffiness/rhinorrhea (Trigeminal autonomic cephalgias; Case 28)), and giant cell arteritis symptoms, in the right age group (jaw claudication, weight loss, anorexia, scalp tenderness, malaise, and arthralgias; Case 32).

The **medical and psychiatric history** may identify a co-morbid condition that could cause or worsen the eye pain and headache. Risk factors for chronic migraine or tension-type headache (more than 15 days/month) include depression, anxiety, stress, snoring, obesity, female gender, lower education level, and lower socioeconomic status. Co-morbidities for migraine and even tension-type headaches include depression, stress, fatigue, sleep apnea irritable bowel syndrome, fibromyalgia, menstruation, Raynaud's, depression, anxiety, and epilepsy. Whereas tension-type headaches are increased in stress, fatigue, lack of sleep, depression, and anxiety. Patients with hypercoagulable risk factors may develop cerebral venous thrombosis. Graves ophthalmopathy can develop months to years after a diagnosis of Graves disease (Case 14). Patients with collagen vascular disease, sarcoidosis, or autoimmune disorders may present with inflammation of the trochlea (Trochleitis; Case 8), sclera (Posterior scleritis; Case 10), orbit (orbital inflammatory disease; Case 11), uvea (Uveitis; Case 12), or the cavernous sinus (primary or secondary Tolosa Hunt syndrome; Cases 39 and 40). Microvascular cranial nerve palsies (Case 18) are more common in patients with diabetes, hypertension, and hypercholesterolemia. Skin cancers removed from the face can recur and travel perineurally causing eye pain and headache (Case 39).

The **medication and drug history** is critical. Medication overuse can easily explain a headache and eye pain. This varies by the type of medication used (opiates and barbituates vs. NSAIDs vs. triptans) and the number of days per week—and if an acute rescue medication is taken more than 2–3 days in a week medication overuse can develop. See Case 20 (Chronic migraine with medication overuse) for details. A number of antihistamines, diuretics, anticholinergics, and antidepressants cause dry eye leading to eye pain.

Eye Pain Examination

The history typically drives the examination. The basic evaluation includes visual acuity, visual fields, assessment of the pupils and eye movements, evaluating the eyelid position, slit lamp examination, fundus examination, and palpation. Visual acuity and visual field are the vital signs of the eye similar to pulse and blood

pressure. The pupils may show anisocoria in Horner syndrome, trigeminal autonomic cephalgia, or third nerve palsy. An afferent pupillary defect occurs in optic nerve disorders such as optic neuritis. Ptosis may indicate involvement of the third nerve or Horner syndrome, whereas eyelid retraction may mean thyroid eye disease or an orbital mass. The slit lamp examination is critical to evaluate for dry eye syndrome (tear break up time, corneal staining, meibomian gland dysfunction), anterior basement membrane dystrophy, or cells in the anterior chamber. The fundus examination helps determine the presence of papilledema or other optic nerve disorders. We like to palpate the temporal arteries, the greater occipital nerve, the infraorbital nerve, the supraorbital nerve, the lacrimal gland, and the trochlea. Improvement with temporal artery pressure may be a clue to migraine or tenderness may suggest temporal arteritis in the older patient. Improvement with an anesthetic drop indicates an ocular surface disorder. It also allows us to check the intraocular pressure. Finally, a brief neurological examination—look for drift of arms outstretched will signify subtle weakness that may signal central event.

Appendix D

Pathophysiology of Eye Pain

That the eye would be a source of pain should not be surprising! The anatomy and physiology play a huge role in why get eye pain.The trigeminal system is the sensory supply to the eye, but it also is the sensory system to most of the head too AND the trigeminal system supplies the blood vessels and parts of the dura (the coverings of the brain). This system is complicated and is modulated by the thalamus and the brain.

First, the anatomy is important. The trigeminal system consists of **primary afferents that sit on the cornea but also on blood vessels, muscles, and tissues of the orbit and head and brain**. The cornea has perhaps the densest set of afferent nociceptors anywhere, and anything that affects these nerves on the cornea will create pain. These nociceptors are mainly C fibers and A Delta fibers—small caliber fibers and project to the Gasserian Ganglion and then on to the trigeminal sensory nuclei of the brainstem. What is important to know is that the trigeminal nerve—first division—also has both sympathetic and parasympathetic fibers that join it. This is why there are so many other findings with certain types of eye pain—like conjunctival injection, tearing, ptosis, anisocoria. The branches of the trigeminal nerve include the lacrimal nerve which innervates the lacrimal gland, conjunctiva, and upper eyelid sensation. The frontal nerve innervates the superior rectus muscle and levator muscle, forehead, skin on the side of the nose and frontal sinus via the supraorbital nerve and supratrochlear nerve. The nasociliary nerve holds the sensory supply to the eye. This is really an important nerve since it gives off the short ciliary nerves that supply the choroidal vessels and long ciliary nerves, which surround the optic nerve and innervate the iris, ciliary body, and cornea. These long ciliary nerves also have sympathetic fibers attached. These nerves supply the nasal septum, turbinate, and skin to the tip of the nose. This is why in herpes zoster we worry about the involvement of the tip of the nose as a sign that the eye itself is involved in the outbreak.

The first division of the trigeminal nerve also innervates the dura of the anterior intracranial fossa and tentorium and even the sagittal sinus. This is why intracranial processes like meningitis can also present with eye pain and headache. These fibers also innervate cerebral blood vessels which play an important role in our understanding of migraine. The importance of migraine is discussed below.

The second division of the trigeminal nerve is the maxillary nerve and it too supplies areas around the eye—the lower eyelid, side of the nose, teeth, maxillary sinus, and roof of the mouth.

The mandibular nerve or the third division of the trigeminal nerve is both sensory and motor, but mainly provides sensation to the lower face.

The next step is for the three branches to coalesce in the Gasserian (also known as the semi-lunar ganglion) and become the sensory root that enters the brainstem. These fibers branch into both ascending and descending directions. The descending fibers become the trigeminal spinal tract—and end in the nucleus of the trigeminal spinal tract or the caudal nucleus. What is interesting about this nucleus is that the nucleus is organized a little differently; it has projections to the mouth, the intermediate face, and the head. This results in a different pattern of sensation when this nucleus is disrupted—instead of the three divisions we classically see in the face, we get kind of an onion skinning appearance of the sensation with the most caudal portion carrying fibers to the forehead and top of the head, the middle section to the eye and the most rostral to the mouth and nose (See Fig. 23.1). The most caudal nucleus (nucleus caudalis) extends to the cervical region—and this is why upper cervical lesions can seem to project pain to around the eye and forehead. Fibers from the upper cervical regions can project to this nucleus caudalis. Interestingly, corneal afferents also project into this spinal nucleus—making it an important center for all of us in neuro-ophthalmology since the nucleus caudalis of the spinal nucleus is thought to play an integral role in migraine.

The trigeminal system has other sensory nuclei including the mesencephalic nucleus which are primary sensory neurons that remain in the central nervous system; these fibers end up going to the thalamus.

All of the trigeminal nuclei ascend after crossing through the medial lemniscus to the thalamus via the ventral spinal thalamic tract and the lateral spinothalamic tract. These fibers end in the posterior thalamic region. Interestingly, these fibers also connect to the limbic system—hence these anatomical structures give an emotional component to eye and head pain! From the thalamus, pain is relayed through the corticothalamic projections into the primary somatic sensory cortex as well as the anterior cingulate cortex, prefrontal cortex (the "pain matrix"). The eye is represented in the homunculus between the forelimb and forehead or nose.

Now, why do we want to know this anatomy anyway? Well, it turns out this anatomy also applies to the primary headache disorders like migraine, cluster headache, and the like! No wonder we get so confused sometimes that eye pain can be a migraine and why migraine can be eye pain! Of great importance to us is the knowledge the ophthalmic division (V1) also has connections to blood vessels around the brain—thereby linking the vascular system and the trigeminal system. Some have called this the trigeminal vascular unit.

In fact, the most recent pathophysiology of migraine states that through the migraine process—maybe starting in the hypothalamus—dural afferents (from our first division of the trigeminal nerve) are stimulated and set up a microscopic dural inflammation which in turn activates the thalamus and brain. This system has centers participating in inhibition of signaling as well—otherwise, we would all have head and eye pain! In migraine, however, once a migraine is started and this trigeminal vascular pathway is ignited, it is hard to turn off and pain can occur in the surrounding areas—in a process called central sensitization. Pain is felt beyond the onset of the headache. In addition, other migraine centers are activated to cause other visual symptoms like photophobia, and visceral symptoms like nausea and vomiting.

There are also autonomic nuclei that play a role in eye pain in the brainstem—including the superior salivatory nucleus which is located in the pons. This nucleus contains the parasympathetic autonomic pathway which is vasodilatory and is also connected to the sphenopalatine ganglion which also connects to the lacrimal gland and participates in tearing, and other autonomic symptoms that are present in migraine and trigeminal autonomic cephalgias like cluster headache. It can be stimulated with any process causing pain in the eye. Many of our eye pain patients have red eye and tearing no matter what the cause, and it is this system that is activated. The sympathetic system can also be activated! It starts in the hypothalamus and heads down the spinal cord to C8-T1 and drapes over the apex of the lung, ascends the carotid artery into the orbit—entering after connecting with nerves including the first division of the trigeminal system. When stimulated it can cause pupillary dilation, when lesioned it causes miosis and ptosis.

The biochemistry of pain is also complicated but interesting! There are now known vasoactive neuro-peptides associated with the trigeminal system as well as the parasympathetic and sympathetic systems. The trigeminal sensory fibers importantly have calcitonin gene-related peptide as well as other neuropeptides like substance p, neurokinin A, and pituitary adenylate-cyclase activity. The parasympathetic fibers associated with the trigeminal fibers contain a peptide called vasoactive intestinal peptide, acetylcholine, and neuropeptide Y; whereas, sympathetic fibers contain norepinephrine and neuropeptide Y. These peptides are important since they play a role in the many varied symptoms and signs we see and importantly many medications that are being investigated to treat migraine pain may be helpful in the future for eye pain from migraine and other disorders.

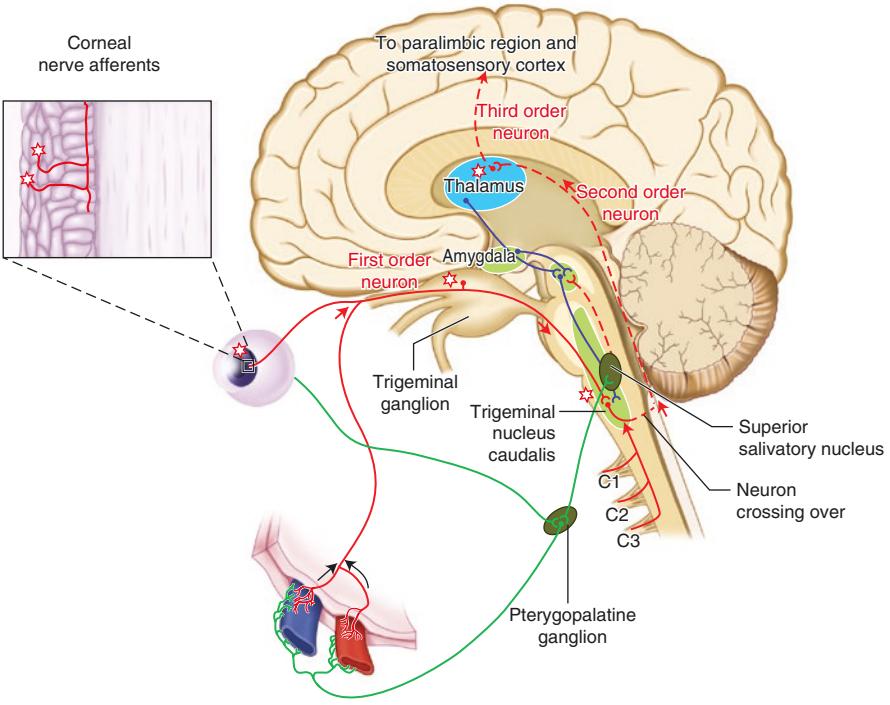
So why do you think that you can get migraine and eye pain from such a diverse anatomy and pathophysiology? First, there is a genetic susceptibility for migraine and even for chronic pain disorders. The anatomy and physiology of the trigeminal system affects the head causing migraine and the eye causing eye pain. In some instances, there is no "pathological" cause of the pain (no signs) but just symptoms. These symptoms are the result of activation of the trigeminal system, autonomic systems, and biochemical peptides. These changes can cause spontaneous eye pain from migraine or continuing eye pain after a corneal injury—the anatomy and physiology is the same. Further, individuals more prone to activation of this system—that is those with migraine, are more susceptible to having more eye pain. In our cases, we are careful to discuss a family history of migraine or fibromyalgia in this

way. For example, not everyone with dry eye gets a lot of eye pain, but eye pain is more actively reported in those with chronic pain conditions.

In our drawing (Fig. D-1), we have paralleled the anatomic pathways for migraine—beginning with the dura and its blood vessels indicating one part of the ophthalmic division of the trigeminal nerve and also the eye—the other major structure innervated by the first division. These pathways are very similar and help us to understand that eye pain and migraines can be very closely related by their anatomy, autonomic connections, and biochemistry. Understanding these factors help to demystify eye pain and give us better clarity on how to approach it and treat eye pain.

Keywords
Eye pain
Migraine
Trigeminal vascular coupling
Central sensitization
Neuro-peptides
CGRP
Autonomic nervous system

Figure D-1



Adapted in part from Goadsby et al N Engl J Med, 2002;346:257–267 and Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain. Is it real? Ocul Surf 2009;7:28–40

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