MAKING CONNECTIONS:

The Neuro-Ophthalmology Issue

INSIDE: Migraine in Your Exam Lane | Photophobia Frontiers | Treating IIH
Moran’s neuro-ophthalmology team, left to right: Alison Crum, MD; Bradley J. Katz, MD, PhD; Judith E.A. Warner, MD; Kathleen B. Digre, MD; Donnell J. Creel, PhD; Meagan Seay, DO.
A Coming of Age

When Kathleen B. Digre, MD, joined the John A. Moran Eye Center in 1987, I asked her to build a world-class neuro-ophthalmology program. It’s clear she took my request to heart. Moran has one of the largest neuro-ophthalmology teams in the country with the recent addition of Meagan Seay, DO, and a deep commitment to meeting the high demand for neuro-ophthalmology services both regionally and nationally.

Our team’s care and research have never been more relevant as physicians, researchers, and patients themselves work to understand the connection between the visual system and brain. Over the past year, trade media, ophthalmic associations, and even mass media have highlighted migraine in particular—and Moran’s specialists have been front and center in the discussion. Dr. Digre is the current president of the American Headache Society and recently presented the American Academy of Ophthalmology’s William F. Hoyt Lecture on migraine. Next year she’ll edit a section on the topic in the Journal of Neuro-Ophthalmology, and she’s planning to speak about new treatments for migraine at the upcoming meeting of the North American Neuro-Ophthalmology Society.

While it all started here at Moran with Dr. Digre, she doesn’t miss the chance to let people know about the quality and dedication of her colleagues, and she’s absolutely right. As I consider each member of the team, I can’t think of a stronger, more cohesive group of clinicians and researchers equipped to tackle some of the most challenging questions in the field today.

This issue of Clinical Focus is full of their insights, from frank discussions about migraine to tips on communicating with patients. I couldn’t be more excited to share this issue with you and hope that it informs, inspires, and enlightens in our common goal to provide the very best care possible to all patients who seek our help.

Sincerely,

Randall J Olson, MD
Professor and Chair, Department of Ophthalmology and Visual Sciences
CEO, John A. Moran Eye Center, University of Utah
Migraine in Your Exam Lane

Kathleen B. Digre, MD

Over the years, I’ve seen more than 30,000 patients at the Moran Eye Center, many of them with migraine. But even those practicing general ophthalmology or a subspecialty can count on seeing migraine patients in their exam lanes on a daily basis.

Why?

- Migraines are more common than asthma and diabetes combined, affecting 18 percent of women and six percent of men.
- They are a sensory processing disorder of both the visual and pain systems.
- They produce visual symptoms, and patients experiencing migraines have heightened visual processing.
- They cause eye pain via trigeminal nerve activation.

Individuals who have chronic migraine are in desperate need of diagnosis and treatment.

At the Moran Eye Center, we recently completed the first study¹ of its kind examining the visual quality of life of migraine patients. In a cross-sectional survey using National Eye Institute instruments, we determined 21 patients with chronic and episodic migraine had visual quality-of-life scores as poor as those previously published for patients with disorders such as multiple sclerosis, Graves’ disease, idiopathic intracranial hypertension, and optic neuritis.

These findings—along with the sheer prevalence of patients with migraine disease who present to ophthalmologists experiencing eye pain or visual symptoms—underscore the need for every practitioner to understand the connection between the eye and migraine, to identify migraine patients, and to help them understand its associated visual symptoms.

Illustration at right adapted from A Case-Based Guide to Eye Pain, by Michael S. Lee and Kathleen B. Digre (Springer, 2018)
Migraine is believed to be an inherited disorder of sensory integration. Two facts connect migraine pain and ocular symptoms: trigeminal activation can cause eye pain; and autonomic dysfunction in either the sympathetic or parasympathetic pathway results in autonomic symptoms such as pupillary changes, lacrimation, redness to the eye, and even blurred vision.

Beyond this systematic connection, our research² has found patients with chronic migraine have structural differences with decreased corneal nerve fiber density. This may be a result of the disease process or may be exacerbating the process. Importantly, we also determined patients with chronic migraine have excessive dry eye symptoms. This indicates the prevalence of dry eye symptoms in chronic migraine may be more than three times that in a normal population. These patients may lack obvious signs of dry eye and may have normal basal tear film secretion. But in chronic migraine, the trigeminal system becomes activated, and central sensitization occurs so that patients feel dry eye symptoms even when they test normal.
Patients with underlying migraine are likely to experience related visual phenomenon.  

**Aura.** A distinct neurological event, defined as a unilateral visual symptom gradually developing over 5-60 minutes and sometimes preceding the headache phase. These may begin as flickering lights or zigzag lines that build up over time. Auras occur in about one-third of patients with migraine. A headache may or may not follow.  

**Photophobia.** Light sensitivity most commonly associated with migraine and an almost ubiquitous symptom during, and sometimes between, attacks.  

**Visual Snow.** Characterized by dynamic dots in the visual field for at least three months and named after badly tuned analog television. While this phenomenon is lesser known than auras or photophobia, about 60 percent of all patients with visual snow have migraine or at least headache.

For patients experiencing visual symptoms or eye pain, ask the following three simple questions from the ID Migraine™ screener to better understand their complaint:

1. Has a headache limited your activities for a day or more in the last three months?
2. Are you nauseated or sick to your stomach when you have a headache?
3. Does light bother you when you have a headache?

If two out of three are positive, there is a nearly 90 percent chance the patient has migraine according to research validating the screener.

Since many adult migraineurs have a family history of the disease or have experienced carsickness or episodic stomach pains during childhood, two additional questions are:

1. Does anyone in your family have migraines? Do you remember your mother being sick with headaches when you were a child?
2. Did you get carsick or have episodic belly pain when you were a child?

As part of an eye exam for migraine patients, use a green light during ophthalmoscopy since the patient will be more comfortable and do not dilate unless you need to.
TREATMENT OPTIONS

Ophthalmologists can confirm and treat migraine, partnering with a neurologist for continued care.

As the first line of treatment, consider treating for dry eye. This may be helpful in slowing down the trigeminal stimulation that keeps the migraine going—and it certainly won’t hurt.

Treatments for visual snow include simple reassurance that the patient’s experience is legitimate. Blue-yellow filters and FL-41 lens filters can also be helpful, while medications including lamotrigine, nortriptyline, carbamazepine, and sertraline have mixed results.

For photophobia associated with migraine, the FL-41 lens filters have also proven remarkably effective, and medications that may help include botulinum toxin injections and use of anticonvulsant drugs.

No matter what the approach, a better understanding of migraine and the experiences of the patients who will inevitably seek our help behooves us all.


What’s the science behind photophobia?
Until recently, it hasn’t been clear how light is transduced into a painful stimulus. Now, we know that transducer appears to be melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells are the beginning of a “photophobia circuit” that transforms light that is too bright into a painful sensation.

How is photophobia diagnosed?
Photophobia is associated with a number of ophthalmic and neurologic conditions. However, in the presence of a normal eye examination, the most common causes are migraine, benign essential blepharospasm, traumatic brain injury, and dry eyes. At right is a helpful diagnostic approach.

How does FL-41 tint eyewear help patients?
If you look at the transmission spectrum of the FL-41 tint, it maximally blocks light around 480 nm. It turns out that this is the same wavelength that maximally stimulates ipRGCs. So, we can make patients feel better by using optical filters that block this wavelength of light.

What are the latest innovations in FL-41?
FL-41 tint appears rose-colored. Although this can be very soothing, it makes everything you look at rose-colored. Axon has developed a thin-film spectacle coating that blocks the same 480-nm wavelength that FL-41 blocks. This coating looks like a mirror coating on the surface of the spectacle lens and causes very little color distortion. Axon was recently awarded a patent for this innovation and is working with the FDA to gain a labeling indication for the coating as a treatment for migraine.

Are you working on any other new treatment options?
We have found that nearly all patients with chronic migraine have symptoms of dry eye syndrome, and two other independent research groups have confirmed our finding. We don’t yet know why these patients have dry eye symptoms or if prescribing dry eye treatment will help their dry eye symptoms or their migraines. We are designing a pilot study to answer these questions.

I’m also very interested in developing non-pharmaceutical approaches to the treatment of migraine as I am increasingly encountering patients who are looking for treatments that do not involve prescription medications or procedures.

I frequently recommend alternative treatments to these patients, such as acupuncture, chiropractic treatment, massage, and physical therapy. Axon has recently developed a drink mix for the treatment of migraine. It contains coenzyme Q-10, butterbur, vitamin B2, and magnesium. All of these supplements have been shown to be effective in the treatment of migraine, but no one has ever tried to combine them into one product.
Photophobia is associated with a number of ophthalmic and neurologic conditions. However, in the presence of a normal eye examination, the most common causes are migraine, benign essential blepharospasm, traumatic brain injury, and dry eyes.

AN APPROACH TO THE PATIENT WITH PHOTOPHOBIA

- Is there evidence on history or physical examination of central process?
  - yes: Evaluate with neuroimaging, lumbar puncture and laboratory studies
  - no

- Is there evidence of dry eyes, iritis, uveitis, corneal staining, Schirmer’s test: +?
  - yes: Treat dry eyes, anterior segment disease: lid hygiene, ointments, artificial tears, anti-inflammatory drugs
  - no

- Does the photophobia resolve with topical anesthetic or dilation?
  - yes: Look for corneal neuropathy, iritis, ciliitis, uveitis, dry eyes
  - no

- Is there history of hemeralopia, nyctalopia, decreased visual acuity?
  - yes: Retinal dystrophy: family history, electrophysiologic studies, genetic testing
  - no

- Is there evidence of excessive blinking, involuntary eye closure to light?
  - yes: Treat blepharospasm: botulinum toxin, medications, surgical myectomy
  - no

- Does the patient have migraine history: HA, eye pain, photophobia, nausea, vomiting?
  - yes: Treat migraine; screen for anxiety, depression
  - no
Surgical Idiopathic Intracranial Hypertension Treatment (SIGHT) Trial

Alison Crum, MD

From 2010 to 2013, Moran Eye Center physicians participated in a watershed study that advanced our ability to treat women with idiopathic intracranial hypertension (IIH) who have mild to moderate vision loss.

As part of the National Institutes of Health (NIH)-funded study,¹ Drs. Kathleen Digre, Bradley Katz, and Judith Warner discovered an inexpensive glaucoma drug—acetazolamide—paired with a weight-reduction plan, can improve and even restore vision for women with IIH.

Today, my colleagues and I are part of a second NIH trial to determine the best treatment for IIH sufferers with moderate to severe vision loss. This time, we will evaluate surgical interventions by randomizing patients to the best therapy:

◆ medical therapy: weight loss, acetazolamide only
◆ medical therapy with ventriculoperitoneal cerebrospinal fluid shunting (VPS)
◆ medical therapy with optic nerve sheath fenestration (ONSF)

We hope this study will lead to important new insights into a drastically frustrating and debilitating visual condition. Along with vision loss, IIH patients experience headaches, blackouts, and constant ringing in their ears. Diagnosis and treatment can pose ongoing challenges for general ophthalmologists. For instance, the medications required for treatment are needed in such high dosages that I routinely get calls from pharmacists who want to verify numbers.

Although we now know that medications and weight loss can alleviate mild to moderate vision loss, we have seen IIH patients with moderate to severe loss go blind, regardless of the highest dosages. Symptoms can come on suddenly, and it’s not unusual to have patients from surrounding states flown to us by medical helicopter for treatment. In extreme cases, we admit them to the hospital for a lumbar drain to alleviate pressure before considering further treatment. Knowing that IIH patients as young as 18 may face 60-80 years of blindness without surgery to reduce fluid and relieve pressure, we may recommend either ONSF or VPS, depending on symptoms.

But are we helping or harming patients in the long run? Can these surgeries treat the patient better than medicine alone?

This study marks an important “first” that will allow us to more confidently offer IIH patients the best option available.

DIAGNOSING IIH

A disorder primarily of overweight women of childbearing age, IIH is characterized by increased intracranial pressure with its associated signs and symptoms, including debilitating headaches and vision loss in an alert and oriented patient.

The onset of symptoms is often insidious, and patients may see several different specialists before the diagnosis of IIH is confirmed. In 2017, an international group including Kathleen Digre, MD, published guidance for investigation and management of adult IIH. At left is a flow diagram of investigation of papilledema adapted from the guidelines.

The Genetics of IIH: Does it Cluster in Families?

To date, no one has performed a rigorous genetic analysis of family members with IIH to better identify IIH-related genes and the potential contribution of genetics to the pathogenesis of this disease.

Yet both observations and studies have reported family members with similar symptoms. Moran’s neuro-ophthalmology team is collaborating with Moran researcher Meg DeAngelis, PhD, and the bioinformatics group at Huntsman Cancer Institute to study a possible genetic link for this baffling condition.

The team has recruited and collected DNA samples and gathered epidemiological information from 47 subjects, including members of a three-generation Utah pedigree characterized by clinical exam, optical coherence tomography, brain imaging, and lumbar puncture to determine disease status. Now, the team is conducting whole exome sequencing on DNA of these well-characterized patients to explain a potential genetic cause.
Doctor-Patient Communication: Ask the Big Question  

Judith E. A. Warner, MD

**Dr. Warner** is Moran’s chief of neuro-ophthalmology. She evaluates complex visual complaints, which can be due to optic nerve or brain disease, and provides treatment for these disorders. Her interests include diplopia, giant cell arteritis, papilledema, optic neuritis, episodic vision loss, IIH, ischemic optic neuropathy, and unexplained vision loss.

In patient experience surveys, patients routinely praise Dr. Warner for her ability to provide clear, comprehensive explanations about their conditions and to include them in discussions with her medical team.

I spend a lot of time talking patients through difficult, sometimes frightening diagnoses such as episodic vision loss or diplopia. Since Moran is a teaching institution, I usually have residents, fellows, and medical students in the clinic with me when I talk to those patients—and that’s a good thing.

Each situation provides an opportunity to share my interpretations of various conditions with students. I also find this allows the patient to be involved in, or at least witness, this teaching process. It can be a circuitous route to see a specialist, and by the time patients come in to see me they deserve the full story. So I generally explain things on an academic level.

I recommend starting off with a basic anatomy lesson. Sometimes it’s as simple as the left side of the brain dealing with the right side of the body, and the left with the right. Or maybe I’ll explain that 12 cranial nerves emerge directly from the brain and that they correlate with all of the actions of the face and eyes.

It’s important to go over what the patient’s exam showed and what that tells me about the anatomy of their problem. We’ll talk about what is reassuring about their exam, what is abnormal, and the various things that could be causing the problem. I’ll explain the ways we are going to explore the possibilities.

In most cases, we have options for treatment. Yet, all too often, patients won’t speak up about their biggest fears. So, if a patient has not asked the big question, I will say, “What worries you the most about your condition?” The answer is usually, “I’m afraid I’m going to go blind.”

That fear is so overwhelming that most people haven’t shared it with anybody. But if they can get that out and I can say, “No, this is not going to make you go blind,” the relief is palpable—and we can move forward.
Ophthalmologists and optometrists routinely ask me which electrophysiology test can best detect the site of their patients’ visual symptoms. The answer depends on symptoms and suspected diagnoses.

As a neuro-ophthalmology team, we consider thousands of symptoms, suspected syndromes, and eye diseases. Each patient is unique, and we use a myriad of electrophysiological testing methods to explore suspected diagnoses and determine whether dysfunction is retinal, optic nerve, or cortical.

Sometimes ruling out a site can be helpful. Using multifocal electroretinograms (mfERGs) can determine if a visual field defect is due to retinal dysfunction. Normal mfERGs point to optic pathways or the cortex as the site of pathology.

Electrophysiology in the pediatric population is even more critical and informative than in adults since infants and children often do not recognize visual symptoms. Their parents may notice signs that indicate vision issues—such as not looking at an object, always looking sideways, or struggling to find toys on the floor.

Even children with severe visual dysfunction may seem normal if acuity remains good enough for them to get around. For example, night blindness, if present from birth, may be normal to children because they have no basis for comparison. Similarly, slow loss of peripheral visual field, such as from a brain tumor, might pass unnoticed by an infant or child.

With electrophysiology we can test the eyes, then the pathways in the brain, and do so without having to rely on verbal feedback.

Electrophysiology technology is similar to an electrocardiogram (ECG) in that it shows the health of the retina, similar to how an ECG reflects the health of the heart muscles. It is key to diagnosing and following the progression of disorders affecting the retina.

Dr. Creel is Moran’s director of the electrophysiology service and research professor of ophthalmology and visual sciences, focusing on the neurobiology of disease.
## Moran Eye Center Activities

### July 1, 2017 – June 30, 2018

122 Publications  
8,365,990 Grants & Contracts  
25 Clinical Trials

### 145,633 Patient Visits

<table>
<thead>
<tr>
<th>Department</th>
<th>Visits</th>
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<tbody>
<tr>
<td>Optometry</td>
<td>30,487</td>
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<td>Comprehensive Ophthalmology</td>
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<td>Neuro-Ophthalmology</td>
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<tr>
<td>Uveitis</td>
<td>3,787</td>
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<tr>
<td>Low Vision</td>
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### Top 5 Neuro-Ophthalmology Diagnoses

<table>
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<tr>
<th>Diagnosis</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Visual disturbance/blindness</td>
<td>22%</td>
</tr>
<tr>
<td>Disorder of optic nerve and visual pathways, e.g. papilledema</td>
<td>18%</td>
</tr>
<tr>
<td>Other disorders of the nervous system</td>
<td>12%</td>
</tr>
<tr>
<td>Disorders of ocular muscles, binocular movement, accommodation and refraction</td>
<td>7%</td>
</tr>
<tr>
<td>Episodic and paroxysmal disorders, e.g. migraine/headache</td>
<td>5%</td>
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*Based on primary diagnosis using ICD-10 insurance codes.*
Physicians provide comprehensive care in nearly all ophthalmic subspecialties, making Moran a major referral center for complex cases. Services include:

- Cataracts
- Cornea & External Eye Disease
- Electrophysiology
- Emergency Care
- Glaucoma
- LASIK and Vision Correction
- Surgery
- Neuro-Ophthalmology
- Oculoplastics and Facial Plastic Surgery
- Optometry
- Patient Support Program for Patients with Vision Loss
- Pediatric Ophthalmology
- Pediatric Retina
- Retinal Diseases
- Strabismus
- Ultrasound
- Uveitis

The John A. Moran Eye Center at the University of Utah is the largest ophthalmology clinical care and research facility in the Intermountain West, with more than 60 faculty members, 10 satellite clinics, and 15 research labs.
New Resources for Diagnosing Eye Pain

Complaints of eye pain in ophthalmology and neurology clinics might be an everyday occurrence, but research and publications on the topic are scarce.

A recent study¹ by Moran researchers outlines the most common underlying causes of eye pain, while a book of case studies provides a new tool for clinicians diagnosing eye pain.

The study examined the most common causes of eye pain in ophthalmology and neurology departments at the University of Utah and the University of Zurich among 2,603 adults. Ophthalmologists evaluating eye pain diagnosed over half of their patients with ocular inflammatory conditions as the cause of eye pain. Neurology department physicians diagnosed more than half of their patients with a headache disorder such as migraine.

Although only three percent of patients had migraine diagnosed in an ophthalmology clinic as the cause of eye pain, migraine proved to be the predominant cause of eye pain in the neurology clinics at 51 percent.

The study concluded ophthalmologists should consider migraine, trigeminal neuralgia, other headache syndromes, and cervicogenic headache in patients with a normal eye and physical exam. These patients may benefit from a neurology referral.

A Case-Based Guide to Eye Pain, newly published by Moran’s Kathleen B. Digre, MD, and University of Minnesota Professor of Ophthalmology, Neurology, and Neurosurgery Michael S. Lee, MD, provides detailed discussions of 43 cases and includes both neurology and ophthalmology perspectives on each.

The first section contains 18 cases demonstrating ocular causes of pain divided into groups of normal and abnormal exams. The book also presents 25 cases demonstrating neurologic causes of pain.

An appendix discusses how to obtain a history and how to examine a patient with eye pain, in addition to the pathophysiology of eye pain. Finally, a table in the front of the book gives the key features of each diagnosis.