Uveitis 2014
Extinguishing the Great Fire

Program Directors
C Stephen Foster MD and Russell W Read MD PhD

In conjunction with the American Uveitis Society

McCormick Place
Chicago, Illinois
Saturday, Oct. 18, 2014

Presented by:
The American Academy of Ophthalmology

Uveitis 2014 Planning Group:
C Stephen Foster MD
Program Director
Russell W Read MD PhD
Program Director
Henry J Kaplan MD
Robert B Nussenblatt MD
Albert T Vitale MD

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2014 Uveitis Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Uveitis Society, it is our pleasure to welcome you to Chicago and Uveitis 2014: Extinguishing the Great Fire.

C Stephen Foster MD
Program Director
Abbott Medical Optics: C,S
Alcon Laboratories, Inc.: C,S
Allergan, Inc.: C,S
Eyegate Pharmaceuticals, Inc.: O,S
Lux Biosciences, Inc.: C,S
Novartis Pharmaceuticals Corp.: C,S

Russell W Read MD PhD
Program Director
EyeSight Foundation of Alabama: S
International Retinal Research Foundation: S
Research to Prevent Blindness: S

Henry J Kaplan MD
Advanced Ocular Technology: O,P
Caremark: C
RegenaSight: O,P
Santen, Inc.: C

Robert B Nussenblatt MD
None

Albert T Vitale MD
None
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CME Credit

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

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for AMA PRA Category 1 Credits™.

Attendees registered as exhibitors, spouses or guests are not eligible to receive CME credit.

2014 Uveitis Subspecialty Day Meeting Learning Objectives
Upon completion of this activity, participants should be able to:
- Identify the challenges in recognizing the various forms of ocular inflammatory diseases, including cicatricial pemphigoid, retinal vasculitis, and anterior, intermediate and posterior uveitis
- Construct a differential diagnosis for various forms of uveitis
- Classify the principles of diagnosis of ocular inflammatory disorders in order to initiate appropriate, disease-directed evaluations
- Identify the important and appropriate role of immunomodulatory therapy for patients with selected, specific ocular inflammatory diseases, and also for patients with steroid-dependent inflammation
- Describe the various gaps that currently exist in the management of uveitis and ocular inflammatory diseases, such as failure to recognize the sight-saving benefits of pursuing durable remission, failure to understand the paradigm shift away from corticosteroid monotherapy to a stepladder algorithm and failure to recognize the elements essential to successful control of uveitic glaucoma, among others
- Describe the potential new treatments for uveitis and ocular inflammatory diseases, including selected therapeutic agents in development, based on recent and current work and studies

2014 Uveitis Subspecialty Day Meeting Target Audience
The intended audience for this program includes general ophthalmologists, comprehensive ophthalmologists, uveitis specialists, and other ophthalmologic subspecialists (cornea, retina, etc.) and allied health personnel who are involved in the management of patients with uveitis and ocular inflammatory diseases.

2014 Uveitis Subspecialty Day CME Credit
The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians.

The American Academy of Ophthalmology designates this live activity for a maximum of 7 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Self-Assessment Credit
This activity meets the Self-Assessment CME requirements defined by the American Board of Ophthalmology (ABO). Please be advised that the ABO is not an accrediting body for purposes of any CME program. The ABO does not sponsor this or any outside activity, and the ABO does not endorse any particular CME activity. Complete information regarding the ABO Self-Assessment CME Maintenance of Certification requirements is available at http://abop.org/maintain-certification/part-2-lifelong-learning-self-assessment/cme/.

NOTE: Credit designated as “self-assessment” is AMA PRA Category 1 Credit™ and is also preapproved by the ABO for the Maintenance of Certification (MOC) Part II CME requirements.

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

Scientific Integrity and Disclosure of Financial Interest
The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application of research findings and the implementation of evidence-based medicine. It seeks to promote balance, objectivity and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.
Attendance Verification for CME Reporting

Before processing your requests for CME credit, the Academy must verify your attendance at Subspecialty Day and/or at AAO 2014. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the Final Program and/or Subspecialty Day Syllabus exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting; or
- Register onsite.

CME Credit Reporting

South, Level 2.5; Academy Resource Center, Booth 508

Attendees whose attendance has been verified (see above) at AAO 2014 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2014 at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2014 credits entered onsite will be available to Academy members on the Academy’s website beginning Nov. 13, 2014.

NOTE: CME credits must be reported by Jan. 15, 2015. After AAO 2014, credits can be claimed at www.aao.org.

The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or AAO 2014.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity, but it does not provide CME credit transcripts. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during AAO 2014 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite Registration Form
- Instruction Course Verification Form

Visit the Academy’s website for detailed CME reporting information.
Faculty

Nisha Acharya MD
San Francisco, CA
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F I Proctor Foundation
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DHU ViewMaintain
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Metropolitan Eye Research and Surgery Institute

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Phuc Lehoang MD PhD
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Cleveland Clinic Cole Eye Institute

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Truhlsen Eye Institute
University of Nebraska Medical Center

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The Ohio State University
President, The Retina Group
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Professor of Epidemiology
Johns Hopkins University Bloomberg School of Public Health

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Director, UW Medicine Eye Institute

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University of Utah

Manfred Zierhut MD
Tuebingen, Germany
Professor of Ophthalmology
University of Tuebingen
### Uveitis 2014: Extinguishing the Great Fire
In conjunction with the American Uveitis Society

**SATURDAY, OCT. 18**

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<tr>
<td>7:00 AM</td>
<td>Continental Breakfast</td>
<td>C. Stephen Foster MD* Russell W Read MD PhD*</td>
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<tr>
<td>7:50 AM</td>
<td>Welcome and Opening Remarks</td>
<td>C. Stephen Foster MD* Russell W Read MD PhD*</td>
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<tr>
<td>7:55 AM</td>
<td>Introduction and Self-assessment</td>
<td>Russell W Read MD PhD*</td>
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<td>8:00 AM</td>
<td>Epidemiology of Uveitis</td>
<td>John H Kempen MD*</td>
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<tr>
<td>8:10 AM</td>
<td>Blindness and Disability Secondary to Uveitis</td>
<td>Eric Suhler MD*</td>
</tr>
<tr>
<td>8:20 AM</td>
<td>Assessment</td>
<td>Stephen D Anesi MD</td>
</tr>
<tr>
<td>8:30 AM</td>
<td>When to Refer</td>
<td>Russell W Read MD PhD*</td>
</tr>
<tr>
<td>8:40 AM</td>
<td>Coordination of Care With Others</td>
<td>Erik Letko MD*</td>
</tr>
<tr>
<td>8:50 AM</td>
<td>Conclusion and Self-assessment</td>
<td>Russell W Read MD PhD*</td>
</tr>
<tr>
<td></td>
<td><strong>Section I:</strong> Kicking the Lantern—Background on Uveitis</td>
<td>Moderator: Russell W Read MD PhD*</td>
</tr>
<tr>
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<td><strong>Section II:</strong> Five-Alarm Call—Assessing the Situation and Fighting the Fire</td>
<td>Moderator: Wendy M Smith MD</td>
</tr>
<tr>
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<td><strong>Section III:</strong> Spontaneous Combustion—Endogenous Ocular Inflammation</td>
<td>Moderator: Thomas A Albini MD*</td>
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<tr>
<td>9:26 AM</td>
<td>Introduction and Self-assessment</td>
<td>Thomas A Albini MD*</td>
</tr>
<tr>
<td>9:28 AM</td>
<td>Episcleritis or Scleritis</td>
<td>Nisha Acharya MD*</td>
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<tr>
<td>9:38 AM</td>
<td>Acute Anterior Uveitis</td>
<td>Howard H Tessler MD*</td>
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<td>9:48 AM</td>
<td>Chronic or Recurrent Anterior Uveitis</td>
<td>Justine R Smith MD*</td>
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<tr>
<td>10:30 AM</td>
<td>REFRESHMENT BREAK and AAO 2014 EXHIBITS</td>
<td>Jose S Pulido MD MS</td>
</tr>
<tr>
<td>10:40 AM</td>
<td>Introduction and Pre-vote</td>
<td>Thomas A Albini MD*</td>
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<tr>
<td>10:42 AM</td>
<td>Pro</td>
<td>Janet Louise Davis MD*</td>
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<td>10:50 AM</td>
<td>Con</td>
<td>Emil Mitchel Opremcak MD*</td>
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<tr>
<td>10:58 AM</td>
<td>Pro Rebuttal and Closing</td>
<td>Janet Louise Davis MD*</td>
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<tr>
<td>11:01 AM</td>
<td>Con Rebuttal</td>
<td>Emil Mitchel Opremcak MD*</td>
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<tr>
<td>11:04 AM</td>
<td>Summary and Post-vote</td>
<td>Thomas A Albini MD*</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
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<td>11:06 AM</td>
<td>Vogt-Koyanagi-Harada and Sympathetic Ophthalmia</td>
<td>Narsing A Rao MD</td>
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<td>11:16 AM</td>
<td>Behçet’s Disease</td>
<td>Sumru Onal MD</td>
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<td>11:26 AM</td>
<td>Retinal Vasculitis</td>
<td>William Ayliffe MBBS*</td>
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<td>11:36 AM</td>
<td>Sarcoidosis</td>
<td>Manfred Zierhut MD</td>
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<tr>
<td>11:46 AM</td>
<td>Puzzling White Dots: What’s a Doctor to Do? Punctate Inner Choroidopathy, Presumed Ocular Histoplasmosis Syndrome, Acute Posterior Multifocal Placoid Pigment Epitheliopathy and “Ampiginous”</td>
<td>Albert T Vitale MD</td>
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<tr>
<td>11:56 AM</td>
<td>Birdshot Retinochoroidopathy</td>
<td>Aniki Rothova MD PhD</td>
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**DEBATE: Birdshot Uveitis: Treatment Is Mandatory in Every Patient**

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<tr>
<td>12:06 PM</td>
<td>Introduction and Pre-vote</td>
<td>Thomas A Albini MD*</td>
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<tr>
<td>12:08 PM</td>
<td>Pro</td>
<td>Douglas A Jabs MD MBA*</td>
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<td>12:16 PM</td>
<td>Con</td>
<td>Ralph D Levinson MD</td>
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<tr>
<td>12:24 PM</td>
<td>Pro Rebuttal and Closing</td>
<td>Douglas A Jabs MD MBA*</td>
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<td>Con Rebuttal</td>
<td>Ralph D Levinson MD</td>
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<tr>
<td>12:30 PM</td>
<td>Summary and Post-vote</td>
<td>Thomas A Albini MD*</td>
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<tr>
<td>12:32 PM</td>
<td>Conclusion and Self-Assessment</td>
<td>Thomas A Albini MD*</td>
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<tr>
<td>12:34 PM</td>
<td>Advocating for Patients</td>
<td>Russell W Read MD PhD*</td>
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<tr>
<td>12:39 PM</td>
<td>LUNCH and AAO 2014 EXHIBITS</td>
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**Section IV: Aftermath—Rebuilding After the Fire**

Moderator: Grace A Levy-Clarke MD

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<td>1:58 PM</td>
<td>Introduction and Self-assessment</td>
<td>Grace A Levy-Clarke MD</td>
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<tr>
<td>2:00 PM</td>
<td>Uveitic Glaucoma</td>
<td>Jennifer E Thorne MD PhD*</td>
<td>57</td>
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<tr>
<td>2:10 PM</td>
<td>Uveitic Cataract</td>
<td>David S Chu MD*</td>
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</table>

**DEBATE: Pediatric Uveitic Cataract: IOLs Should NOT Be Implanted**

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<tr>
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<td>Introduction and Pre-vote</td>
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<td>2:22 PM</td>
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<td>Sofia N Androudi MD PhD*</td>
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<td>2:30 PM</td>
<td>Con</td>
<td>Careen Yen Lowder MD PhD</td>
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<tr>
<td>2:38 PM</td>
<td>Pro Rebuttal and Closing</td>
<td>Sofia N Androudi MD PhD*</td>
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<td>Careen Yen Lowder MD PhD</td>
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<tr>
<td>2:46 PM</td>
<td>Uveitic Vitreoretinal Pathology</td>
<td>Marc Dominique De Smet MD PhD FRSCS FRCOphth*</td>
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<tr>
<td>2:56 PM</td>
<td>Uveitic Macular Edema</td>
<td>Phuc Lehoang MD PhD*</td>
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<tr>
<td>3:06 PM</td>
<td>Conclusion and Self-assessment</td>
<td>Grace A Levy-Clarke MD</td>
<td></td>
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</table>

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
### Section V: Accelerants—Infectious Uveitis

**Moderator:** Daniel V Vasconcelos-Santos MD PhD

<table>
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<tr>
<th>Time</th>
<th>Session Title</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>3:08 PM</td>
<td>Introduction and Self-assessment</td>
<td>Daniel V Vasconcelos-Santos MD PhD</td>
</tr>
<tr>
<td>3:10 PM</td>
<td>Viral Uveitis, Anterior and Posterior</td>
<td>Quan Dong Nguyen MD* 73</td>
</tr>
<tr>
<td>3:20 PM</td>
<td>Toxoplasmosis</td>
<td>Rubens Belfort Jr MD PhD* 74</td>
</tr>
<tr>
<td>3:30 PM</td>
<td>REFRESHMENT BREAK and AAO 2014 EXHIBITS</td>
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<td></td>
<td>DEBATE: Toxoplasmosis Therapy: Triple Therapy Is Superior to Other Options</td>
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<tr>
<td>4:00 PM</td>
<td>Introduction and Pre-vote</td>
<td>Daniel V Vasconcelos-Santos MD PhD</td>
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<tr>
<td>4:02 PM</td>
<td>Pro</td>
<td>Gary N Holland MD* 76</td>
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### Section VI: The Fire That Won’t Die—Treatment-Resistant Disease

**Moderator:** Andrea D Birnbaum MD PhD

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<td>Is It Infectious, Autoimmune, or Malignant? The Importance of Diagnostic Surgery</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
Uveitis: The Extent of the Problem

John H Kempen MD MPH MHS PhD

Estimates of the risk of eye disease typically are based on population-based prevalence/incidence studies. Because such studies are progressively more difficult to execute with increasingly sample sizes, they typically do not address uncommon conditions. Neither do they typically address the <40 year old population because non-refractive eye disease is uncommon in younger people. Therefore, data regarding the risk of uveitis rarely are available from such studies. Two examples, from Southern India, estimated that 730 (all ages)\(^1\) and 270/100,000 (≥40 years)\(^2\) had signs of present or past uveitis on examination, often choriotinal scars (perhaps reflecting past infectious chorioretinitis).

Alternative methods rely on ascertainment of cases based on ICD-9 coding from a defined beneficiary population, such as a health maintenance organization, or the assumption that all cases in a population will be seen by a regional uveitis center. Both approaches may underestimate risk, as some cases may never present for care or may not present to the center in question. These studies typically have focused on the period prevalence of active uveitis. Estimates of the prevalence of uveitis activity during a one year period have ranged 38 to 115/100,000,\(^3\)\(^-\)\(^6\) and the incidence in a one year period to be 17-52 new cases/100,000/ year. Estimates of the ten year prevalence of uveitis activity have ranged from 204-603/100,000.\(^3\)\(^,\)\(^4\) Some reports indicate the risk of (the average case of) uveitis is higher with female sex and increasing age,\(^4\)\(^,\)\(^6\) and some evidence suggests a higher risk in African-derived persons than other races (D. Gritz, past AAO meeting). If higher age and African race truly are risk factors, the global prevalence will increase over the coming years. Data from general ophthalmology practices suggest ~90% of uveitis encountered is anterior uveitis.\(^7\)

If one accepts the conservative assumptions that one-third of scleritis patients have rheumatoid arthritis,\(^8\) and that 0.7% of patients with rheumatoid arthritis have scleritis,\(^8\) an estimate of the prevalence can be calculated from the prevalence of rheumatoid arthritis and the U.S. adult population (it is rare for children to develop scleritis). Based on a prevalence of rheumatoid arthritis in adults of 0.9%,\(^9\) and the Census Bureau’s 2013 estimate result that there are 242,470,820 adults age 18 and higher in the United States (www.census.gov), the prevalence of scleritis is estimated:

\[
(1) \text{Prev(RA)} = (\text{US Adult Popn}*0.009 = (242,470,820)*0.009 = 2,182,237
\]

\[
(2) \text{Prev(Scleritis)} = (\text{Prev(RA)}*0.007)/1/3 = [(2,182,237)*0.007]/1/3 = 45,827 \text{ US cases}
\]

Because the population has grown since 2013 and because this estimate makes conservative assumptions, the true US prevalence may be higher, likely in the range of 55,000 individuals affected.

The population impact of ocular inflammation on visual loss is even harder to estimate. Population-based data are limited to the Andhra Pradesh Eye Study, which found that 0.27% and 0.16% of the entire population had best-corrected visual acuity in the better eye worse than 6/18 and 6/60 respectively as a result of uveitis (mostly chorioretinal scars). Estimates that uveitis may cause 10% of blindness in the US\(^5\)\(^,\)\(^10\) probably have become high now that effective treatment has been available for most of the lifetime of those living. Uveitis has been estimated to be the 4th-7th leading cause of blindness in older studies, with a lower rank with more recent data.\(^6\)\(^,\)\(^11\) Large proportions of patients at tertiary centers have visual loss, but tend to be stable to improved under tertiary management (J. Kempen, unpublished data). With uveitis, visual loss and disease chronicity are associated with reduced quality of life\(^12\)\(^,\)\(^13\) and unemployment.\(^14\) Treatment can be very expensive.\(^15\) Given the average onset decades before AMD, cataract, and glaucoma—on average—the impact per case of uveitis-related visual loss is proportionately much higher,\(^16\) making uveitis a leading cause of visual loss from either a burden of disease or health economic perspective.

References
Blindness and Disability Secondary to Uveitis

*Eric Suhler MD*

Questions to be answered by this talk:

- How important a cause of blindness is uveitis in the general population?
- How often does uveitis cause blindness or visual disability?
- What are the important causes of blindness and visual disability caused by uveitis?
- What modifiable risk factors exist to lessen the likelihood of blindness and disability secondary to uveitis?
Assessment

Stephen D Anesi MD

I. History of Disease: Getting to Know the Patient Better
   A. Chief complaint, associated complaints
      1. Symptoms, duration, severity: Listen to the patient’s words: often hints to nature of disease
      2. History of therapy: Response to therapy, types of therapy employed
      3. History of related surgery
   B. Past medical history
      1. Associated systemic inflammatory / infectious disease?
      2. Always consider trauma, malignancy
   C. Detailed review of systems: questionnaire

II. Examination: Identify and Recognize Disease Process
   A. Standardization of Uveitis Nomenclature (SUN) criteria
      1. Classification by location
      2. Severity
      3. Acute vs. chronic; recurrent
      4. Other involvement . . . retinal vasculitis, neuritis
   B. Secondary complications (ie, synechiae, cataract, glaucoma)

III. Workup/Diagnostics
   A. Office testing
      1. Angiography: fluorescein / indocyanine green
      2. OCT: macula and/or nerve
      3. Perimetry/field testing
      4. Ultrasonography
      5. Electroretinography
   B. Imaging
      1. Radiology: chest film, spinal films, sacroiliac
      2. CT: chest, sinus, orbit, brain
      3. MRI: brain/spinal cord, orbit
      4. Ultrasound: renal, liver
      5. Gallium scan
   C. Laboratories
      1. Basic blood testing
         a. CBC with differential
         b. BUN, creatinine, microscopic urinalysis
         c. ALT, AST

II. Serologies: Tailor to suspected disease process
   a. Infectious
      i. QuantiFERON (TB), herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, RPR/FTA-ABS/VDR/TP-PA (syphilis), Toxoplasma, Toxocara, Bartonella, Lyme ELISA/WB
      ii. IgG vs. IgM studies
   b. Noninfectious
      i. ANA, ESR, CRP
      ii. Angiotensin converting enzyme, lysozyme
      iii. Antineutrophil cytoplasmic antibody, C3, C4, total complement (CH50), immune complexes
      iv. Human leukocyte antigen panel
      v. Rheumatoid factor, anti-citrullinated peptide (anti-CCP) Ab

D. Tissue analysis
   1. Anterior chamber paracentesis: culture / polymerase chain reaction (PCR) for infectious etiologies
   2. Vitreous biopsy / vitreous tap (± injection antibiotics) vs. pars plana vitrectomy
      a. Evaluate for masquerade / lymphoma: cytopathology, IgH rearrangement, IL-6:IL-10 ratio
      b. Culture/PCR for infectious

IV. Referral
   A. Uveitis specialist: Has this process gone beyond?
   B. Other disciplines as needed
      1. Rheumatology: rheumatic disease, inflammatory arthritis, psoriasis, vasculitis
      2. Dermatology: psoriasis, other suspected associated cutaneous findings
      3. Pulmonology: nodules / adenopathy on chest imaging
      4. Neurology: demyelinating or other neurologic disease
      5. Infectious disease: assessment / management of suspected infectious uveitis
      6. Oncologist/ocular oncologist: suspected masquerade / malignancy
Section I: Kicking the Lantern—Background on Uveitis

V. Trial Response to Therapy: Will the Patient Respond?
   A. Antiviral
   B. NSAIDs
   C. Corticosteroid: topical, systemic
      Avoid injectable if unsure of noninfectious vs. infectious etiology.

References

When to Refer

Russell W Read MD PhD

Several studies suggest that outcomes in several forms of uveitis are worse when referral to a uveitis specialist is delayed. While these studies do not inform us when, specifically, referral to a uveitis specialist is indicated, some general guidelines can be proposed:

- If one is unsure what workup needs to be done in the context of the clinical scenario
- When the disease doesn’t respond as expected
- Resistant to treatment expected to be successful
- Initially responsive, then resistant
- Worsens with anti-inflammatory therapy
- When treatment beyond what you are comfortable and capable of supplying is required
- Immunosuppression
- Pediatrics
- Long-term systemic therapy with systemic comorbidities
- Recurrent disease
- Severe disease
- When multiple comorbidities exist (ocular and/or systemic) that would be best handled by a multimember team approach at a referral center
- Glaucoma
- Retinal disease
- Corneal disease
- Neurological disease
- Prior to surgery
  - Ensures an adequate workup has been completed
  - Ensures uveitis has been controlled before surgery
  - Allows planning for perioperative management
  - Allows uveitis specialist to view the eye before surgery, thus establishing a baseline to which to compare, in case a flare-up occurs regardless of above
- Any time the non-uveitis specialist is uncomfortable or unsure

Many referrals may be one-time visits to reassure the patient and primary ophthalmologist that everything is being done correctly.

References

Coordination of Care With Others

*Erik Letko MD*

I. Introduction
   A. Uveitis workup and treatment frequently require multispecialty approach.
   B. All physicians involved in any patient care should be kept updated on a uveitis patient.

II. Factors Influencing the Extent and Frequency of Multispecialty Approach
   A. Geographic area (where patient lives, practice location)
   B. Presence of systemic disease
   C. Need for systemic therapy
   D. Need for surgery
   E. Physician’s training and background

III. Tips
   A. All communications cc-ed to all MDs involved in patient’s care
   B. Keep timely communication
   C. Patients appreciate “one-stop” shopping
   D. Do as much as you feel comfortable, but inform others at all times.
   E. Recognize the need for referral.
   F. EMRs can facilitate efficiency of coordination of care.

IV. Conclusion
   Efficient coordination of care for uveitis patients can optimize diagnosis and treatment, consequently reducing patient exposure to risks.
General Philosophy Overview and Stepladder Paradigm

C Stephen Foster MD

I. Prevalence of Visual Disability and Blindness Despite Corticosteroid Therapy: It’s a Disgrace!
   A. Steroids: A major advance in 1950: Gordon
   B. Steroids: Remain the cornerstone for uveitis
   C. Steroids: Always produce trouble if used chronically or repeatedly

II. Lessons From Rheumatology
   A. Rheumatologists learned the lesson the hard way, too:
      1. Steroids and NSAID therapy first, reserving immunomodulatory therapy for patients with advanced disease, resulted in progressive joint damage and great disability.
      2. Early employment of steroid-sparing immunomodulatory, disease-modifying agents results in vastly superior outcomes.
      3. The toxicity of medication side effects is less with this approach, too.
   B. The battle cry throughout the world of rheumatology has, therefore, become: “The mission is remission!”
   C. We can and should learn from them.
   D. Ophthalmologists should embrace this model of early steroid-sparing, remission-inducing therapy with even more vigor than does rheumatology, since the eye is so much less forgiving of chronic inflammation than is the joint, with profound life-altering consequences.

III. Recommended Model of Care of Patients With Uveitis
   A. Diagnosis
      1. Infectious
      2. Autoimmune
      3. Malignant or other masquerade
      4. Idiopathic
   B. If unsure, refer
   C. If chronic, refer
   D. If appropriate for immunomodulatory therapy, refer or partner with a chemotherapist (hematologist or rheumatologist)

IV. Therapy: General Principles
   A. Antimicrobial therapy for infectious uveitis, ± steroids;
   B. Corticosteroids for idiopathic and autoimmune uveitis
      1. Topical
      2. Regional injection
      3. Intravenous
      4. Intraocular
      5. Put out the fire, and do so quickly.
   B. Nonsteroidal anti-inflammatory agents
      1. Topical
      2. Systemic
      3. Systemic NSAID therapy is especially good and is an underappreciated strategy to prevent recurrences of inflammation in patients with idiopathic and with HLA-B27-associated recurrent nongranulomatous anterior uveitis. Usual caveats vis-à-vis potential side effects.

V. Recommended Model of Care of Patients With Uveitis
   A. Steroid-sparing immunomodulatory therapy (IMT)
      1. Mandatory
      2. Potentially life-threatening disease
         a. Wegener granulomatosis (GPA)
         b. Polyarteritis nodosa
         c. Behçet with retinal vasculitis
         d. Rheumatoid arthritis with necrotizing scleritis or peripheral ulcerative keratitis
         e. Relapsing polychondritis with scleritis or with retinal vasculitis
         f. Systemic lupus erythematosus with retinal vasculitis or choroidopathy
      3. Blinding ocular disease for which evidence in peer-reviewed literature strongly indicates that long-term outcomes with corticosteroid monotherapy are poor
         a. Sympathetic ophthalmia
         b. Vogt-Koyanagi-Harada
         c. Multifocal choroiditis and panuveitis
         d. Birdshot retinochoroidopathy
         e. Serpiginous choroiditis
      4. Recommended strongly if chronic or recurrent
         a. Juvenile idiopathic arthritis sooner rather than later
         b. Sarcoid
c. Tubulointerstitial nephritis
d. Pars planitis
e. HLA-B27-associated
f. Idiopathic

B. Therapeutic principles
1. Preservation of function
2. Risk-benefit ratio
3. Understand the diagnosis
4. Stepladder algorithm
5. Expert chemotherapist
6. Use enough, soon enough
7. Informed consent, document

The Stepladder

VI. Treating Inflammation: Immunomodulatory Agents
A. Methotrexate
B. Azathioprine
C. Mycophenolate
D. Chlorambucil
E. Daclizumab
F. Cyclosporin
G. Cyclophosphamide
H. Interferon
I. Tacrolimus
J. Ara-C
K. IV Ig
L. Leflunomide
M. Rituximab
N. Zenapax
O. Tocilizumab
P. Abatacept

VII. International Uveitis Study Group Guidelines for Use of Immunosuppressive Chemotherapy: Relative Indications
A. Intermediate uveitis
B. Retinal vasculitis
C. Juvenile rheumatoid arthritis (JRA) uveitis
D. Severe chronic uveitis

VIII. American Uveitis Society: Consensus Panel on Immunosuppression for Ocular Inflammatory Disorders
A. Participants: 12 physicians with expertise in the use of immunosuppressive drugs in rheumatology, pediatrics, and ophthalmology

B. Conclusions: Good evidence for the effectiveness and for the need for immunosuppression
1. Ocular cicatricial pemphigoid
2. Necrotizing scleritis
3. Sympathetic
4. Multifocal choroiditis and panuveitis
5. Serpiginous
6. Behçet
7. Birdshot
8. JRA and others

IX. Methotrexate Therapy for Chronic Noninfectious Uveitis: The Massachusetts Eye and Ear Infirmary Experience
A. Samson CM, Waheed N, Foster C Stephen
1. Indications
   a. Uveitis uncontrolled with steroids
   b. Unacceptable steroid side effects
2. Contraindications
   a. Alcoholism or liver abnormality
   b. History of poor compliance

B. Study
1. \( N = 160 \) patients
2. Duration of study: 1985-1999
3. Age: 33 years (3-77)
4. Duration of uveitis: 5 years (1-30)
5. Follow-up: 14 months (4-96)
6. Dose: 5-40 mg

C. Results
1. Control of inflammation: 76%
2. Control by diagnosis
   a. Sarcoid: 100%
   b. Idiopathic: 79%
   c. HLA-B27: 73%
   d. JRA: 59%
   e. Other: 89%
3. Side effects requiring discontinuation of drugs

X. Systemic Immunosuppressive Therapy and the Occurrence of Malignancy in Patients With Ocular Inflammatory Disease
A. Lane L, Tamesis R, Rodriguez A, Christen W, Akova Y, Messmer E, Barney NP, Foster C Stephen
B. Chemotherapy and malignancy
1. \( N = 543 \) patients
2. 1261 person-years of follow-up
3. Five malignancies: 2 in patients with systemic disease risk factors
4. Four patients without risk factors
   a. Prednisone: cervical carcinoma
   b. Cyclosporin: CNS lymphoma

XI. Uveitis Standard of Care
XII. Therapy
A. Acute
   1. Corticosteroids
   2. Topical
   3. Regional/periocular
   4. Systemic
   5. Oral
   6. Intravenous
   7. Cycloplegic
   8. Pressure management
   9. Hypotensives
   10. Laser iridotomy: blue iris
   11. Surgical iridectomy: brown iris
B. Subacute
   1. Steroid taper
   2. Pressure management
   3. Selective laser trabeculoplasty
   4. Valve
   5. Mitomycin C trabeculectomy
C. Chronic
   1. Bone preservation
      a. Baseline DEXA scan
      b. Smoking cessation
      c. Calcium (1500 mg) + vitamin D (800 IU)
      d. Exercise
      e. Bisphosphonates
   2. Steroid-sparing IMT
      a. Methotrexate
      b. Cyclosporin
      c. Azathioprine
      d. Mycophenolate mofetil
      e. Chlorambucil
      f. Cyclophosphamide
      g. Biologic response modifiers
   3. Drug implants
      a. Retisert
      b. Posurdex
      c. Medidur

4. Biologic response modifiers
   a. Remicade
   b. Zenapax
   c. Rituxan
   d. Humira
   e. IV-Ig

E. Surgery
XIII. Recommended Model of Care of Patients With Uveitis
A. The importance of early referral to a fellowship-trained ocular immunology/uveitis specialist cannot be overemphasized.
B. The importance of partnering, with collegial collaboration, with excellent and frequent communication cannot be overemphasized.
C. The preferred model of care strives for steroid-free durable remission, doing whatever it takes to achieve that goal.
XIV. Summary
A. The standard of care of a patient with uveitis requires:
   1. Appropriate evaluation
   2. Extinguish the fire: prevent retinal damage
   3. Beware of masquerade syndrome
   4. Cure infection (HSV, TB, syphilis, etc.)
B. Limit corticosteroid use
   1. Prevent cataract
   2. Prevent glaucoma
C. Limit drug side effects
   1. Corticosteroids: bone and eye
   2. Immunomodulatory agents
D. Therapeutic approach
   1. Elimination of active inflammation
   2. Appropriate antimicrobial medication
   3. Limited tolerance for steroids
   4. Early implementation of steroid-sparing immunomodulatory medication
E. Stepladder algorithm
   1. Aggressive topical steroids, cycloplegia
   2. Periocular steroid; general anesthesia as required
   3. Iontophoresis of corticosteroid
   4. Intravenous corticosteroid (SoluMedrol)
5. NSAIDs (tolmetin, naproxyn)
6. Brief (3 months) systemic corticosteroid therapy
7. Diagnostic and therapeutic pars plana vitrectomy with or without endolaser

F. Immunomodulatory therapy
1. Weekly methotrexate (10-30 mg/m²)
   a. Folic acid, 1 mg daily
   b. Minimum 2 years after inflammatory quiescence
   c. Off all steroids
2. Azathioprine (3 mg/kg/day)
3. Mycophenolate mofetil (2-3 g/day)
4. Cyclosporine (5 mg/kg/day)
5. Chlorambucil (0.1 mg/kg/day)
6. Cyclophosphamide (1-2.5 mg/kg/day)

G. Pulsed intravenous cyclophosphamide: 500 mg-kg/m² once to twice monthly
H. Intravenous immunoglobulin: 2 g/kg/cycle, once monthly
I. TNF-α
   1. Infliximab: Higher dose and more frequent administration required for control of uveitis than for control of arthritis.
   2. Adalimumab: 40 mg weekly to biweekly
Update on Diagnostic Technology

Russell N Van Gelder MD PhD

Diagnostic testing remains a critical component of uveitis practice. Identification of underlying infection or systemic condition is essential to proper management of the patient with ocular inflammation. In this presentation, I will highlight recent advances in laboratory testing for uveitis. I will not be covering ocular imaging technologies, which warrant their own discussion.

I. Systemic Disease Testing

A. Syphilis

1. FTA-Abs and MHA-TP tests are being replaced by syphilis IgG.¹
2. Syphilis IgG should be a first-line screening test.
   a. If positive, follow with rapid plasma reagin (RPR); if RPR is negative, check T. pallidum particle agglutination (TP-PA) or fluorescent treponemal antibody (FTA-Abs).
   b. If syphilis IgG is negative, patient is not exposed to disease.
3. Polymerase chain reaction (PCR) can be used in challenging cases.²

B. Tuberculosis

1. Interferon-gamma release assays (IGRA) = QuantiFERON-TB Gold or TB.Spot are supplanting tuberculin skin testing.³,⁴
   a. Should always be used in patients with history of bacillus Calmette-Guérin vaccination; also should be used in patients where return for reading is questionable.
   b. Centers for Disease Control now recommends QuantiFERON-TB Gold as first-line testing, while the World Health Organization recommends the tuberculin skin test.
   c. Remember that positive test can be consistent with latent TB or active TB.
2. PCR of ocular fluids can be used in challenging cases.⁶,⁷

C. Sarcoidosis

1. Utility of angiotensin converting enzyme and lysozyme remain limited; cannot rule out disease.⁸
2. Recommend chest x-ray for screening; if positive chest CT follow-up.
3. Possible utility for vitreous biopsy and cytology.⁹

D. Testing for granulomatosis with polyangiitis (Wegener)

1. Antineutrophil cytoplasmic antibodies (ANCA) being replaced by specific antigen ELISAs
   a. C-ANCA = myeloperoxidase
   b. P-ANCA = proteinase 3

II. Ocular Fluid Testing

A. Goldmann-Witmer testing

1. Widely used in Europe; limited availability in the United States
2. Newly recognized utility in ocular toxocariasis¹⁰

B. PCR testing

1. Viral PCR
   a. Generally done in multiplex for HSV 1/2, VZV, CMV, (EBV)¹¹
   b. Quantitative PCR¹²
      i. Utilizes SYBR dye or TaqMan probes
      ii. High utility in distinguishing latent virus from active infection
2. Pan-bacterial 16S PCR
   a. Universal ribosomal sequence allows for amplification of most bacteria.
   b. Subsequent sequencing required for identification of genus. Utility in corneal ulceration,¹³ endogenous endophthalmitis¹⁴
3. Pan-fungal 5.8S/ITR/18S PCR: Similar utility to pan-bacterial PCR¹³
4. Comprehensive PCR approaches
   a. Combination of viral, bacterial, fungal
   b. Utility in cases of suspected infection¹⁵,¹⁶

C. Deep DNA sequencing

References


Update on Emerging Therapy

Robert B Nussenblatt MD

An increased understanding of underlying mechanisms of ocular inflammatory disease has opened many new avenues for therapy. In the short term, medications widely used for other indications are being evaluated for the treatment, both locally and systemically, of ocular inflammatory disease. These include medications directed against several mediators of inflammation such as interleukin-1, B cells, interleukin 6, and mTOR inhibitors. The discovery of new signaling pathways such as Janus kinase-signal transducer and STAT signaling pathways provide new targets for therapy. Other therapies include cellular therapy such as dendritic cell and T-regulatory therapy, oral tolerance, and epigenetic therapy. All of these will develop, and with time it will be clear if, how, and when these can be utilized to treat ocular inflammation.
Episcleritis or Scleritis
Nisha Acharya MD

I. Introduction to Episcleritis and Scleritis
A. Inflammatory disorders of the wall of the globe
B. Focus of this talk
1. Clinical features
2. Diagnostic evaluation
3. Treatment

II. Episcleritis
A. Clinical features
1. Inflammation involving the episcleral tissue (superficial episcleral plexus)
2. Blood vessels radiate from the limbus and can be moved over the sclera.
3. Mild pain/irritation or asymptomatic
4. Usually unilateral, can recur
5. Does not cause tissue damage
6. Simple or nodular
7. Lasts weeks to months
B. Evaluation
1. Examine in natural light.
2. Typically blanches with topical phenylephrine
3. Usually idiopathic, but up to one-third of patients may have an associated systemic disease, so consider evaluation for recurrent cases (see evaluation for scleritis).
C. Treatment
1. May not need treatment
2. Topical or oral NSAIDs
3. Topical steroids
D. Prognosis is good.

III. Scleritis
A. Clinical features
1. Deep episcleral plexus inflammation
2. Pain: deep ache, radiating, with eye movement
3. Violaceous hue
4. Cannot move inflamed vessels
5. Scleral edema
6. Unilateral or bilateral
7. Women more affected than men
8. Fourth to sixth decade of life most common
B. Anatomical subtypes
1. Diffuse anterior
2. Nodular
3. Necrotizing
4. Posterior
5. Scleromalacia perforans (necrotizing without inflammation)
6. May be associated with uveitis or peripheral ulcerative keratitis
C. Evaluation
1. Clinical
   a. Natural light to look at coloring
   b. Does not blanche with phenylephrine
   c. Dilate to look for posterior scleritis: retinal/choroidal folds, exudative RD, choroidal detachments, disk edema
   d. Sens scleritis scale: Photographs can be used to grade severity.
2. Diagnostic tools
   a. Ultrasound helpful to look for posterior scleritis (T sign)
   b. Evaluate for associated systemic diseases (50% of the time).
   c. Rheumatoid arthritis most common association
   d. Usually systemic diagnosis is known, but scleritis may be the first presentation, particularly with vasculitides.
   e. Associated diseases: rheumatoid arthritis (RA), inflammatory bowel disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, relapsing polychondritis, systemic lupus erythematosus, Churg-Strauss, Cogan syndrome, tuberculosis, syphilis, herpes zoster, Acanthamoeba, other bacteria
   f. Other associations: ocular surgery, medications (bisphosphonates)
   g. Think about masquerades (lymphoma, foreign body, metastatic cancer).
   h. Labs to check: RF, CCP (for RA), ANCA, ESR, CBC with diff, BUN/Cr, urinalysis, chest radiograph, purified protein derivative or QuantiFERON, rapid plasma reagin, fluorescent treponemal antibody absorption (FTA-
D. Treatment

1. Mild scleritis: topical corticosteroids or oral NSAIDs

2. More severe: systemic corticosteroids, immunomodulatory therapy
   a. Methotrexate commonly used
   b. Mycophenolate mofetil may be effective in cases failing other therapies.
   c. Other agents used: azathioprine, cyclosporine, cyclophosphamide, chlorambucil
   d. TNF-alpha inhibitors in more severe or refractory cases
   e. Rituximab: anti-CD20 monoclonal Ab
   f. Necrotizing scleritis: Must use immunosuppressive therapy
   g. Periocular corticosteroid injections: May be a safe option in non-necrotizing scleritis
   h. Surgery: For scleral perforation (but must control inflammation to prevent progression)

Selected Readings

Acute Anterior Uveitis

Howard H Tessler MD

I. Acute Anterior Uveitis (AAU): Definition
Iritis or iridocyclitis of sudden onset lasting less than 3 months
A. 50%-90% of uveitis cases
B. Patient complaints: usually unilateral pain, redness, photophobia
C. Signs
1. Cornea: keratic precipitates (KP), typically non-granulomatous, and endothelial fibrin
2. Anterior chamber: cells, flare, fibrin, hypopyon
3. Iris: synechiae
4. Lens: fibrin plaques
5. Vitreous: cells
D. Complications beyond cataracts and glaucoma
1. CME
2. Permanent breakdown of blood-aqueous barrier

II. Etiology or Associated Disease
A. Idiopathic
1. 17.1% incidence, 48.5% prevalence
2. 27%-50% of AAU
B. HLA-B27 and AAU
1. 18%-32% of uveitis cases in Western countries
2. HLA-B27 prevalence in anterior uveitis of 50% (19%-88%)
3. Cumulative incidence of AAU in general population: 0.2%
4. Cumulative incidence of AAU in HLA-B27 population: 1%
5. First episode in young adults age 20-40
C. Non-HLA-B27 associations
1. Herpetic herpes simplex virus and herpes zoster virus-elevated IOP, iris atrophy, corneal changes
2. Sarcoidosis: usually granulomatous and becomes chronic, bilateral, panuveitis
3. Behçet’s disease: lack of fibrin, transient hypopyon, retinal vasculitis
4. Metastatic endophthalmitis: never wrong to tap vitreous
5. Lens induced: history of lens trauma or hypermature cataract, granulomatous
6. Kawasaki disease: children, bilateral, palmar desquamation, mild
7. Posner-Schlossman syndrome: unilateral, a few KP, elevated IOP
8. Cytomegalovirus: small KP, unilateral, elevated IOP, pupil abnormalities
9. Drug induced: bilateral, fluoroquinolone, ipilimumab (Yervoy)
D. Bilateral simultaneous nongranulomatous onset:
1% of AAU cases
1. Postinfectious/antibiotic (52%)
2. Postinfectious + B27 (5%)
3. Idiopathic (34%)
4. Tubulointerstitial nephritis and uveitis syndrome (5%)
5. Inflammatory bowel disease (IBD) (2%)
6. Kawasaki (2%)

III. HLA-B27 (see Table 1)
A. Prevalence in United States: 6.1%
1. 7.5%: Non-Hispanic whites
2. 4.6%: Mexican Americans
3. 1.1%: Non-Hispanic Blacks
4. Frequency of HLA-B27 decreases after age 50, raising possibility of early death.
   a. 3.6%: Age 50-69
   b. 7.3%: Age 20-49
B. HLA-B27 diseases and AAU
1. Subclinical gut inflammation in ankylosing spondylitis (AS) patients-transgenic mice raised in germ-free environment need bacteria to develop AS.
2. Toll-like receptors abnormal function found in AAU
C. Homozygosity for HLA-B27 increases risk of uveitis.
D. Theories of how HLA-B27 influences susceptibility to disease
1. Molecular mimicry to microbial peptides
2. Aberrant peptide presentation
3. Misfolding of HLA-B27 in endoplasmic reticulum produces inflammatory response.
4. Affects human gut microbial flora; HLA-B27 regulates selection of T cells in thymus; HLA-B27 defective in killing intracellular microbes (Gram-negative enterobacteria).

D. HLA-B27 subtypes (over 116)
E. HLA-B27 advantages
1. Slows development of AIDS in HIV+; HLA-A29 speeds progression to AIDS in HIV+.
2. Spontaneous clearance of HCV (Hep C)
F. Depression and stress are probable factors in recurrence of uveitis.

IV. Workup of AAU
A. Ask patient about low back pain, stiffness after inactivity, IBD, skin rashes.
B. HLA-B27, FTA-ABS, other tests if not typical unilateral case

V. Treatment of AAU
A. Aggressive early treatment to prevent permanent damage and development of chronicity
B. Topical strong corticosteroid (eg, difluprednate 0.05%, prednisolone acetate 1%, q 1-2 h)
C. Cycloplegia early to break synechiae and for comfort; may stop as disease remits.

D. If hypopyon is present and vitreous is very cloudy, consider vitreous tap and culture.
E. Oral prednisone (1 mg/kg/day) for severe cases when you are sure there is no infection
F. Periocular corticosteroid injection for recalcitrant cases when glaucoma not a risk
G. Explain to patient that attack of uveitis may persist for several months.
H. For frequent recurrent inflammation, consider an oral NSAID, methotrexate, or TNF inhibitor.

Selected Readings

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA-B27 Prevalence</th>
<th>% Developing AAU</th>
<th>% AAU Developing Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>90%</td>
<td>20%-30%</td>
<td>55%-90%</td>
</tr>
<tr>
<td>Reactive Arthritis</td>
<td>40%-80%</td>
<td>12%-37%</td>
<td>2%-25%</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>40%-50%</td>
<td>7%-16%</td>
<td>0%-2%</td>
</tr>
<tr>
<td>IBD &amp; Arthritis</td>
<td>35%-75%</td>
<td>2%-9%</td>
<td>2%-3%</td>
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</table>

Chronic or Recurrent Anterior Uveitis

Justine R Smith MD

I. Definitions

Uveitis is defined by Standardization of Uveitis Nomenclature, 2005:

A. Anterior: “Primary site of inflammation is anterior chamber. Includes iritis, iridocyclitis and anterior cyclitis.”

B. Recurrent: “Repeated episodes separated by periods of inactivity without treatment ≥ 3 months in duration”

C. Chronic: “Persistent uveitis with relapse in < 3 months after discontinuing treatment”

II. Diagnoses

A. Systemic immune-mediated diseases
   1. HLA-B27-associated sero-negative spondyloarthropathies
   2. Inflammatory bowel disease
   3. Juvenile idiopathic arthritis
   4. Sarcoidosis
   5. Tubulointerstitial nephritis and uveitis syndrome
   6. Multiple sclerosis
   7. Behçet disease

B. Ocular syndromes
   1. Fuchs heterochromic iridocyclitis
   2. Glaucomatocyclitic crisis

C. Infectious diseases
   1. Herpes simplex virus infection
   2. Varicella zoster virus infection
   3. Cytomegalovirus infection
   4. Syphilis
   5. Tuberculosis

D. Masquerade syndromes

E. Undifferentiated (also termed “idiopathic”)

III. Management

A. Obtain complete ophthalmic and general medical history, including review of systems.

B. Conduct complete ophthalmic examination, including dilated fundoscopy.

C. Investigations
   1. Directed by history and examination findings
   2. Include syphilis testing and chest x-ray for every case.
   3. ANA is not indicated as a screening test.

D. Treatment
   1. Although eye drops are the primary mode for delivery of drugs to the anterior segment, systemic drugs may be indicated in patients with specific forms of uveitis.
   2. For immune-mediated anterior uveitis, treat with sufficient Pred Forte 1% to control the inflammation before tapering; Fuchs is an exception. If long-term treatment is required, up to 2x daily frequency does not pose a compliance issue and carries low risk of cataract, but IOP should be followed for corticosteroid response.
   3. For immune-mediated anterior uveitis, risk of local complications and presence of systemic disease may indicate systemic immunosuppressive treatment.
   4. For infectious anterior uveitis, antiviral drugs or antibiotics are administered systemically; ganciclovir gel is an exception.
   5. Mydriatic eye drops prevent formation of posterior synechiae.

Selected Readings


Pars Planitis

Jose S Pulido MD MS

Prevalence in Uveitis Clinics
- Variable: More common in higher latitudes?
- Germany: 12.3% of cases of uveitis
- England: 11% idiopathic intermediate uveitis (IIU)
- Northern Italy: 6%
- Singapore: 6%
- Turkey 9%

The number of cases that really are pars planitis/IIU are decreasing as we find other causes.

Monozygotic Diseases
- ADNIV: Associated with mutations in calpain causes an autoinflammatory disease. Stage 1; rare cells in the vitreous and Stage 2 moderate cells in the vitreous and decreased b wave; Stage III peripheral fibrosis, neovascularization, and moderate cells.
- Blau’s/Jab’s: NOD/CARD15 same gene noted in about 20% of patients with Crohn disease. Also known as “juvenile sarcoidosis.”
- Sarcoidosis: Noted in older whites. Causes a mild-moderate vitreitis. Inferior punched out lesions and macular edema. The ensuing inflammation can cause cataracts, and some patients have had cataract surgery and then they are noted to have some cells in the vitreous and cystoid macular edema and are thought to have Irvine-Gass. The inferior retinochoroidal lesions may be very subtle but are important clues to this diagnosis. Systemically they have borderline or minimally elevated ACE, Ca levels. They can also have hilar adenopathy. If the diagnosis is confirmed they should have an ECG, and any arrhythmia should be sent for evaluation of possible cardiac sarcoidosis by cardiac MRI.
- Tattoo-induced sarcoidosis: The pigments in the tattoo can cause a sarcoid-like reaction in the tattoo and occasionally elsewhere.
- Cancer-associated granulomas: A vitreitis with snowballs in patients with known cancers
- Whipple’s: Also has snowballs. Can have GI symptoms but may not as well. PCR can be used to make the diagnosis.
- TNF alpha inhibitors associated with the development of sarcoidosis and IU

Other Regional Associations
- Lyme and TB in Germany in children with IU
- Actual IU
  - Epidemiology: Second and third decades of life. There are some that occur earlier on, and the earlier cases might be boys and the older cases women but this is still not completely sure.
  - Olmsted: no difference in male to female at age of onset ($P = .6$, Donaldson Pulido et al)
  - Germany: 59% boys in children with IIU vs. 66% of women
  - There is an association with the development of optic neuritis and multiple sclerosis. We showed that, and subsequently this has been confirmed by others. Around 12%-20%. But it appears to be dependent upon country; for instance Singapore only 3% develop MS.
  - The association is in part because of the same HLA risk factor, HLA DR1501.
  - Visual outcome in the long run is good. Initial vision is related to final vision.
  - Smoking: Here is a strong association between smoking and uveitis, refractoriness to therapy and cystoid macular edema.
    - Donaldson, Pulido et al showed that in Olmsted County 52% of IU patients smoked compared to 16% of the county population.
  - TNF alpha inhibitors: Has caused the development of MS in at least 500 cases in the literature. As per Drs Goldstein there is a risk of using this in patients with IU. FDA website: Prescribers should exercise caution in considering the use of . . . in patients with pre-existing or recent-onset central nervous system demyelinating disorders.
  - Treatment is dependent on the initial vision and severity. Because of the age of the patients, length of treatment and the fact that the final vision is dependent upon initial vision, it is best to try local therapy first.
  - Local therapy: Intense peripheral laser photocoagulation is useful especially in the presence of macular edema and peripheral capillary dropout. Periocular corticosteroids are helpful.12
  - Fluocinolone implants: For bilateral disease very expensive for quality-adjusted life years achieved. Also concern of traction on snowbank and causing retinal detachment
  - Ozurdex implants: For long-term disease need to repeat multiple times. Efficacious but expensive and same concern regarding traction on the snowbanks
  - Intravitreal methotrexate: Need to perform paracentesis before giving it to avoid extravasation. Works slowly (results seen after 1 month and lasts about 2 months), and need to use it in conjunction with periocular corticosteroids and/or laser photocoagulation.
  - Vitrectomy: Efficacy from the vitrectomy or from the laser photocoagulation?

Systemic Therapy
- Methotrexate helps in about 40% of cases. Pregnancy risk X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
- Cellcept helpful in about 65% of cases. Pregnancy Risk D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits
Figure 1. Kaplan-Meier estimation of the incidence of resolution of inflammation (improvement in inflammation to no activity) by uveitis site.

Figure 2. Kaplan-Meier estimation of the incidence of resolution of macular edema causing vision loss to <20/40 by uveitis site.

Figure 3. Kaplan-Meier estimation of the incident IOP elevation to ≥ 24 mmHg by uveitis site.
may warrant use of the drug in pregnant women despite potential risks.

- FDA site: Confirm that the woman is not pregnant. Before initiating therapy, women of childbearing potential should have a negative serum or urine pregnancy test (sensitivity at least 25 mIU/mL) within 1 week prior to starting treatment with MMF or MPA. Do not initiate treatment before obtaining the results of the pregnancy test.

- Immunosuppressants: Immunosuppressants may warrant use of the drug in pregnant women despite potential risks. Since patients in their 20s with IIU are at least as likely to be women as men (may be more common in women), be careful with systemic therapy in this population. All 3 agents are teratogenic.

- Cyclosporine: Cyclosporine has been assigned to pregnancy category C by the FDA. Human data have revealed evidence of premature birth and low birth weight for gestational age.

- TNF antibodies: Category B; Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Conclusion

As Dr. Foster would say: Treat to target. For me in IIU this means:

Goal 1. Keep the eye without macular edema and good vision.
Goal 2: Decrease the floaters as much as possible, but do not use systemic therapy only for this last goal.

Methods: The poorer the initial vision the more agents needed initially. But start with local therapy and add systemic therapy if the goals are not met expeditiously.

Reference and Selected Readings


Pro—Pars Planitis Therapy: Immunosuppression Is Preferable to Vitrectomy and Peripheral Retinal Ablation

Janet Louise Davis MD

Pretest Question

What is the best reason that “pars planitis” is inappropriate in the nomenclature of uveitis?

A. The name is ungrammatical.
B. The pars plana rarely shows signs of inflammation.
C. The uvea rarely shows signs of inflammation.
D. The term is excluded under the Standardization of Uveitis Nomenclature (SUN) classification for uveitis.

I. Evidence From Clinical Practice of the Primacy of Medical Treatment

A. Publications: Medline search “pars planitis treatment” 1974 to 2014
   1. 54 articles retrieved
   2. Divided into articles that report medical vs. surgical vs. review articles (see Figure 1)

II. Evidence That Pars Planitis Is a Systemic Disease Requiring Systemic Treatment

A. Cases of pars planitis are related to other systemic disease.15-21
   1. Multiple sclerosis
   2. Sarcoidosis
B. Undifferentiated pars planitis has biomarkers that indicate a systemic autoimmune response.22-25
   1. HLA type is HLA DR2(15) in most North American studies.
   2. Circulating blood factors

III. Potential Complications From Medical Therapy vs. Surgical Therapy

<table>
<thead>
<tr>
<th></th>
<th>Favors Medical</th>
<th>Favors Surgical</th>
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<tbody>
<tr>
<td>Persistent floaters</td>
<td>✗</td>
<td></td>
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<tr>
<td>Retinal detachment</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Cataract</td>
<td>✗</td>
<td></td>
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<tr>
<td>Persistent CME</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Duration of treatment</td>
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Selected Readings

Medical Therapy and General Review Articles


Con—Pars Planitis Therapy: Immunosuppression Is Preferable to Vitrectomy and Peripheral Retinal Ablation

Emit Mitchell Opremcak MD

I. Vitrectomy for Repair of Structural Complications of Uveitis
   A. Vitreous opacification, debris, and hemorrhage
   B. Lens-induced uveitis
   C. Epiretinal membranes, macular holes, and cystoid macular edema (CME)
   D. Traction or rhegmatogenous retinal detachment
   E. Hyptony and cyclitic membranes
   F. Uveitic glaucoma and posterior tube placement
   G. Choroidal neovascular membranes and submacular surgery

II. Vitrectomy for the Control of Uveitis Activity
   A. Theoretic mechanism of action
      1. Removal of ocular autoantigens: Type II collagen and lens antigens
      2. Removal of autoreactive immune cells and cytokines (IL-1, IL-2, TNF-α, etc.)
      3. Alter the immunologic milieu with aqueous humor – ACAID
         a. Anti-inflammatory cytokines: TGF-β and VIP
         b. Inhibition of complement fixation
         c. Apoptosis
   B. Clinical evidence for vitrectomy with or without peripheral retinal ablation, selected reports
         a. Pars plana vitrectomy (PPV) and lensectomy (PPL) in 15 uveitis patients
         b. Increased vision, decreased CME and reduced uveitis activity
         a. PPV alone in 14 patients with chronic uveitis
         b. Improved vision in 10 and “cells disappeared from the aqueous”
         a. Literature review of PPV in 1575 uveitis patients and 1762 eyes from 44 articles
         b. Intermediate uveitis in 841 eyes (48%)
         c. Biased, noncontrolled, heterogeneous diagnoses and nonstandard visual acuities (VA)
         d. Improved vision in 68%, reduced systemic medications in 57%, and CME reduced from 36% to 18%
         e. PPV for uveitis was recommended in 41 of 44 papers (93%).
         f. Complications included retinal detachment (4%), cataract (6%), and vitreous hemorrhage (1%).
         g. “Based on the evidence in the literature, PPV is possibly relevant to the outcomes of improving vision and reducing inflammation and CME.”
         h. Randomized and controlled trials are needed for PPV as an adjunct to the medical treatment of uveitis.
         a. Retrospective review of PPV in 41 eyes in 38 patients with endogenous posterior uveitis
         b. Intermediate uveitis (46%), panuveitis (32%), and posterior uveitis (22%)
         c. VA improved by 2 Snellen lines in 61% ($P < .05$) and CME was reduced from 44% to 20% ($P < .05$).
         d. Significant increase in the percentage of eyes per month that did not suffer any episodes of uveitis from 70% to 84% ($P < .0012$)
         e. Complications included retinal detachment ($n = 1$) and cataract ($n = 1$).
      5. Tranos, Scott, Zambardaki, Ayliffe, Pavesio, and Charteris; randomized and controlled (2006)
         a. Prospective, randomized, and controlled pilot study of PPV in 23 medically unresponsive patients with intermediate or posterior uveitis
         b. Randomized into PPV ($n = 12$) and corticosteroid / immunomodulatory therapy (IMT) ($n = 11$) arms
         c. PPV group had statistically significantly improved VA from logMAR 1.0 to 0.55 ($P < .01$) and 42% at 20/40 or better, while the medical arm had no significant improvement in VA.
d. CME improved in 4 eyes (33%) following PPV and 1 eye (14%) with medical therapy.
e. No significant intraoperative or postoperative complications
a. Retrospective review of 29 eyes in 23 pediatric patients with chronic uveitis following therapeutic PPV
b. Intermediate uveitis \( (n = 22) \) and retinal vasculitis \( (n = 7) \)
c. Statistically significant, with improved logMAR VA \( P < .001 \) from 0.91 to 0.33, CME resolution in 8 of 10 eyes \( P < .021 \), and active disease from 15 eyes (62%) to 7 eyes (30%) \( P < .042 \)
d. Three eyes developed cataract and 1 eye developed hypotony.
a. Retrospective review of 28 eyes following vitrectomy for pediatric uveitis \( (N = 20 \) patients)
b. Pars planitis \( (n = 15) \), idiopathic panuveitis \( (n = 8) \), and JIA-associated iridocyclitis \( (n = 5) \)
c. All 28 eyes had active uveitis on medications at PPV.
d. 27 eyes (96%) were controlled at last follow-up \( (13.5 \) months average) with reduced systemic medications following PPV.
e. Five of 6 eyes with associated retinal vasculitis were now controlled.
f. Two eyes had intraoperative retinal tear, and 4 developed a cataract.
a. Prospective, randomized pilot study on 18 eyes \( (N = 16 \) patients) with recalcitrant intermediate uveitis
b. The PPV group: 9 of 11 eyes (82%) had disease resolution off systemic medications at 5.93 years with better VA, IOP, and vitreous cell reduction.
c. The IMT group: 4 of 7 eyes (57%) failed and required PPV.
d. CME resolved in 3 of 3 eyes with PPV and in 2 of 3 with IMT.
e. There were no surgical complications with PPV, and 2 patients on IMT had a reversible anemia and leukopenia.
a. Retrospective review of 31 eyes \( (N = 25 \) patients) with uveitic glaucoma (33% pars planitis) treated with PPV, gas tamponade, and posterior glaucoma tube placement between 1994 and 2011 with average follow-up of 33 months \( (1-204 \) months).
b. Preoperative IOP on maximal medical therapy \( (average: 2.5 \) meds) was 32 mmHg, and postoperative IOP was 13 mmHg \( (average: 0.69 \) meds).
c. VA was unchanged or improved in 29/31 eyes (94%).
d. Twenty of 31 eyes (65%) had no recurrence of uveitis following PPV.
e. Complications included choroidals \( (n = 1) \), tube occlusion by vitreous resolved with YAG laser \( (n = 2) \), and elevated IOP requiring cyclophotocoagulation \( (n = 1) \).
f. PPV, gas tamponade, and posterior tube placement controlled both IOP and uveitis complications.
C. Cost / Risk / Benefit Ratio and Quality of Life
1. Pars planitis is a noninfectious, local, ocular inflammatory disease. It occurs in healthy children and young adults. Patients have no systemic manifestations.
2. What are the costs, risks (systemic and ocular), and benefits of doing nothing for pars planitis?
3. What are the costs, risks (systemic and ocular), and benefits of oral corticosteroids with corticosteroid-sparing IMT (methotrexate to biological agents) with the obligatory office visits to monitor for systemic side effects, disease activity, and laboratory testing every 6 weeks over an 18-24 month period of time?
4. What are the costs, risks (systemic and ocular), and benefits of a single, therapeutic, small-gauge vitrectomy?
D. Conclusions
1. PPV appears to be safe and helpful in controlling inflammation, reducing CME, improving VA, and reducing the number of medications required to control uveitis in patients with pars planitis and other selected patients.
2. A multicentered, well-designed, randomized, and controlled clinical trial is needed to confirm these observations and conclusions.
3. Variables and impediments to uveitis clinical trials
   a. Many forms of noninfectious uveitis
   b. Systemic disease vs. local ocular forms
   c. Anterior, posterior, intermediate, and panuveitis forms
   d. Stages, severity, and duration of the disease
   e. The presence of CME, cataract, epiretinal membrane, and glaucoma
f. Timing of surgery and surgical expertise

 g. Adjunctive use of steroids and IMT

 h. End points: VA vs. OCT vs. fluorescein angiogram vs. biomicroscopy for cells

References and Selected Readings


Vogt-Koyanagi-Harada and Sympathetic Ophthalmia

Narsing A Rao MD

I. Introduction

Vogt-Koyanagi-Harada disease (VKH) and sympathetic ophthalmia (SO) are virtually identical granulomatous intraocular inflammations of T cell-mediated autoimmune processes primarily directed at tyrosinase peptide of uveal melanocytes. However, there are few a differences between VKH and SO.

A. Presence of penetrating injury in SO and absence of such trauma in VKH

B. VKH develops predominantly in pigmented individuals of various ethnic and racial groups: Asians, Latinos, Middle-Eastern and South Europeans. There is no such proclivity in the development of SO.

C. VKH is relatively more common in women, and SO is more common in men.

D. In patients with VKH, average age at presentation varies from 32 to 35 years, and in contrast in SO the average age is 46 years.

E. Extraocular changes (vitiligo, poliosis, and tinnitus) are reported frequently in patients with VKH, and such changes including depigmented ocular fundus (sunset glow fundus) are rare in SO.

II. Clinical features of VKH depend on phase of the inflammatory process.

A. Prodromal phase: headache, nausea, vertigo, meningismus, fever, and orbital pain

B. Acute phase: bilateral uveitis most evident in the posterior pole and usually associated with swelling and hyperemia of the optic nerve head and serous detachment (s) of the retina

C. Convalescent/chronic phase: Depigmentation of the choroid, resulting in display of bright orange-red appearance of the fundus (sunset glow fundus), nummular chorioretinal scars, and in some patients vitiligo and/or poliosis

D. Chronic recurrent phase: Characterized by acute episodes of granulomatous anterior uveitis or pan-uveitis with exacerbations usually resistant to corticosteroid therapy. This phase is also marked by complications such as subretinal fibrosis, subretinal neovascular membranes, and cataract.

III. Imaging, etc.

Investigations are helpful in supporting the diagnosis, and recent advances in imaging technology have been instrumental in evaluating the progression of disease and efficacy of treatment effectively. Some imaging methods are suitable for supporting the diagnosis in the acute phase, and others are used during the convalescent/chronic phases of the disease. Currently OCT is increasingly used to support the diagnosis, followed by fluorescein angiography. However, in Japan and Europe it appears that the imaging and lumbar puncture/CSF analysis is frequently used to support the diagnosis during acute phase.

A. Acute phase

1. OCT shows increased thickness of the choroid as well as the presence of subretinal fluid and exudative retinal detachments.

2. Fluorescein angiography typically reveals pinpoint areas of hyperfluorescence and subsequent leakage of dye (exudate) into subretinal space and optic disc hyperfluorescence.

3. Indocyanine green angiography shows segmental hyperfluorescence and hypofluorescent areas and hypofluorescent dark dots.

4. Ultrasonography exhibits diffusely thickened choroid, and the thickness is prominent in the posterior pole and juxtapapillary area.

5. Lumbar puncture/CSF analysis reveals pleocytosis and may contain melanophages.

B. Convalescent and chronic phases

1. OCT shows resolved subretinal fluid and thinning of choroid, which is prominent during chronic phase.

2. Fundus autofluorescence has been useful in detecting early retinal pigment epithelium (RPE) changes, which vary from foci of increased autofluorescence to absence of fluorescence. It is believed that enhanced autofluorescence foci reflect presence of active focal inflammatory process of the choroid affecting overlying RPE.

IV. Diagnosis

VKH diagnosis is straightforward in the acute phase in the vast majority of individuals presenting with bilateral posterior or panuveitis with serous multifocal or bullous retinal detachments.

A. The bilateral intraocular inflammation associated with exudative retinal detachments carried a positive predictive value (PPV) of 100 and a negative predictive value of 88.4.

B. In patients with chronic intraocular inflammation, a sunset glow fundus carried a positive predictive value of 94.5 and a negative predictive value of 89.2.
VII. Sympathetic ophthalmia is rare bilateral granulomatous intraocular inflammation that develops following penetrating ocular surgical or nonsurgical injuries and cyclodestructive procedures.

A. Diagnosis is clinical, and it is usually made when features of intraocular inflammation develops in the nontraumatized eye (sympathizing eye) following penetrating injury in the opposite eye (exciting eye). The majority of cases are diagnosed within 3 months following the ocular trauma to an eye (exciting eye).

1. The incidence is relatively high following nonsurgical trauma (0.2% to 0.5%), and following surgery the reported incidence is about 0.01%. Among surgical interventions, pars plana vitrectomy accounts for about 50% of SO cases.

2. Bacterial endophthalmitis following penetrating injury or surgery cannot prevent development of SO.

3. Early systemic corticosteroid administration following the trauma cannot prevent development of SO.

B. Prevention and treatment of SO

1. Although in the past enucleation of the unsalvageable traumatized globe was recommended to prevent the development of SO, recent surgical advances and effective immunosuppressive treatment modalities suggest that prophylactic enucleation following open globe injury may not be required, and anatomic reconstruction is recommended.

2. There is no clear evidence for enucleation of the exciting eye to improve visual prognosis in the sympathizing eye once SO develops.

3. Effective anti-inflammatory treatment of SO includes primarily high-dose systemic corticosteroids and usually additional immunomodulatory agent(s). The immunomodulatory agents are required for sparing the corticosteroid or effectively suppressing the ocular inflammation.

4. The immunomodulatory agents include cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and biologicals such as anti-TNF agents.

Selected Readings


Behçet’s Disease

Sumru Onal MD

I. Introduction

A. Behçet’s disease (BD) is a multisystem disorder characterized by relapsing inflammation of unknown etiology.
B. BD is an obliterative and necrotizing systemic vasculitis involving different organ systems and leading to a wide range of clinical manifestations.
C. The course is characterized by recurrent inflammatory episodes.

II. Epidemiology and Demographics

A. Prevalence: Common in Middle/Far East and Mediterranean basin
   1. Turkey: 20-420/100,000
   2. Middle/Far Eastern countries: 2.1-120/100,000
   3. Mediterranean Europe: 2.4-7.5/100,000; Northern Europe: 0.27-0.64/100,000
   4. United States: 0.12-5.2/100,000
B. Onset: 25-35 years of age
C. Genders equally affected in large series
D. Males more frequently develop eye disease and have a more severe disease course.

III. Systemic Manifestations

A. Earliest and universal sign: Recurrent oral ulceration (commonly accompanied by recurrent genital ulcers and skin lesions)
B. Behçet uveitis (BU): Most common manifestation associated with significant morbidity
C. BU occurs within 2-4 years of disease onset.
D. BU is the initial manifestation in up to 20% of the patients.
E. Other systemic manifestations: variable incidence
   1. Arthritis
   2. Superficial thrombophlebitis
   3. Epididymitis
   4. Major vessel disease
   5. Gastrointestinal involvement
   6. Central nervous system involvement

IV. Diagnosis

A. No specific diagnostic test: based on clinical findings
B. The International Study Group (ISG) for BD criteria set (see Table 1) became widely used in the clinical setting.

Table 1. The International Study Group for Behçet’s Disease: Diagnostic Criteria for Behçet’s Disease, Established in 1990

<table>
<thead>
<tr>
<th>Recurrent oral ulcers (at least 3 times per year) plus 2 of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recurrent genital ulcers (aphthous or scarring ulcers)</td>
</tr>
<tr>
<td>2. Ocular inflammation (anterior uveitis / posterior uveitis, cells in the vitreous on slitlamp examination, or retinal vasculitis)</td>
</tr>
<tr>
<td>3. Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules in postadolescent patients not on corticosteroid treatment)</td>
</tr>
<tr>
<td>4. Positive pathergy skin test (read by the physician at 24–48 hours after a prick to the forearm by a sterile needle)</td>
</tr>
</tbody>
</table>

V. Etiology and Pathogenesis

A. Still unknown
B. Represents an enhanced or dysregulated immune response triggered by environmental factors in immunogenetically susceptible individuals
C. HLA-B51 confers predisposition.
D. Genome wide-association study (GWAS) outcomes
   1. Polymorphisms in loci of genes encoding interleukin-10 (IL-10), IL-23R, IL12RB2, STAT4 confer risk in Turkish, Japanese, and Chinese populations.
   3. Other susceptibility genes: endoplasmic reticulum aminopeptidase 1 (ERAP1) and C-C chemokine receptor type 1 (CCR1)-CCR3

E. Immune response

1. Pathogens activate both innate and adaptive immunity.
2. Consequent interaction of T-lymphocytes (Th1 and Th17 phenotype) with activated neutrophils
3. Resultant tissue damage (pathergy skin test, hypopyon, pseudofolliculitis, vascular involvement)

F. Other factors: defect in complement system, upregulation of endothelial cell surface molecules, abnormality in hemodynamics and coagulation factors

G. Environmental factors

1. Infectious agents
2. Reduced risk in emigrants from endemic countries to non-Behçet regions
3. Decreased incidence and severity of BD in Japan, despite genetic stability

VI. Behçet Uveitis
A. Course: relapsing remitting uveitis attacks of explosive nature and spontaneous remissions
B. Incidence: > 50% in hospital cohorts; higher rate in male patients (70%-90%)
C. Involves anterior or posterior segment of the eye
D. Posterior segment lesions are persistent, cause significant vision loss.
E. Both anterior and posterior segment are ultimately involved bilaterally in majority.
F. Characterized by bilateral nongranulomatous panuveitis with retinal vasculitis
G. Spontaneous resolution of acute inflammatory signs differentiates BU from other severe noninfectious and infectious posterior uveitides.

VII. Signs of Anterior Uveitis in BD
A. Nongranulomatous
B. Isolated finding in about 10% of patients (common in females)
C. No fibrinous exudation, inflammatory cells circulate freely.
D. Hypopyon
   1. Smooth-layered, shifts with gravity
   2. Maybe white-eyed despite severe inflammation: so-called “cold hypopyon”
   3. Transient
   4. Implies severe posterior segment involvement
   5. Incidence: 5%-30% of eyes (True incidence may be higher as it is transient.)
   6. Five times increased risk of hypopyon in BD in a nonendemic population
E. Subclinical elevated flare levels in the anterior chamber by laser flare meter implicate higher risk of recurrent attacks.

VIII. Signs of Posterior Uveitis in BD
A. Diffuse vitritis
   1. Diffuse cellular infiltration
   2. Vitreous haze: Most severe at the onset of the uveitis attack, indicates activity
   3. During resolution, cellular vitreous infiltration precipitates and aligns in a string-like configuration in inferior peripheral retina-pathognomonic sign.
B. Retinal vasculitis
   1. Incidence: 80%-100% of patients
   2. Segmental or diffuse perivenous fluffy white haziness
   3. Retinal veins are more commonly affected.
   4. Retinal arteriitis may accompany
   5. Retinal capillaritis: Evident on fluorescein angiography (FA) as diffuse capillary leakage in a fern-like pattern
   6. Diffuse gliotic sheathing: following resolution of perivascular inflammation
   7. Very severe breakdown of blood-retina barrier may lead to a fundus appearance similar to frosted-branch angiitis.
   8. Retinal vein occlusion: From central retinal vein to small branches
   9. Retinal hemorrhages: Frequent along affected vein distribution
10. Occlusive periphlebitis: FA shows extensive retinal capillary nonperfusion, may lead to neovascularization of the disc (NVD) or elsewhere (NVE).
11. Thrombotic retinal vascular occlusion in absence of significant ocular inflammation
C. Superficial and/or deep retinal infiltrates
D. Optic disc inflammation and/or cystoid macular edema (CME)
E. FA signs suggesting persistent inflammation during apparently quiescent periods between attacks (subclinical inflammation)
   1. Staining of the optic disc
   2. Retinal capillary leakage
   3. NVD in the absence of retinal ischemia

IX. Complications
A. Caused by recurrent uveitis attacks
B. Common: cataract, posterior synechiae, CME, optic atrophy, epiretinal membrane, glaucoma
C. Rare: NVD, NVE, macular hole, retinal detachment, phthisis bulbi
D. CME and optic atrophy cause irreversible and severe vision loss.
E. OCT is useful in diagnosing and assessing the response to treatment of CME and diagnosing foveal atrophy.
F. End-stage fundus: optic atrophy, ghost retinal vessels, diffuse retinal atrophy and gliosis with pigment deposits, macular scarring, clear vitreous

X. Treatment
A. Rapid control of acute posterior uveitis attack(s)
   1. Intravenous pulse methylprednisolone (1 g/day, single or 3 consecutive doses)
2. Oral prednisone (1 mg/kg/day or equivalent) tapered to a maintenance dose of ≤ 7.5 mg/day
3. Adjunct periocular / intravitreal corticosteroids for unilateral severe panuveitis and/or CME when high-dose systemic corticosteroid is ineffective or contraindicated
4. A single infusion (5 mg/kg) or intravitreal injection of infliximab

B. Prevention of recurrences of uveitis attacks
1. Posterior segment intraocular inflammation in BD is an absolute indication for immunomodulatory therapy (IMT)
2. Conventional IMT
   a. Azathioprine and/or cyclosporine A: Efficacy proven in randomized controlled trials (RCTs)
   b. Mycophenolate mofetil: Effective in uncontrolled studies including BU patients
   c. Tacrolimus: Limited data
   d. Cyclophosphamide: Intravenous monthly pulses inferior to cyclosporine A
   e. Chlorambucil: Efficacious in open-label trials, used as last resort until biologic era
3. Colchicine: Efficacious for mucocutaneous signs, efficacy not shown for BU
4. Biologic agents
   a. Antitumor necrosis factor alpha (Anti-TNFα) agents
      i. Infliximab: Suggested as first-line IMT for BU based on systematic review of published data
      ii. Adalimumab: Suggested as first-line IMT for BU based on systematic review of published data
      iii. Etanercept: Associated with development of uveitis in other diseases
   b. Interferon-alpha (IFN-α)
      i. Efficacy shown in open-label trials
      ii. Response rate: 85%-98%
      iii. A low-dose regimen is better tolerated.
   c. Others
      i. Gevokizumab (IL-1β regulating monoclonal antibody), rituximab (B cell antigen CD20 antibody), and tocilizumab (anti-IL6 receptor antibody) were found effective in case reports or small pilot studies.
      ii. Daclizumab (anti-IL2R antibody) and secukinumab (anti-IL17A antibody) were found ineffective in RCTs.

5. The European League Against Rheumatism proposal
   a. BD patients with posterior segment involvement should be started on azathioprine and systemic corticosteroids.
   b. Patients with severe eye disease (more than 2 lines of drop in visual acuity or retinal vasculitis or macular involvement) should have either cyclosporine A or infliximab added to their regimen or should receive IFN-α instead.

C. Ultimate goal: Durable remission after discontinuation of treatment

XI. Prognosis
A. Change in treatment approach and improvement in environmental factors held responsible for a milder disease course and improved visual prognosis over decades
B. VA ≤ 20/200 at 10 years: 25% between 1980 and 1998, 13% between 2000 and 2010
C. Still 1/4 of patients reported to be blind despite IMT.
D. Visual outcome is determined by cumulative damage of recurrent uveitis attacks.

XII. Summary
A. BU is characterized by recurrences of nongranulomatous panuveitis and occlusive retinal vasculitis.
B. BU occurs most frequently in the third to fourth decade of life.
C. BU is more common and severe in male patients.
D. Uncontrolled intraocular inflammation leads to vision-threatening complications.
E. Both the frequency and severity of uveitis attacks determine the magnitude of irreversible damage to intraocular structures and the long-term visual prognosis.
F. BU is still a severe form of uveitis and is a potentially blinding disease.
G. Early-aggressive IMT and use of biologics resulted in improved visual prognosis.

References and Selected Readings


Retinal Vasculitis

William Ayliffe MBBS

Retinal vasculitis is an uncommon inflammatory disease of the retinal blood vessels. It is estimated that the incidence is 2/100,000/year, with about 10% of uveitis cases having retinal vasculitis.

The condition is diagnosed by the ophthalmoscopic observation of focal perivascular cream-colored cuffs surrounding the vessels. These changes usually occur around veins, and the term “retinal periphlebitis” is sometimes used.

Much less commonly, inflammation affects the retinal arterioles. There may also be hemorrhage, retinal edema, cotton-wool spots, areas of nonperfusion, and ischemia or even large vessel occlusions. Neovascularization and vitreous hemorrhage occur as a consequence and may be the presenting feature, typically in eyes with idiopathic occlusive retinal vasculitis, formerly called Eales disease.

After the inflammation has subsided, the vessels can develop a well-defined greyish fibrous sheath. This tends to affect long stretches of the vessel wall, unlike the focal cuffing seen in the active phase. These inactive sclerotic changes may also be the end result of noninflammatory vascular diseases.

To distinguish noninflammatory changes from active focal inflammation, the term “cuffing” refers to the characteristic changes of active retinal periphlebitis, and “sheathing” describes the noninflammatory fibrosis of vessel walls.

The clinical diagnosis of retinal vasculitis is supported by evidence of inflammation in the anterior chamber or vitreous and leakage or staining of the vessel wall seen by fluorescein angiography.
Retinal vasculitis may occur as a primary syndrome called idiopathic retinal vasculitis, which affects the eye vasculature without any evidence of any systemic or other eye disease. However, the eye may be the herald organ, and a tiny minority of these patients will go on to develop a systemic disease over the next decade, usually multiple sclerosis or sarcoidosis.

Retinal vasculitis may be a manifestation of established systemic diseases, including sarcoidosis, Amantiades-Behçet disease, collagen-vascular autoimmune disorders, malignancy, neurologic conditions, and systemic infections.

It also occurs in ocular inflammatory conditions such as pars planitis or birdshot retinochoroidopathy, as well as in infections of the eye.

Surprisingly, systemic vasculitis rarely causes retinal vasculitis, although microscopic ischemic retinopathies occur in many of these conditions, particularly systemic lupus erythematosus.1

Figure 4. Retinopathy in systemic lupus.

Symptoms
Inflammation of the vessels of the peripheral retina may be asymptomatic. This is why it is important to dilate the pupils and examine the fundus of patients who appear to have isolated anterior uveitis.

Some patients may complain of painless blurring of central vision because of macular edema and scotomata caused by retinal bleeds or ischemia. Rarely, the first symptom is sudden extensive loss of vision from vitreous hemorrhage.

The history and examination should also try to elicit clues as to any underlying systemic disease, and a variety of questionnaires have been designed for patients to fill out. Answers to these questions help the clinician to target investigations more effectively.

Some of the More Common Causes of Retinal Vasculitis

Retinal Vasculitis in Ocular Disease
- Idiopathic retinal vasculitis
- Eales disease
- Idiopathic retinal vasculitis, aneurysms, and neuroretinitis
- Bilateral iridocyclitis with retinal capillaritis
- Acute multifocal hemorrhagic retinal vasculitis
- Frosted branch angiitis
- Idiopathic recurrent branch retinal arteriolar occlusion
- Idiopathic recurrent branch retinal arteriolar occlusion

Retinal Vasculitis as a Manifestation of Neurologic Disease
- Multiple sclerosis
- Microangiopathic syndrome of encephalopathy, hearing loss, and retinal arteriolar occlusions
- Isolated central nervous system angiitis

Retinal Vasculitis in Systemic Autoimmune Disease
- Sarcoidosis
- Adamantiades-Behçet disease
- Buerger disease
- Inflammatory bowel disease
- Rheumatoid disease
- HLA-B27-associated uveitis
- Sjögren syndrome

Retinal Vasculopathy in Systemic Vasculitis
- Systemic lupus erythematosus
- Wegener granulomatosis
- Polyarteritis nodosa
- Relapsing polychondritis

Infections Associated with Retinal Vasculitis
- Tuberculosis
- Syphilis
- Borrelia (Lyme disease)
- Whipple disease
- Brucellosis
- Bartonella (Catscratch)
- Rickettsiosis
- Toxoplasmosis
- Cytomegalovirus
- Herpes
- Human immunodeficiency
- Human T-cell lymphoma virus
- Rift Valley fever
- Viral-like upper respiratory disease

Drug-induced
Secondary to malignancy

Investigations
Because it is not practical to biopsy the retina, the diagnosis is based on ophthalmoscopic findings supported by history, imaging, and occasionally systemic investigation.

Most underlying causes can be deduced from a careful history, an eye examination, and a limited examination of the patient’s face, mouth, hands, joints, or skin, determined by whether the history suggests involvement of these organs. Cough, loss of weight, or other more serious symptoms require specialist referral to a physician with expertise in inflammatory disease.

Fluorescein angiography is helpful in delineating the extent of the disease and picks up areas not recognized by ophthalmoscopy. In addition, ischemic areas and patches of diffuse retinal edema are identified. (See Figures 5 and 6.)
Section III: Spontaneous Combustion—Endogenous Ocular Inflammation

Treatment

The management of retinal vasculitis is to reduce inflammation, thereby reducing the risk of permanent harm to the retina or irreversible damage to the macula.

Systemic prednisone, 1 mg/kg/day, is the first-line drug for those patients in whom infection is not suspected. It is tapered in 5-mg steps each week to 5 mg a day maintenance. If the disease is not controlled on 5 mg a day, a second-line immunomodulatory agent is preferable to long-term steroid treatment. This requires prompt referral to a specialist, skilled in the use of these drugs and their complications.

Patients with infection require the appropriate antimicrobial therapy for their condition. In India, cases of Eales disease (a subset of patients with idiopathic ischemic retinal vasculitis) routinely receive antituberculous chemotherapy along with steroid and retinal laser. Intraocular injections of steroids, antiviral, and anti-VEGF drugs have increasing roles in managing aspects of retinal vasculitis.

Retinal photocoagulation is used in ischemic cases to control neovascularization and has a limited role in persistent neovascular snowbanks in eyes with pars planitis. Vitrectomy is required for cases of prolonged or recurrent vitreous hemorrhage and for secondary complications such as epiretinal membranes.

References and Selected Readings


Sarcoidosis

Manfred Zierhut MD

Introduction
Sarcoidosis is a granulomatous multisystem disorder. About 30%-60% of patients with sarcoidosis develop ophthalmic manifestations. The prevalence is the highest in Scandinavia and in African Americans.

Clinical Findings and Diagnosis
The history should rule out dyspnoea, fever attacks and night sweat, but may be without any of these typical signs. Often patients with sarcoidosis uveitis have no extensive lung or other organ involvement.

The most important suspicion of ocular sarcoidosis comes from the clinical findings. Bilateral granulomatous uveitis is the most frequent presentation.\textsuperscript{1,3} Table 1 summarizes the findings most often seen in ocular sarcoidosis.

Table 1. Clinical Signs Suggestive of Ocular Sarcoidosis\textsuperscript{4}

| 1. Mutton-fat keratic precipitates and/or iris nodules at pupillary margin or on stroma |
| 2. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae |
| 3. Snowballs/strings of pearls vitreous opacities |
| 4. Multifocal peripheral chorioretinal lesions (active and atrophic) |
| 5. Nodular and/or segmental periphlebitis (with or without candle-wax exudate) and/or macroaneurysm |
| 6. Optic disc nodules/granuloma and/or solitary choroidal nodule |
| 7. Bilateral inflammation |

Various laboratory tests have been shown to be helpful in the disclosure of sarcoidosis, summarized in Table 2. Especially tuberculosis has to be excluded. The combination of clinical and laboratory findings then allows one to name the diagnosis adequately.

Table 2. Laboratory Investigations in Suspected Ocular Sarcoidosis\textsuperscript{4}

| Criteria |
| 1. Negative tuberculin test |
| 2. Elevated serum angiotensin converting enzyme and/or elevated serum lysozyme |
| 3. Chest x-ray: bilateral hilar lymphadenopathy |
| 4. Abnormal liver enzyme tests (any of: alkaline phosphatase, aspartate transaminases, alanine transaminases) |
| 5. Chest CT scan in patients with normal chest x-ray |

Nowadays the determination of soluble IL-2 receptor seems to play an increasing role in the diagnosis of sarcoidosis, being more specific than angiotensin converting enzyme (ACE). In a revised version of the above-mentioned criteria, this parameter may replace ACE in the future.

If sarcoidosis is suspected as the cause of uveitis, only a biopsy will confirm the diagnosis of “Definite Sarcoidosis with Ocular Involvement.” The biopsy will disclose noncaseating granulomatous inflammation. But often a biopsy remains impossible to perform because of unclear location. Therefore various degrees of certainty have led to the formulation of “International Criteria for the Diagnosis of Ocular Sarcoidosis.”\textsuperscript{4}

Table 3. Diagnostic Criteria for Ocular Sarcoidosis\textsuperscript{4}

| Criteria |
| 1. Biopsy-supported diagnosis with compatible uveitis |
| 2. Biopsy n.d., bilateral hilar lymphadenopathy with compatible uveitis |
| 3. Biopsy n.d., chest x-ray normal; 3 suggestive ocular signs and 2 positive investigational tests |
| 4. Biopsy negative; 4 suggestive ocular findings and 2 positive investigations |

Unclear at this moment is what type of tuberculosis (TB) test has to be done to exclude TB. We suggest using the QuantiFERON test, which would be negative in case of bacillus Calmette-Guérin vaccination. In case we have a high suspicion for sarcoid because of clinical findings, we go on directly to the more sensitive CT scan, without x-ray. Bronchoalveolar lavage or transbronchial lung biopsy may then allow harvesting a biopsy. Gallium scan seems to be less often used nowadays, as a panel of experts recently communicated.\textsuperscript{5} It has been replaced by PET/CT scan, at least in some countries. We suggest imaging methods only without or with very low corticosteroid dosages because granulomas of a low-grade sarcoidosis would quickly disappear in chest x-ray and even CT-scan under corticosteroids.

One should be aware that general sarcoidosis may develop in the years following a uveitis attack. Therefore one has to keep in mind the need to repeat the laboratory findings regularly for chronic recurrent uveitis.

The diagnosis of sarcoidosis in young patients is even more difficult. In this age the presenting sign often is arthritis; only with increasing age does the likelihood of lung involvement increase. ACE also is typically elevated in children, so it is not really helpful as a diagnostic marker. Therefore sarcoid-induced uveitis in childhood may mimic the uveitis of juvenile idiopathic arthritis.
Differential Diagnosis

Typical for sarcoidosis-associated uveitis is bilateral disease, which in the case of anterior uveitis is not very often seen. Here especially the tubulointerstitial nephritis and uveitis (TINU) syndrome and other infectious disorders, like syphilis and tuberculosis, have to be excluded.

Intermediate uveitis is often associated with sarcoidosis in adults, and here especially multiple sclerosis has to be excluded, and in older patients intraocular lymphoma.

In posterior uveitis the list of differential diagnoses is longer, but typically all types not associated with vitreous inflammation can be excluded. Especially the combination of snowballs with multifocal peripheral chorioretinal lesions (most often atrophic) is highly typical for sarcoidosis and hardly found in other uveitic disorders.

Treatment

Typically sarcoidosis uveitis responds well to corticosteroids (CS). While topical CS are mostly sufficient for anterior uveitis, peribulbar or even systemic CS treatment will be needed for intermediate or posterior uveitis (prednisolone 1 mg/kg bw. for 1 week, reduction for 10 mg per week).

The second-line treatment for systemic therapy would be immunosuppressive drugs, like methotrexate, azathioprine, or mycophenolic acid. An impressive effect of anti-TNF-alpha drugs has not been clearly demonstrated in the literature yet, but they may serve as a third-line treatment.

References

Puzzling White Dots: What’s a Doctor to Do?  
Punctate Inner Choroidopathy and Presumed Ocular Histoplasmosis Syndrome, Acute Posterior Multifocal Placoid Pigment Epitheliopathy and “Ampiginous”

Albert T Vitale MD

I. White Dot Syndromes
   Heterogeneous group of chorioretinal inflammatory diseases
   A. Overlapping clinical features
   B. Multiple, well-circumscribed, white-yellow lesions
   C. Outer retina, retinal pigment epithelium (RPE), choriocapillaris / choroid

II. White Dot Syndromes
   A. Birdshot retinochoroidopathy (BSRC)
   B. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
   C. Serpiginous choroidopathy
   D. Multifocal choroiditis and panuveitis (MFC)
   E. Punctate inner choroiditis (PIC)
   F. Subretinal fibrosis and uveitis syndrome (SFU)
   G. Multiple evanescent white dot syndrome (MEWDS)
   H. Acute retinal pigment epitheliitis (ARPE)
   I. Acute zonal occult outer retinopathy (AZOOR)

III. White Dot Differential
   A. Presumed ocular histoplasmosis (POHS)
   B. Syphilis
   C. Tuberculosis
   D. Toxoplasmosis
   E. Pneumocystis choroidopathy
   F. Candidiasis
   G. Necrotizing viral retinopathy
   H. Ophthalmomyiasis
   I. Sarcodeiosis
   J. Diffuse unilateral subacute neuroretinitis (DUSN)
   K. Sympathetic ophthalmia
   L. Vogt-Koyanagi-Harada syndrome (VKH)
   M. Intraocular lymphoma

IV. Shared Features
   A. Demographics
      1. Age: < 50 years, except BSCR, serpiginous
      2. Sex: ♀ predominance BSCR, MEWDS, MCP, PIC
   B. Presentation
      1. Bilateral: except MEWDS
      2. Photopsias, blurred visual acuity (VA), nyctalopia, floaters, visual field loss (blind spot enlargement)
      3. Viral syndrome preceding ocular disease
         a. MFC, PIC, APMPPE, ARPE, MEWDS

V. Pathogenesis
   A. Infectious etiology?
   B. Autoimmune/inflammatory?
      1. Common non-disease specific genetics
      2. Exogenous (environmental, microbial) trigger
   C. Spectrum of single disease vs. distinct entities
      1. APMPPE, “ampiginous,” serpiginous choroiditis
      2. MCP vs. PIC

VI. Autoimmunity and White Dot Syndromes (see Table 1)

Table 1.

<table>
<thead>
<tr>
<th>White Dot Syndrome</th>
<th>WDS No. (%) (N = 114)</th>
<th>Systemic Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFC/PIC</td>
<td>54 (47)</td>
<td>14/54 (26)</td>
</tr>
<tr>
<td>AZOOR</td>
<td>21 (18)</td>
<td>5/21 (24)</td>
</tr>
<tr>
<td>Birdshot choriorinetopathy</td>
<td>16 (14)</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>MEWDS</td>
<td>11 (10)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Serpiginous choroiditis</td>
<td>5 (4)</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>APMPPE</td>
<td>4 (4)</td>
<td>0/4</td>
</tr>
<tr>
<td>AMN</td>
<td>3 (3)</td>
<td>0/3</td>
</tr>
<tr>
<td>RPC</td>
<td>1 (1)</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

VII. Clinical Differentiation
   A. Variable lesion morphology and evolution
   B. Distinct natural histories
   C. Disease-specific treatment indications
   D. Visual prognosis
Section III: Spontaneous Combustion—Endogenous Ocular Inflammation

II. Differentiating PIC From POHS
   A. Epidemiology
   B. Systemic associations
   C. Symptoms
   D. Signs
   E. Multimodal imaging
      1. Delineation of inflammatory component of disease
      2. Identification choroidal neovascular membrane (CMVM)

IX. Epidemiology (see Table 2)

X. Systemic Associations (see Table 3)

XI. Clinical Manifestations: Symptoms (see Table 4)
XII. Clinical Manifestations: Signs (see Table 5)

Table 5.

<table>
<thead>
<tr>
<th></th>
<th>POHS</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior chamber cells</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vitreous cells</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Peripapillary atrophy</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Choroidal lesions</td>
<td>Multiple (5-100)</td>
<td>Multiple (5-20)</td>
</tr>
<tr>
<td></td>
<td>Posterior pole</td>
<td>Posterior pole</td>
</tr>
<tr>
<td></td>
<td>Mid periphery</td>
<td>100-200 µm diameter</td>
</tr>
<tr>
<td></td>
<td>300-1000 µm diameter</td>
<td></td>
</tr>
<tr>
<td>Active choroiditis</td>
<td>Rare (solitary lesion)</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Yellow/grey active lesion (several)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serous retinal detachment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linear pattern (occasional)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence (less often than MCP)</td>
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</tr>
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</table>

XIII. Clinical Manifestations: Complications (see Table 6)

Table 6.

<table>
<thead>
<tr>
<th></th>
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<th>PIC</th>
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<tbody>
<tr>
<td>CNVM</td>
<td>3%-5%</td>
<td>17%-77%</td>
</tr>
<tr>
<td></td>
<td>Subretinal fluid</td>
<td>Incidence new: 0.04/EY</td>
</tr>
<tr>
<td></td>
<td>Subretinal heme</td>
<td>Incidence recurrent: 0.02/EY</td>
</tr>
<tr>
<td></td>
<td>Subretinal exudate</td>
<td>Same as POHS</td>
</tr>
<tr>
<td>Subretinal fibrosis</td>
<td>Involuted CNVM</td>
<td>Same as POHS</td>
</tr>
<tr>
<td>CME</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ERM</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cataract</td>
<td>No</td>
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</tr>
</tbody>
</table>

XIV. Differential Diagnosis, POHS and PIC

A. Clinical diagnosis: Characteristic ocular and fundusscopic findings

B. Active intraocular/chorioretinal inflammation: Directed laboratory evaluation

C. Findings characteristic of POHS from endemic area: No laboratory evaluation

XV. Differential Diagnosis

A. POHS
   1. MCP
   2. PIC
   3. Syphilis/sarcoid/TB
   4. Exudative AMD
   5. Myopic degeneration / CNVM

B. PIC
   1. POHS
   2. MCP
   3. Syphilis/sarcoid/TB
   4. Subretinal fibrosis and uveitis syndrome (SFU)
   5. Serpiginous choroidopathy
   6. Birdshot retinochoroidopathy
   7. Myopic degeneration/ CNVM

XVI. Inflammatory/Neovascular Components of POHS/PIC: Multimodal Imaging

A. Fluorescein angiography (FA), see Table 7.

B. Indocyanine green angiography (ICGA), see Table 8.

C. Ocular coherence tomography (OCT), see Table 9.

D. Fundus autofluorescence (FAF), see Table 10.

Table 7.

<table>
<thead>
<tr>
<th></th>
<th>POHS</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CNVM</td>
<td>Hyperfluorescent staining of chorioretinal, peripapillary scars</td>
<td>Early hyperfluorescence with late staining and variable leakage with active choroiditis</td>
</tr>
<tr>
<td></td>
<td>Hyperfluorescent staining and ill-defined leakage in rare instance of choroiditis</td>
<td>Pooling with neurosensory retinal detachment</td>
</tr>
<tr>
<td></td>
<td>Pooling with neurosensory retinal detachment</td>
<td>Window defects later stages</td>
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<tr>
<td>CNVM</td>
<td>Early, defined, hyperfluorescence and late leakage</td>
<td>Early, defined, hyperfluorescence and late leakage</td>
</tr>
<tr>
<td></td>
<td>Dumbbell-shaped pattern subretinal fibrosis</td>
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Table 8.

<table>
<thead>
<tr>
<th></th>
<th>POHS</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommonly used</td>
<td></td>
<td>Numerous hypofluorescent spots in posterior pole, early, mid, late phase</td>
</tr>
<tr>
<td>Helpul if subretinal hemorrhage obscures underlying CNV</td>
<td></td>
<td>Typically more numerous than those seen clinically or on FA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choroidal vasculitis?</td>
</tr>
</tbody>
</table>
Table 9.

<table>
<thead>
<tr>
<th>POHS</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease, without CNV</td>
<td>• Areas of RPE attenuation corresponding to scars</td>
</tr>
<tr>
<td>• Sub-RPE hyper-reflective material, elevation, compression EZ, may extend to outer retina</td>
<td></td>
</tr>
<tr>
<td>• Disruption ELM, EZ, IZ adjacent to and beyond visible lesions</td>
<td></td>
</tr>
<tr>
<td>CNVM</td>
<td>• Subretinal CNVM</td>
</tr>
<tr>
<td>• Overlying subretinal fluid / edema</td>
<td></td>
</tr>
</tbody>
</table>

Table 10.

<table>
<thead>
<tr>
<th>POHS</th>
<th>PIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoautofluorescent peripapillary, macular, and midperipheral scars</td>
<td>• Hypoautofluorescent spots inactive posterior pole lesions</td>
</tr>
<tr>
<td>• Hypoautofluorescent halo surrounding active lesions and associated CNVM</td>
<td></td>
</tr>
<tr>
<td>– Diminished with inactivity/treatment, IMT</td>
<td></td>
</tr>
<tr>
<td>– Persistence associated recurrence?</td>
<td></td>
</tr>
<tr>
<td>• Hyperautofluorescence adjacent to and beyond hypoautofluorescent lesions</td>
<td></td>
</tr>
<tr>
<td>– Correspond to PR loss and outer retinal disruption seen on OCT</td>
<td></td>
</tr>
</tbody>
</table>

XVII. Inflammatory Component of POHS: Focal choroiditis

A. Rare
B. Symptoms metamorphopsia, enlarging scotoma
C. Absence of CNVM, cells anterior chamber / vitreous
D. New chorioretinal scars (histo spots) in 20% of patients
E. Greater risk of developing CNVM

XVIII. Inflammatory Component of PIC: Angiography

A. FA
1. Early hyperfluorescence late staining, variable leakage with active choroiditis
2. Pooling with neurosensory RD
3. Window defect late stages
4. Early, discrete hyperfluorescence, late leakage with CNVM
B. ICG
1. Hypofluorescence (all phases)
2. More numerous than exam, FA
3. Focal choroidal vasculitis?

XIX. Inflammatory Component of PIC: FAF

A. Hypoautofluorescence with RPE death and PIC lesions
B. Hyperautofluorescent halo surrounding active lesions
C. Diminished intensity with immunomodulatory therapy (IMT)
D. Persistence of pattern associated with a risk of recurrent disease
E. Hyperautofluorescence adjacent to and beyond hypoautofluorescent lesions correspond to PR loss and outer retinal abnormalities (external limiting membrane, ellipsoid zone, interdigitation zone disruption) on spectral domain OCT

XX. Inflammatory Component of PIC: OCT

A. Active
1. Sub-RPE hyper-reflectivity
2. Elevation, distortion EZ
3. Extension to outer retina
4. Neurosensory detachment
B. Inactive
1. Sub-RPE hyper-reflectivity
2. Localized disruption EZ
3. Bruch/choroid uninvolved
C. CNVM
1. Hyper-reflective subretinal
2. Intraretinal fluid, subretinal fluid, retinal edema

XXI. POHS Treatment: Focal Choroiditis

A. Uncommon
B. New chorioretinal scars (histo spots) in 20% of patients
C. Systemic, periocular, intravitreal corticosteroids
D. Antifungal agents of marginal value recurrent disease
E. Greater risk development of CNVM

XXII. POHS Treatment: CNVM

A. Extrafoveal
1. Focal laser
   a. Risk SVL (loss 6 lines) reduced from 44% to 9% at 5 years
   b. 26% recurrence/persistence
B. Juxtafoveal
1. Focal laser
   a. Proportion eyes SVL reduced from 28% to 12% at 5 years
   b. > 33% recurrence/persistence
XXIII. POHS Treatment: CNVM

A. Subfoveal

1. Natural history: 14% ≥ 20/40, 69% ≤ 20/200 at 3 years
2. Photodynamic therapy?: VOH study
   a. 22 patients with lesions < 5400 µ GLD
   b. Mean 2.9 PDT treatments over 24 months
   c. 45% with 7-letter improvement
   d. 18% with 8-letter improvement
   e. 85% angiographic stabilization

XXIV. POHS Treatment: CNVM

A. Subfoveal: Submacular surgery (SST H)

1. No statistically significant benefit surgical arm. Median VA 20/160 (surgical) vs. 20/200 (observation).
2. Potential benefit large peripapillary/subfoveal nets with poor VA (20/100), extrafoveal ingrowth site. Surgical complications may obfuscate potential benefit.

XXV. POHS Treatment: CNVM

Anti-VEGF: intravitreal bevacizumab (IVB)/Ranibizumab (IVR)

   1. 85% of 28 eyes stabilized/improved VA.
   2. Mean 1.8 IVB injections over 22 weeks
   3. Mean ↑ VA 20/88 to 20/54 with 43% ≥ 3 lines at 22 weeks

   1. 24 treatment naive eyes
   2. Mean 6.8 IVB injections/year
   3. Mean ↑ VA 20/114 to 20/55 (3 months) and 20/150-20/45 (year)
   4. 58% final VA ≥ 20/40

XXVI. POHS Treatment: CNVM

Anti-VEGF: Intravitreal bevacizumab (IVB) / ranibizumab (IVR)

   1. 54 eyes IVB or IVR
   2. Mean ↑ VA 20/53 to 20/26 over average 26.8 months
   3. Mean 4.5 injections/year

   81 eyes with inflammatory CNVM treated with IVB.
   1. 13 eyes with POHS

XXVII. POHS Treatment: CNVM

Anti-VEGF and PDT

   1. Three eyes sub/juxtafoveal CNVM IVB/PDT combination therapy
   2. 100% of eyes (3/3) improved ≥ 2 lines at final follow-up.

   1. Five patients with IVB alone vs. 4 PDT monotherapy
   2. Mean ΔVA 19.6 letters IVB vs. 21 PDT. 80% IVB and 50% PDT > 15 letter gain at 1 year.
   3. All PDT patients required IVB rescue therapy.

   1. 117 eyes IVB monotherapy and 34 IVB/PDT combination
   2. Mean follow-up 21 months with 4.24 IVB injections/year
   3. 81% maintained/improved initial VA at 1 year. 38% gained ≥ 3 lines 1 year, 30% maintained at 2 and 3 years.
   4. No significant difference VA outcome IVB alone vs. IVB/PDT combo

XXVIII. POHS Treatment: Peripapillary CNVM

A. Focal laser for small lesions
B. Subfoveal surgery for larger lesions
C. Anti-VEGF therapy

XXIX. POHS Treatment: CNVM

A. Anti-VEGF therapy: intravitreal bevacizumab (IVB)/ranibizumab (IVR)
   1. Six reports, 4 retrospective studies with POHS only
   2. 80% maintain VA after mean of 4 injections IVB.
   3. One-third or more may gain ≥ 3 lines VA
   4. Multiple injections required (up to 6/year)
   5. 20% persistent/recurrent and require ongoing therapy.
   6. No uniformly accepted protocol

B. Combination therapy
   1. Reduce need for ongoing intravitreal anti-VEGF injections?
   2. Provide sustained treatment effect than anti-VEGF injections alone?
3. Allow reduction in spot size for laser?
4. No significant difference in VA outcome IVB vs. IVB/PDT combo
5. RTC to determine role of PDT in POHS CNVM, optimize treatment regimens

XXX. POHS: Prognosis
A. Peripheral scar, no macular involvement: excellent
B. CNVM
1. Extrafoveal: Good. > 70% VA ≥ 20/40
2. Juxtafoveal/subfoveal: Guarded
   a. 77% subfoveal CNVM eventuate VA ≤ 20/100 in 3 years
   b. Positive prognostic factors subfoveal CNVM
      i. age 30 years
      ii. small CNVM
      iii. no VA loss fellow eye due to CNVM
3. Recurrence risk: 26% in 5 years following laser
4. Contralateral risk: 20% in 3 years in eye with macular “hista spots”

XXXI. PIC Treatment: Focal Choroiditis
A. Acute phase: Corticosteroids (systemic, subTenon, intravitreal)
   1. Poor initial VA
   2. Multiple acute lesions proximate for foveal avascular zone, neurosensory detachment
   3. Limit RPE derangement, scar formation, CNVM
   4. Restoration outer retinal architecture
B. Chronic phase: Combination corticosteroids and IMT
   1. Recurrent, new lesions/CNVM especially proximate to FAZ
   2. Fellow eye with poor outcome
   3. Reduce recurrences, new lesions, incidence CNVM

XXXII. PIC Treatment: IMT
   1. 8 eyes with recurrent PIC lesions/CNVM, Tx with mycophenolate mofetil
   2. Reduced attack rate 1.09 to 0.23 (P = .036) over 1 year
   3. Hyperautofluorescent halo active lesions/ CNVM.
   4. Monitor response to therapy, predict recurrence?
   1. 47 eyes with PIC; mean follow-up 3.4 years (2 months to 8.7 years)

XXXIII. PIC Treatment: CNVM
A. Corticosteroids (systemic, subTenon, intravitreal)
B. IMT
C. Laser: Thermal, PDT monotherapy or combined with IVT, prednisone
D. Intravitreal anti-VEFG agents; 7 reports. One-year prospective study; 12 eyes sub/juxtafoveal CNVM
   1. Mean: 1.9 injections bevacizumab / eye
   2. VA improvement 20/62 to 20/34 (P < .001); mean: 2.6 lines
   3. 100% stable/improved VA, 75% ≥ 2 lines
   4. Reduced mean CMT: 333 to 241
   5. All lesions cicatricial, no recurrences
   6. VA improvement similar/better than PDT mono or combination therapy

XXXIV. PIC Prognosis
A. Visual prognosis
   1. Presence inflammatory lesions/CNVM macula
   2. 77% VA ≥ 20/40
      a. Incidence VA ≤ 20/50 0.06/EY; fewer after 2005
      b. Incidence VA ≤ 20/200 0.006/EY; none after 2005
B. CNVM: Incidence new 0.04/EY, recurrent 0.02/EY
   1. Lower than expected
   3. 67% patients on IMT did not have new or recurrent CNVM.

XXXV. POHS vs PIC
A. Distinct entities
   1. Clinical exam
   2. Epidemiology
   3. Systemic associations
B. Multimodal imaging: Delineation inflammatory and neovascular components
C. Treatment
   1. Corticosteroids and IMT
      a. Not relevant to POHS
      b. Possibly important for acute and recurrent choroiditis/CNVM with PIC
2. Intravitreal anti-VGEF therapy for CNVM
   a. Alone or in combination with PDT for POHS
   b. Alone or in combination with anti-inflammatory therapy in PIC

XXXVI. Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

A. Epidemiology
   1. Healthy adults, age 20-50 (mean: 25 years)
   2. Male = female
   3. HLA-B7 (40%) and HLA-DR2 (57%)

B. Systemic disease associations
   1. One-third report viral prodrome
   2. CNS: cerebral vasculitis, stroke, cavernous sinus thrombosis
      a. Headaches, meningismus, neurologic deficit
      b. White matter lesions on MRI (steroid responsive)
      c. CSF pleocytosis
   3. Other reported associations: Polyangiitis with granulomatosis, polyarteritis nodosa (PAN), scleritis, JIA, sarcoidosis, ulcerative colitis, group A strep, TB, Lyme, post vaccination, hepatitis B, mumps

XXXVII. APMPPE: Presentation

A. Symptoms
   1. Rapid onset blurred vision
   2. Associated central, paracentral scotomas
   3. Photopsias (may precede visual loss)

B. Bilateral, asymmetric; fellow eye involved within days-weeks

XXXVIII. APMPPE: Signs

A. Anterior segment: 0 to 2+ cells
B. Posterior pole
   1. Multiple, large, flat, white-yellow, plaques
   2. Level of RPE
   3. Variable size (1-2 DA)
   4. May extend to equator
   5. New peripheral lesions (linear/radial) 3 weeks
   6. CME uncommon
C. Vitritis (mild-moderate) in 50%
D. Atypical findings: Papillitis, vasculitis, central vein occlusion, neovascularization of the disc, exudative RD

XXXIX. APMPPE: FA

A. Acute stage
   1. Early hypofluorescence: More numerous than on fundus exam
   2. Late staining

B. Subacute (2 weeks)
   1. ↑ early central hyperfluorescence of lesion with late stain

C. Resolution
   1. Transmission defect
   2. Choroidal vessels may be visualized.

XL. APMPPE: ICGA

A. Acute stage: Early and late choroidal hypofluorescence
   1. More numerous than on fundus exam
   2. Choroidal vessels visible
   3. Lesions well demarcated late

B. Inactive stage: Early and late choroidal hypofluorescence.
   Less defined and smaller than acute lesions

XL. APMPPE: FAF

A. Acute phase
   1. Early hypofluorescent areas on FA unassociated with RPE abnormality on FAF.
   2. Late staining on FA correspond to size/shape of hypoautofluorescence on FAF.

B. Healing phase
   1. Hyperpigmentation lesion with depigmented halo
   2. Corresponding central hyperautofluorescence with surrounding hypoautofluorescence.
   3. Centripetal contraction placoid lesion

XLII. Pathophysiologic Interpretation: FA and ICG in AMPPPE

A. Primary inflammation of the RPE
B. Choriocapillary/choroidal perfusion defect with secondary involvement RPE, PRs
   1. Early FA/ICG lesions show more choroidal perfusion abnormalities than overlying placoid lesions seen on exam.
   2. FAF abnormalities lag appearance of placoid lesions
      a. Less numerous than those seen on FA, ICG
      b. No changes acute phase
      c. Mirror FA lesions in subacute phase
   3. RPE alterations well after choroid affected
XLIII. APMPPE: OCT

A. Acute
1. Hyper-reflectivity outer retinal layers (PR); inflammatory cells/tissue vs. ischemic edema
2. Subretinal and intraretinal fluid
3. Choroidal thickening reported but atypical.

B. Resolution
1. Decreased outer layer hyper-reflectivity; nodular hyper-reflective lesions plane of RPE
2. PR and RPE disruption

XLIV. APMPPE: Pathogenesis

A. Choriocapillary/choroidal perfusion defect with secondary involvement RPE, photoreceptors
1. FAF lesions lag appearance of placoid lesions
2. Less numerous than those seen on FA, ICG
3. RPE alterations well after choroid affected

B. Degree of choroidal ischemia
1. Variable lesion size
2. Larger, confluent lesions poorer visual prognosis
3. Unusual sequelae (neurosensory detachment)

C. Etiology unknown
1. Postviral syndrome
2. Possible systemic vasculitis

D. Mechanism
1. Molecular mimicry
2. Delayed-type hypersensitivity (DTH)

XLV. APMPPE: Differential Diagnosis

A. Serpiginous chorioidopathy
B. “Ampiginous” aka Relentless Placoid Chorioretinitis
C. Persistent placoid maculopathy
D. Birdshot retinochoroidopathy
E. DUSN
F. MCP, PIC, MEWDS
G. Sarcoidosis
H. VKH
I. Intraocular lymphoma
J. Multifocal choriocapillaris infarcts
1. Hypertension, systemic lupus erythematosus, disseminated intravascular coagulation, pre-eclampsia,

XLVI. APMPPE: Course and Prognosis

A. Spontaneous resolution 3-6 weeks
1. Pigment epithelial mottling, hyperpigmentation
2. Recurrences rare

B. Visual prognosis
1. 80%: VA ≥ 20/40 in 6 months historically
2. 87% (295 eyes): VA ≥ 20/25 no foveal involvement
   a. 60%: residual visual symptoms
   b. 25%: VA ≤ 20/40
   c. 53%: VA ≤ 20/25 with foveal involvement
3. Risks poor prognosis
   a. Foveal involvement at presentation (70%)
   b. Older age (> 60)
   c. Unilateral disease
   d. Longer interval between initial and fellow eye disease
   e. Recurrence

XLVII. APMPPE: Treatment

A. Observation
B. Systemic steroids
1. Associated CNS involvement
2. Poor prognostic features?
   a. Foveal involvement at presentation
   b. Recurrence

XLVIII. “Ampiginous”: Relentless Placoid Chorioretinitis (RPC)

1. Unusual variant of APMPPE, serpiginous?
2. Atypical time course, lesion distribution

B. Epidemiology

C. Systemic associations: Hashimoto thyroiditis, aseptic meningitis, type 1 DM, CNS lesions
D. Symptoms: Sudden painless blurred VA, metamorphopsia, floaters

E. Signs
1. Numerous (> 50) lesions
2. Anterior to the equator; may predate posterior pole lesions
3. Resolve with chorioretinal atrophy
4. Recurrence in months to years

XLIX. “Ampiginous” RPC: Multimodal Imaging

A. FA: Early hypofluorescence with later staining
Table 11.

<table>
<thead>
<tr>
<th></th>
<th>APMPPE</th>
<th>“Ampiginous” (RPC)</th>
<th>Serpiginous</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean: 25 years</td>
<td>Mean: 24 years</td>
<td>Mean: 47.5 years</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Acute, limited</td>
<td>Chronic, progressive</td>
<td>Chronic, progressive</td>
</tr>
<tr>
<td></td>
<td>Lesions heal over weeks</td>
<td>Growth of lesions, new lesions</td>
<td>Lesions heal over weeks to months</td>
</tr>
<tr>
<td><strong>Ocular exam</strong></td>
<td>Posterior pole</td>
<td>Posterior pole</td>
<td>Posterior pole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior to equator</td>
<td>Peripapillary, macular</td>
</tr>
<tr>
<td><strong>Systemic features</strong></td>
<td>HA, CNS signs</td>
<td>Hashimoto, DM, aseptic meningitis</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Many associations</td>
<td></td>
<td></td>
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<tr>
<td><strong>Recurrences</strong></td>
<td>Uniphasic</td>
<td>Recurrences, noncontiguous</td>
<td>Recurrences, contiguous</td>
</tr>
<tr>
<td><strong>Visual prognosis</strong></td>
<td>Favorable</td>
<td>Guarded, poor, with foveal involvement</td>
<td>Guarded, poor, with foveal involvement</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Usually none</td>
<td>IMT</td>
<td>IMT</td>
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<td></td>
<td>Systemic steroids?</td>
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</table>

L. “Ampiginous” RPC: Pathogenesis

Shared pathogenesis with APMPPE/serpiginous choroiditis?

A. Autoinflammatory/immune process: Association with Hashimoto thyroiditis

B. Small vessel vasculitis? Association with a patient with CNS lesions

C. Primary or secondary choroidal ischemia

LI. “Ampiginous” RPC: Treatment and Prognosis

A. Optimal treatment regimen unknown

1. Systemic steroids

2. IMT: Cyclosporine, azathioprine, cyclophosphamide

B. Visual outcome: variable

1. New lesions may appear in spite of therapy.

2. Central VA affected untreated eyes

3. Treated eyes had better VA outcome.


5. 92% 26 eyes favorable VA outcome. Improved (15.4%), stable (76.9%), worse (7.7)

LII. Panretinal Acute Multifocal Placoid Pigment Epitheliopathy (PAMPPP)

Variant of APMPPE and “ampiginous”/RPC.

A. Three white patients (2 male), age 16-27 years

B. All preceding viral prodrome, 1 with IBD

C. Acute VA loss over 4-8 weeks

D. Multifocal, creamy-white lesions, post pole to periphery. FA early blockage, late staining

E. Nonprogressive, nonrecurrent

F. 100% HLA-A3 and HLA-A C7; 66% HLA-A2 and HLA-B7

G. Treatment with prednisone (2), famciclovir (1)

H. VA ≥ 20/40 in 4/5 eyes; 20/20 in 3/5 eyes (Opremcak)

LIII. APMPPE vs. “Ampiginous”/RPC

Distinct entities vs. continuum of same disease

A. Similar

1. Epidemiology

2. Shared features multimodal imaging FA/ICG

3. Similar pathogenesis? Autoimmune / autoinflammatory disease associations

B. Distinct

1. Clinical exam: number, size, location of lesions

2. Time course: uniphasic vs. recurrent

3. Disease specific treatment indications: observation vs. IMT

4. Visual prognosis

LIV. Comparison of Clinical Features

(see Table 11)
References

POHS


PIC


32. Mansour AM, Mackensen F, Mahendradas P, Khairallah M, Lai TY, Bashshur Z. Five-year visual results of intravitreal bevacizumab


APMPPE


Relentless Placoid Chorioretinitis


Birdshot Chorioretinopathy

Aniki Rothova MD PhD

Introduction

Birdshot chorioretinopathy (BSCR) is a well-known form of posterior uveitis, characterized by retinal vasculitis and formation of multiple hypopigmented choroidal lesions. BSCR is responsible for 1%-7% of all uveitis cases and is strongly associated with human leukocyte antigen (HLA)-A29. BSCR is a chronic and progressive inflammatory disease that occurs predominantly in white adult patients and has a profound effect on visual quality of life. BSCR might lead to extensive retinal atrophy resulting in visual field loss and is potentially blinding. It is considered to represent an ocular disorder without any associated systemic manifestations.

Clinical Manifestations

The majority of patients with BSCR are older than 40 years at the time of first presentation; the average age at first presentation is approximately 53 years. The onset is insidious, and patients usually complain of blurred vision, especially in low light conditions, and report floaters and difficulties in distinguishing colors, recognizing faces and reading, while on examination their central visual acuity might be within the normal range. Typically, anterior segment is clear, cells and opacities are located in the vitreous, but the most characteristic disease hallmark consists of the scattered white-yellow choroidal spots. Birdshot lesions are mostly found in the nasal part of the retina along the big vessels, but they may be scattered throughout the fundus. These typical birdshot lesions might be present at the initial examination but may also develop long after the onset of other symptoms. In the active stage, diffuse retinal vasculitis can be seen on fluorescein angiography. The end stage of BSCR might resemble hereditary retinal dystrophy with extensive retinal atrophy, atrophic optic disc, and attenuated retinal vessels. BSCR might be associated with severely disturbed retinal functions, sometimes present even in patients with preserved central visual acuity.

Pathogenesis

The strong association of BSCR and HLA A29 is widely known. HLA-A29 is common in European populations (7%-9%), whereas BSCR is a rare disease, which obviously suggests involvement of other processes, of which one has been recently elucidated by the finding of a strong association between BSCR and endoplasmic reticulum aminopeptidase (ERAP) 2 gene located on chromosome 5. The main function of HLA class I molecules is to present peptides to the immune system. These peptides are produced from the foreign proteins by proteolytic ERAPs in the cytoplasmic reticulum. The small peptides are subsequently transported to the cell surface and presented by HLA class I molecules (including HLA A29) to the immune system. The current hypothesis is that BSCR is an organ-limited autoimmune disorder, possibly induced by peptides that are cleaved from antigenic proteins by aminopeptidase ERAP 2 and presented to the immune system by HLA A29. These peptides are presumably HLA A29-restricted and recognized by the cells of the immune system, which subsequently produce intraocular inflammation (by a hypothetical mimicry of these peptides to intraocular resident antigens).

Diagnostic Investigations

Diagnosis of BSCR is essentially clinical and supported by positive HLA A29. However, HLA A29 is present in a substantial part of the population and therefore not considered as a diagnostic test. BSCR lesions might not be detectable on fluorescein angiography but are clearly noted on indocyanine green images.

To monitor the course of the disease and the efficacy of treatment, it is essential to follow peripheral retinal functions by visual fields and/or ERG and not to rely only on central visual acuity. Fundus autofluorescence might become an additional useful test to evaluate the associated RPE atrophy.

Prognosis and Treatment

The long-term follow-up studies have shown that visual prognosis of BSCR is not satisfactory. Moreover, the patients with BSCR are often being undertreated because their central visual acuity (measured in optimal light circumstances) may remain unaffected for a long time.

Opinions are divided on whether it is advisable to treat all BSCR patients. Though BSCR is a chronic and commonly progressive disease, not all patients show visual deterioration. It is not known whether aggressive treatment in the early stages might prevent the late retinal atrophy.

The cause and pathogenesis of BSCR are not yet elucidated, and so far only general immunosuppressive treatments are used. The efficacy of immunosuppressive treatment is undoubtedly related to the stage of the disease; the anti-inflammatory treatment is effective in the early stage, which is characterized by active inflammation. In the late atrophic stages this type of treatment is less effective, though it might prevent further progression. Several treatment approaches with conventional immunosuppressive drugs were proven to improve and/or maintain visual functions. Long-term monotherapy with systemic corticosteroids was repeatedly reported not be effective. Corticosteroid intraocular devices were effective in reducing inflammation and decreased the need for systemic medications, but their long-term efficacy is not yet known. The benefits should also be weighed against the high rates of cataract and glaucoma in this bilateral ocular disorder. More recently, satisfactory effect was noted with tumor necrosis factor inhibitors such as adalimumab and infliximab. The emerging use of fully humanized monoclonal antibodies directed to involved cytokines will hopefully provide new treatment opportunities for BSCR.

Selected Readings


Pro—Birdshot Uveitis: Treatment Is Mandatory in Every Patient
Debate on Treatment of Birdshot Chorioretinopathy

Douglas A Jabs MD MBA

Selected Readings


Con—Birdshot Uveitis: Treatment Is Mandatory in Every Patient
Not Everybody Needs Treatment for Birdshot Chorioretinopathy

Ralph D Levinson MD

Perhaps everybody with birdshot chorioretinopathy (BCR) deserves at least a trial of therapy, and indeed there is no question: many require long-term therapy. But can we say, “one size fits all” when we are talking about decades of immunosuppression or repeated steroid injections/steroid implants requiring potentially sight-threatening surgeries and with potentially sight-threatening complications (albeit uncommon—though again, we are talking decades) in a disease whose causes and pathophysiology and natural history we don’t understand?

Little or no controversy: macular edema, clearly active vitritis, posterior pole vasculitis by examination, or more often on fluorescein angiography

Some controversy: mild leakage on fluorescein angiography in the peripheral retina; symptoms; mildly abnormal testing (visual field, electrophysiology) without progression in a defined period (How is this period to be defined given the often very slow progression?)

More controversy: few or no abnormalities beyond perhaps a trace of vitreous cells and subretinal lesions that may even disappear (albeit with early treatment); abnormal findings that have resolved with treatment on steroids; very severe findings (atrophic retina, abnormal electrophysiology and visual field) but no active vitritis, no clinical or angiographic evidence of active vasculitis, no macular edema (or even atrophy on coherence tomography)?

Even if one decides that everybody deserves a trial on some therapy, which therapy (are steroids fair?), and does treatment need to be forever are important questions.

Do we really know that long-term treatment prevents what may be “degenerative” or secondary changes (which may be secondary to damage long in the past or even processes like apoptosis or autophagy or problems like antiretinal antibodies, which may not respond well to many agents we use) that may lead to long-term retinal atrophy and dysfunction? Can we predict who will develop such changes? If not, how do we know how many we are subjecting to risk, often systemic, however low, for what may be no good reason other than our ignorance?
2014 Advocating for Patients

Russell W Read MD PhD

Ophthalmology’s goal in protecting quality patient eye care remains a key priority for the American Academy of Ophthalmology (the Academy). All Eye M.D.s should consider their contributions to the following three funds as (a) part of their costs of doing business and (b) their individual responsibility in advocating for patients:

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

Your Eye M.D. colleagues serving on the Academy’s Secretariat for State Affairs commit many hours on your behalf while strategizing and collaborating with state ophthalmology society leaders to ensure the success of Surgery by Surgeons. Their ultimate goal—protecting quality patient eye care in the states—requires a robust Surgical Scope Fund, and we need every single Eye M.D. to step up to the plate and deliver with their checkbooks.

The Academy’s federal advocacy arm works to protect ophthalmology practices from payment cuts, burdensome regulations, and scope of practice threats, as well as to advance the profession by promoting funding for vision research and expanded inclusion of ophthalmology in public and private programs. It is critical for our OPHTHPAC Fund to also be strong.

Surgical Scope Fund

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their legislative, regulatory and public education efforts. Since its inception, the Surgery by Surgeons campaign, in partnership with state ophthalmology societies and with support from the SSF, has helped 31 state/territorial ophthalmology societies reject optometric surgery proposals.

2014 has proved to be a challenging year, with several battleground states facing major optometric surgery initiatives. A number of state ophthalmic societies benefited from SSF disbursements and were able to successfully implement patient safety advocacy campaigns to defeat attempts by optometry to expand its scope of practice to include surgery. The Nebraska Academy of Eye Physicians and Surgeons was successful in its patient advocacy and public education efforts to derail legislation that would have granted optometrists the authority to perform eyelid surgery and injections. Additionally, the Arizona Ophthalmological Society succeeded in protecting patients by stopping legislation that would have allowed optometrists to gain authority to perform injections. The SSF is also at work assisting ophthalmic societies with their efforts to protect patients in California, Delaware and Massachusetts.

Proactively, the Georgia Society of Ophthalmology introduced a bill that would establish a formal definition of “surgery” into state law. While the legislative session expired before the bill could advance, Georgia ophthalmologists will be back in 2015 in an effort to pass this important safeguard for their patients.

2014 was certainly not without its challenges. Despite a vigorous battle for patient safety on the part of the Tennessee Academy of Ophthalmology, the Tennessee Medical Association and the Academy, the legislature passed a bill allowing optometrists to inject anesthesia into the eyelids. Previously, optometrists were authorized to perform only therapeutic injections and any surgical procedure that required no more than a topical anesthetic.

And in Louisiana, the Academy, the Louisiana Ophthalmology Association and the Louisiana State Medical Society vigorously opposed legislation that would authorize optometrists to perform certain scalpel and laser surgeries and injections. On June 1, 2014, Louisiana Governor Bobby Jindal signed into law a laser surgery bill that will allow optometrists to perform scanning laser trabeculoplasty and argon laser trabeculoplasty glaucoma surgery procedures, as well as YAG capsulotomy surgery procedures, with the completion of as little as 32 hours coursework. The Academy’s Secretariat for State Affairs knows from past experience that with this success in Louisiana, organized optometry will push hard in 2015 to see if they can gain additional surgery states. This is why everyone must “advocate for patients,” engage in the state political process, and aggressively support the SSF.

California, Delaware and Massachusetts remain “in play” and are still faced with active O.D. surgery legislation. When it comes to state legislation of any kind, California and Massachusetts are often considered bellwether states for the rest of the nation. Now more than ever, your contribution to the SSF is needed as a critical tool of the Surgery by Surgeons campaign to protect quality surgical care for our patients. The Academy relies not only on the financial contributions to the SSF from individual Eye M.D.s and their business practices, but also on the contributions made by ophthalmic state, subspecialty and specialized interest societies. The American Uveitis Society contributed to the Surgical Scope Fund in 2013, and the Academy counts on its contributions in 2014.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy’s strategy to protect and advance ophthalmology’s interests in key areas, including physician payments from Medicare as well as protecting ophthalmology from federal scope-of-practice threats. Established in 1985, today OPHTHPAC is one of the largest and most successful political action committees in the physician community. In the past, Politico highlighted OPHTHPAC as one of the most successful health PACs in strategic giving. By making strategic election campaign contributions and independent expenditures, OPHTHPAC helps us elect friends of ophthalmology to federal leadership positions, ultimately resulting in beneficial outcomes for all Eye M.D.s. For example, in the 2012 election cycle, OPHTHPAC was able to help retain 20 physicians in Congress.

Among the significant impacts made by OPHTHPAC are the following:

- Prevented onerous national patient prescription requirements for compounded drugs and preserved access to most ophthalmic compounded drugs for office use
- Averted significant cuts to Medicare payments due to the Sustainable Growth Rate (SGR) formula
Advocating for Patients

### Surgical Scope Fund

- To derail optometric surgical scope-of-practice initiatives that threaten patient eye safety and quality of surgical care
- Protected ophthalmologists’ ability to provide in-office diagnostic testing without triggering self-referral violation
- Prompted congressional action that helped reduce ophthalmology’s multiple procedure payment reduction
- Secured appointment of full-time ophthalmology national program director in the U.S. Department of Veterans Affairs
- Provided further exemptions from both the Electronic Preparing and Meaningful Use EHR penalties

Leaders of the AUS are part of the Academy’s Ophthalmic Advocacy Leadership Group (OALG), which has met for the past seven years in January in the Washington, D.C., area to provide critical input and to discuss and collaborate on the Academy’s advocacy agenda. The topics discussed at the 2014 OALG meeting included a focus on the collaboration needed among the Academy and its OALG partners on the issue of compound. As a 2014 Congressional Advocacy Day (CAD) partner, the AUS ensured a strong presence of uveitis specialists to support ophthalmology’s priorities as nearly 400 Eye M.D.s had scheduled CAD visits to members of Congress in conjunction with the Academy’s 2014 Mid-Year Forum in Washington, D.C. The AUS remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

### State Eye PAC

We all must also support our respective State Eye PACs, because state ophthalmology societies cannot count on the Academy’s SSF alone. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is also critical. The Secretariat for State Affairs strategizes with state ophthalmology societies on target goals for state eye PAC levels.

**ACTION REQUESTED: Advocate for your patients!!**

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. PAC contributions are necessary at the state and federal level to help elect officials who will support the interests of our patients. Contributions to each of these three funds are necessary and should be considered the costs of doing business. Surgical Scope Fund contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues who are volunteering their time on your behalf to serve on the OPHTHPAC* and Surgical Scope Fund** Committees, as well as your state ophthalmology society leaders, when they call on you and your subspecialty society to contribute. Advocate for your patients now!

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Uveitic Glaucoma

Jennifer E Thorne MD PhD

I. Uveitic Glaucoma
   A. Epidemiology and impact
   B. Mechanism of IOP elevation / glaucoma in uveitis
      1. Trabeculitis driven
      2. Steroid driven
      3. Peripheral anterior synechiae driven
      4. Mixed mechanism
   C. Risk factors of uveitic ocular hypertension / uveitic glaucoma

II. Approach
   A. Workup
      1. Gonio, gonio, gonio
      2. History
         a. Risk factors for glaucoma
         b. Corticosteroid use
      3. If patient presents with elevated IOP or glaucoma, you may need to modify your differential of the uveitis.
      4. Visual fields and OCT

B. The effect of elevated IOP on your differential diagnosis
   1. Posner-Schlossman syndrome (glaucomatocyclitic crisis)
   2. Fuchs uveitis
   3. Viral (herpes simplex virus, varicella zoster virus, cytomegalovirus)
   4. Sarcoidosis

III. Treatment Considerations
   A. Topical corticosteroids
      Topical corticosteroids to “treat” IOP are a no-no.
   B. IOP-lowering medications
   C. Surgery

IV. Limitations/Caveats
Uveitic Cataract

David S Chu MD

Introduction

Patients with uveitis can develop cataracts from ocular inflammation as well as any form of corticosteroids used to treat the condition; most cases are due to both causes, as steroids remain a mainstay of therapy. Furthermore, many patients with uveitic cataract may have systemic disease that requires systemic or extraocular steroid as chronic therapy.

Epidemiology

Uveitic and steroid-induced cataract are a common occurrence in practice. The exact prevalence and incidence is difficult to determine as uveitis has a heterogeneous etiology and the disease course varies greatly. The literature has wide and varied documentation of incidence and prevalence. In clinical practice, it is a common comorbidity of uveitis.

Clinical Findings

Initially, most uveitic and steroid-induced cataract cases present as posterior subcapsular cataract. Cataract progression rates may vary, depending on the control of disease as well as the route and amount of steroid used for the treatment of uveitis. Symptoms noted by patients include blurred vision and glare.

Management Options

Uveitic and steroid-induced cataract can frequently become visually significant. If possible and appropriate, steroid use should be minimized to reduce the progression of the cataract. Steroid-sparing immunomodulatory therapy (IMT) should be considered in patients with chronic uveitis. When the activities of daily living are affected or if the physician’s view of the posterior segment is sufficiently diminished, then surgical intervention should be considered.

History of Cataract Surgery

Historically, cataract surgery has been well documented; there are references to couching in Hindu texts from 800 BCE and to cataract extraction with metallic instruments in Chinese texts from 200 CE. Uveitis has also been well documented in texts from ancient Egypt. However, very few historical references to uveitic cataract surgery exist prior to 1950.

With use of topical and systemic steroids in uveitis patients in the late 1950s to 1960s, more reports pertaining to management of uveitic cataract became available; however, the results were generally poor compared with today’s standards. Starting in the 1990s when small-incision cataract surgery with foldable IOL became available and ophthalmologists gained more awareness of IMT, better surgical results were observed.

Preoperative Considerations

Studies have shown that when the inflammatory disease is in remission and there is no intraocular inflammation, surgical outcome is generally better and more predictable, at least in the short term. Most uveitis specialists consider the longer the period of inactivity prior to the surgery, the better, with the minimum preferred period of 3 months. Steroid-sparing IMT is an important part of management of uveitic cataract.

Today, IOL placement at the time of cataract surgery is the standard of care in almost all cases of cataract performed. One of the few circumstances where placement of IOL requires consideration is in patients with uveitis. Patients with chronic uveitis, especially those with active disease including low-grade flare in the anterior chamber that is resistant to anti-inflammatory therapies, may be better off without concurrent placement of IOL at the time of cataract extraction.

However, in cases where intraocular inflammation is well controlled, IOL placement at the time of cataract extraction appears to be safe. The outcomes with IOL placement has improved significantly over the past decade, likely because of advancement of surgical techniques, with emphasis on minimally invasive microsurgery, refined surgical instruments and foldable IOLs. Some of the existing studies suggest acrylic and PMMA lenses are better tolerated than silicone lenses in patients with uveitis, while a few showed no difference between them.

Premium IOLs, toric, multifocal, and accommodative, are rapidly becoming routine in cataract surgery; however, special consideration must be given to uveitis patients. Long-term stability of vision and IOL location are essential in successful outcome of premium IOL placement. In patients with uveitis, due to various factors, premium IOLs may be suitable only in very select cases.

Perioperative Considerations

To best control postsurgical inflammation and to prevent flare of uveitis, perioperative steroids should be a part of the surgical plan. Steroids can be given topically, orally, intravenously, periocularly, and intraocularly. Each approach has different risks and benefits, and frequently a combination is employed. There is no consensus as to the best method, as the risk of flare likely depends on several factors, including the degree of control of the disease prior to the surgery, the amount of tissue manipulation required to accomplish the procedure, and so forth.

Cataract surgery itself is frequently complicated by the presence of posterior synechia, fibrotic or abnormal lens capsule, or loss of lens zonules, among other ocular anatomical abnormalities that can be seen in patients with uveitis. Surgeons attempting uveitic cataract extraction must be familiar with the use of iris retractors, dyes for visualization of lens capsule, and capsule stabilization devices.

Femtosecond laser-assisted cataract surgery has been evolving rapidly in recent years; however, its application in uveitic cataract has been limited so far. Generally, patients with posterior synechiae would not sufficiently benefit from this procedure.
Patients with loss of lens zonule loss, however, may possibly benefit by achieving more predictable capsulorrhexis; however, further refinement of this technology is needed for extraction of complicated uveitic cataract.

**Postoperative Considerations**

Flare of uveitis, ocular hypertension, hypotony, cystoid macula edema, capsular opacification, and IOL dislocation are among the long list of potential postoperative complications in these cases. Frequently, these complications are the result of the complexity of the surgery compared to routine cases. When treating these cases, ophthalmologists must react quickly and decisively with anti-inflammatory therapy and possibly additional surgical intervention.

**Summary and Conclusions**

Cataract formation and progression are frequently seen in patients with uveitis as a result of chronic inflammation and chronic steroid use. Although cataract surgery has evolved into one of the safest and most frequently performed procedures, uveitic cataract management remains complex, with many pitfalls. When surgical intervention is required, control of inflammation is one of the most important aspects of management to ensure the best possible visual outcome.
Intraocular inflammation before, during, and after surgery. The frequency. Detachment, and even phthisis bulbi still occur with appreciable incidence. CME, epiretinal membranes, vitreous hemorrhages, retinal detachment, and even phthisis bulbi still occur with appreciable incidence. The mechanism by which steroids produce posterior subcapsular cataract is also unknown, although it has been suggested to be related to abnormal cellular metabolism induced by electrolytic imbalance. Clinical studies have shown that the tendency to develop cataracts increases with the dose and duration of steroid treatment.

Cataract surgery in uveitic eyes remains a challenge to ophthalmologists, with its intraoperative risks and the uncertainty of the postoperative course: presentation in children and young adults, possibly uncontrolled inflammation, presence of anterior synechiae and/or poor mydriasis and associated glaucoma or hypotony often require a different surgical approach than for other types of cataracts.

There are several misconceptions about surgery in uveitic eyes, such as a uniformly poor outcome. This was true in some part until the advent of corticosteroids in the early 1960s, when uveitic inflammation was difficult and often impossible to control, and articles discussing the results of cataract extraction in inflamed eyes reported a high incidence of severe complications: intraocular hemorrhage, choroidal detachment, postsurgical exacerbation of inflammation resulting in papillary membrane formation and glaucoma, or ciliary body detachment and phthisis.

Intracapsular or extracapsular cataract extraction (ECCE) has been the preferred surgical method in the past. The introduction of safer surgical techniques (phacoemulsification) and the development of new technologies (high-quality ophthalmic viscosurgical device [OVD], and foldable IOLs) has resulted in an incidence decrease of intraoperative and postoperative complications. In addition, uveitis is no longer a contraindication for the implantation of IOLs: better lens design, small-incision surgical techniques, and improved lens biocompatibility have resulted in IOLs being used more frequently. Despite an improvement in their overall incidence, complications such as band keratopathy, glaucoma, early capsular opacification, lens deposits, synechiae, iris atrophy or neovascularization, cystoid macular edema (CME), epiretinal membranes, vitreous hemorrhages, retinal detachment, and even phthisis bulbi still occur with appreciable frequency.

It is of the utmost importance to achieve proper control of intraocular inflammation before, during, and after surgery. The definition of optimally controlled inflammation is a patient with no cells and up to 1+ flare in the anterior chamber, no active retinal inflammation, and no CME. The purpose of uveitis therapy is to reduce cellular activity in the anterior chamber to less than 1+, with a minimal vitreous infiltration by the time of surgery; however, in some eyes, it may be impossible to eliminate the inflammation. In cases where this cannot be assessed, a prophylactic therapy should be prescribed for a few days before surgery and the patient managed as if an active inflammation was present. Elective surgery should be performed when inflammation has been controlled as much as possible for at least 3 months prior to surgery.

Making the decision to perform cataract surgery in children with uveitis is challenging. The patient’s age, diagnosis, degree of inflammation, preoperative visual acuities, and current therapy all play important roles in the decision. It has been established that cataract in children with JIA often coexists with problems such as significant postoperative uveitis flare-ups, glaucoma, secondary pupillary membranes, and hypotony.

BenEzra and Cohen emphasized that children with JIA uveitis tend to have a complicated postoperative course secondary to increased disease severity. This statement may sound outdated 10 years later, with the advent of modern phacoemulsification techniques and the use of modern immunomodulatory drugs. Most of the uveitis experts share the view that control of inflammation is the major factor that influences the outcomes.

Several authors describe successful IOL implantation in pediatric patients. Although IOL implantation is an acceptable way of optics management in children older than 2 years having nonuveitic cataract surgery, it is controversial in cases of JIA-associated cataract. The presence of an IOL can stimulate ocular inflammation and serve as a scaffold for the accumulation of inflammatory cells and debris, with the subsequent development of a fibrotic membrane. BenEzra and Cohen evaluated IOL implantation in 5 eyes of children with JIA-associated uveitis, finding visual acuities of 20/200 or worse in 80% of the eyes after 5 years of follow-up. It is important to emphasize that these patients did not receive aggressive therapy to control intraocular inflammation perioperatively. Other studies documenting successful IOL implantation in pediatric uveitic patients report implementing stringent control of ocular inflammation before and after cataract surgery.

Quiones et al reported the outcomes of cataract surgery in children with chronic uveitis. In their cohort of 41 eyes, 27 (67%) were affected by JIA-associated uveitis. Ninety percent of children who had surgery at age 5 years or younger (9/10) had JIA. The mean age at which this group had cataract surgery was 8.8 years. Overall, 25 of 27 eyes of children with JIA maintained or improved visual acuity after surgery.

Adan and colleagues reported 2 cases of JIA-associated uveitis in which the IOLs were removed because of severe damage to the macula secondary to persistent and uncontrolled intraocular inflammation. The preoperative conditions in the 2 patients were similar: lack of control of inflammation before cataract surgery, oligoarticular ANA subgroup of JIA, and younger than 10 years. Patients with JIA-associated uveitis develop inflammatory membranes around the IOL and can develop membranes on the ciliary body, leading to hypotony and severe visual loss. Some surgeons advocate a 3-port pars plana approach for these cases. The pars plana approach is better for proper cleaning of the lens capsules, peripheral retina, and pars plana space. IOL removal can serve an important purpose by eliminating the scaffold on which inflammatory membranes can form, thereby reducing the risk for subsequent hypotony and loss of vision.
References

Con—Pediatric Uveitic Cataract: IOLs Should NOT Be Implanted

Careen Yen Lowder MD PhD and Francesco Pichi MD

Surgical treatment of pediatric uveitic cataract remains controversial, with no currently accepted standard of care. Chronic uveitis in children is complicated by development of cataracts in 20%-70% of cases. Cataract aspiration with primary IOL implantation has been shown to be safe and effective in children older than age 2 without uveitis; however, these results cannot be extrapolated to the management of pediatric uveitic cataracts, which are often associated with other complications, such as posterior synechiae, band keratopathy, glaucoma, and pupillary membranes. In the 1990s, reports of pediatric uveitic cataract surgery without lens implantation revealed a high degree of postoperative complications, such as fibrin formation, posterior synechiae, hypotony, macular edema, and even phthisis. Those reports recommended against IOL implantation in pediatric uveitic cataract surgery and recommended pars plana vitrectomy, lensectomy, and aphakia.

Disadvantages of Aphakia

Although aphakia minimizes the risk of the visual axis being obscured because of secondary capsule opacification, it is also associated with disadvantages. The use of contact lens is necessary in unilateral aphakia, but this option is not always practical as the patient or parents may not have dexterity for contact lens manipulation. Also, in unilateral cataract, the patient faces a high risk for irreversible amblyopia.

Advantages of Pseudophakia

IOL implantation reduces the risk of bacterial keratitis in children who must wear a contact lens and are on chronic steroids or systemic immunosuppressive therapy. Contact lens intolerance has been reported in 17%-38% of children. IOL implantation would eliminate difficult contact lens fitting due to presence of band keratopathy or glaucoma blebs. Therefore, as in otherwise healthy adults with cataract, IOL implantation would be the better option, provided that sufficient perioperative control of inflammation is possible. A major point of controversy in the issue of whether to implant an IOL is the thought that IOLs might aggravate inflammation, mainly in cases of juvenile idiopathic arthritis (JIA)-associated uveitis, where the IOL may act as a scaffold for cyclitic membrane formation, leading to chronic hypotony and phthisis bulbi.

Outcomes of Cataract Surgery With IOL Implants in Children With Chronic Uveitis

In 1996, Probst and Holland were the first to report on IOL implants: on 7 patients (8 eyes); 2 were younger than 10 years at the time of surgery. A final visual acuity of 20/40 or better was achieved in 7 of 8 eyes. Postoperative complications were more common in the 3 youngest patients, suggesting that IOL implants in younger patients may have more complications.

In 2000, BenEzra and Cohen examined the outcomes after cataract surgery with PC-IOL in 5 eyes of 5 children (aged 4-8 years) with JIA uveitis. Three eyes had postoperative visual acuity of 6/240 or less, and complications included posterior synechiae, macular edema, persistent inflammation, and glaucoma. BenEzra and Cohen did not report use of preoperative systemic or topical corticosteroid or immunosuppressive therapy in any of the children.

Lam, Lowder, et al reported in 2003 on 5 children (6 eyes); 4 females, 1 male; age 7-12 with JIA-associated uveitis who underwent surgery with IOL. Median age at surgery was 8.5 years. Three eyes underwent cataract surgery with PC-IOL, and 3 eyes underwent combined cataract surgery with PC-IOL and trabeculectomy. 20/40 or better was achieved in all eyes. Four of 5 patients were on systemic methotrexate for a median of 1.25 years before surgery, and 2 of 5 patients were on additional immunosuppressive treatment. The authors concluded that with long-term preoperative and postoperative control of intraocular inflammation, children with JIA-associated uveitis can have favorable surgical outcome after cataract surgery with PC-IOL.

Nemet et al reported in 2007 on the visual outcome and postoperative complications of 19 eyes of 18 patients (9 girls, 9 boys) who underwent cataract surgery with IOL implant; age at surgery ranged from 4 to 24 years. Ten patients had JIA. Age when first seen was 11 months to 14 years in the JIA group and 4.6 to 17 years in the non-JIA group. Children with JIA were seen and operated on at an earlier age, their vision was worse when first seen, and they had more complications, including glaucoma, band keratopathy, and posterior synechiae. After cataract surgery with IOL implantation, both groups showed marked improvement and there was no difference in postoperative inflammation. The authors concluded that IOL implantation should no longer be considered a contraindication in pediatric uveitis.

Zaborowski et al reviewed the results of cataract surgery with IOL implant in 6 patients (9 eyes) aged 2 to 15 years, 3 with JIA, 3 non JIA; 5 were immunosuppressed with methotrexate pre- and postoperatively, and infliximab and mycophenolate were used selectively postoperatively. All achieved 20/30 or better.

In 2008, Quinones et al reported on the outcomes of cataract surgery in 34 children (41 eyes), age range 4-17. Twenty-one had JIA-associated uveitis, 7 pars planitis, and 6, other conditions. Twenty-five patients (32 eyes) received perioperative immunomodulatory therapy; the other 9 patients were in remission on systemic oral nonsteroidal anti-inflammatory therapy. Thirteen eyes of 13 patients received an IOL. Twelve of 13 had improved visual acuity postoperatively. There was no difference in postoperative inflammation between patients who received an IOL and those who did not. Four patients with JIA received an IOL implant—all 4 were using methotrexate and received intraocular
steroid treatment intraoperatively. The outcomes in children who had IOL were better than in those without IOL. Patients who received perioperative immunomodulatory therapy achieved better visual acuities at the end of follow-up.

In 2012, Grajewski et al reported results of cataract surgery with IOL implantation in 16 patients (17 eyes) with JIA-associated uveitis. Mean age at uveitis onset was 5, and mean age at surgery was 11. Fifteen patients were receiving systemic immunosuppression or biologicals. All patients received an intravitreal triamcinolone injection at the time of surgery. After surgery, there was no significant worsening of inflammation. Visual acuity was improved in all patients.

Conclusions
This change in attitude when approaching uveitis-related pediatric cataract reflects the improvement in the medical control of inflammation (systemic immunosuppressive agents, biologicals, intravitreal steroid injections, intravitreal steroid implants) and surgical techniques. Although children with JIA-associated uveitis tend to develop a greater inflammatory response and have more severe and chronic eye disease, once they are on a good immunomodulatory therapeutic scheme and have achieved a quiescent inflammatory status, primary IOL implantation may be proposed, as intraoperative use of immunomodulatory therapy and intravitreal injections of steroids and implants are now available.

References
Uveitic Vitreoretinal Pathology

Marc D de Smet MD PhD FRCSC FRCOphth

Introduction

Inflammation will lead to changes in the vitreous and its interface with the retina. Age is an important contributor to the type of pathology observed, probably related to the strength of the vitreoretinal adhesion prior to the onset of ocular inflammation. An important distinction should be made between cases with an infectious etiology and those with a noninfectious etiology.

Vitreous involvement with uveitis can be divided among its influence on the optical quality of the vitreous (floaters), the vitreoretinal interface (traction), and fibrosis (epiretinal membrane, ciliary body fibrosis). Certain complications such as rhegmatogenous detachments have a low incidence (less than 2% in purely inflammatory conditions) and 8% in infectious conditions. Management of these complications differ significantly if they occur in the presence of active inflammation or quiescence. When present with active inflammation, a more aggressive approach is required, both in an attempt to control postoperative inflammation as well as because of the risk of intraocular fibrosis. When occurring while inflammation is absent, avoidance of a recurrence usually ensures that the outcome is similar to that of noninflamed patients. The surgical approach in this context is the same.

Vitreous Opacities

Floaters and persistent vitreous debris can be the cause of vision loss. Several series have shown that pars plana vitrectomy during periods of quiescence can lead to improvement in vision as well as reduced asthenopic symptoms. Vision improvement following removal of floaters can be significant. Flare-ups of uveitis are often less frequent or severe after a vitrectomy. There is usually a reduction in the need for immunosuppressive therapy but this effect is not sustained, with recurrences occurring 6 to 12 months after the vitrectomy, indicating the need for continued follow-up. However, the required dosage of immunosuppression is often reduced.1

Vitreomacular Traction

OCT studies in patients with juvenile idiopathic arthritis have revealed a high prevalence of macular edema, much of it associated with vitreomacular traction (VMT).2 Macular edema carries a poor prognosis for vision in children with intermediate uveitis, while the presence of an epiretinal membrane is associated with a poorer visual outcome in young adults.3 With a more adherent vitreoretinal interface, traction is more significant in children. If edema does not resolve by medical means, surgery with internal limiting membrane (ILM) peel can lead to a sustained improvement in vision.4 Peeling of the ILM also avoids secondary epiretinal membrane formation, often seen in (25% of) children with uveitis and the cause of postoperative vision loss.

In addition to macular traction, peripheral vitreous traction is often present in children, implying the need for a complete vitrectomy with dissection of the vitreous base if surgery is required.

Peripheral Vitreous Traction, Serous Detachment, and Hypotony

Peripheral vitreous traction is seen with some frequency in intermediate uveitis and pars planitis that has not been adequately treated at an early stage. Serous detachments do not require surgery and can be followed expectantly, as most do not progress. Inflammation should be treated as needed. When long-standing, these detachments can take on the appearance of a schisis cavity. Surgery will be required if a combined rhegmatogenous/tractional detachment develops. The peripheral vitreous contraction is often extensive, with several layers of membranes present. These may coalesce in a thick fibrous scar. External indentation is preferred over vitrectomy when possible, as the latter often requires a peripheral retinectomy to reattach the retina.

Hypotony can arise as a result of reduced ciliary body secretion from cyclitis or as a result of a detachment of the ciliary body. This can be due to a taut anterior hyaloid, contraction of the capsular bag, or vitreous condensation over the pars plana. Hypotony unresponsive to medical treatment and due to fibrotic scar tissue over the ciliary body responds well to surgical removal, with improvement in both ocular tension and vision.5 Removal of the lens or IOL can resolve traction from a contracted capsular bag. In all instances of cataract surgery, an anterior vitrectomy will reduce significantly the risk of traction due to a taut anterior hyaloid, and should be performed prophylactically in all cases where inflammation of the peripheral retinal structures is a prominent feature.

Retinal Detachments

These are more commonly seen concurrent with or following ocular inflammation of infectious origin. They result from an anomalous vitreous separation in which traction persists at the edge of a zone of retinal necrosis or atrophy (cytomegalovirus, varicella zoster virus, toxoplasmosis). As in all such cases, it is important to remove the causative traction and provide an adequate tamponade following application of laser or cryotherapy to the edge of the remaining healthy retina. In these cases, a vitrectomy is the preferred approach. If the infection is still active or there is a high likelihood of recurrence, silicone oil will be preferred over gas or air.

In noninfectious cases, vitreous traction is usually present and its extent and location needs to be determined preoperatively. If inflammation is still active, silicone oil will be preferred as it may be difficult to control scarring in the postoperative period. In the presence of important anterior vitreous involvement, vitrectomy is best combined with a lentectomy and complete vitreous removal over the pars plana and ciliary body. In such cases, silicone oil will be preferred as a tamponading agent, and laser as a means of establishing retinal adhesion. In the absence of active inflammation, the most appropriate approach deemed reasonable for nonuveitic cases should be selected.
References


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# Uveitic Macular Edema

*Phuc Lehoang MD PhD*

## I. Definition

Macular edema is broadly defined as an abnormal thickening of the macula related to the accumulation of fluid in the extracellular space of the neurosensory retina. The fluid is predominantly located in the outer plexiform layer but can extend into the inner nuclear layer and even into the inner layers of the retina. Several patterns of macular edema may be described according to the amount and location of fluid in the retina.

Swelling and degeneration of the Müller cells are present in early cystoid macular edema, indicating that dysfunction of Müller cells may lead to an accumulation of extracellular fluid in the retina with formation of cystoid spaces. These cystoid spaces may coalesce to form large macular cysts, and full-thickness or lamellar holes may also develop.

The term “cystoid macular edema” (CME) is used when there is evidence by biomicroscopy, fluorescein angiography (FA), and/or OCT of fluid accumulation into multiple cyst-like spaces within the macula. Although the classic pathology of CME consists of large cystoid spaces in the outer plexiform layer, such fluid-filled spaces can be observed in various layers of the retina.

Macular edema in its various forms can be considered the leading cause of central vision loss in the developed world, and it is therefore of enormous medical and socioeconomic importance.

We will deliberately exclude macular retinal edema secondary to direct involvement of the macular retina by retinochoroiditis or necrotizing retinitis.

## II. Incidence

CME is the major and the most common cause of visual loss and of legal blindness in patients with uveitis. It can complicate virtually any type of acute or chronic, anterior or posterior uveitis. Several retrospective, epidemiological studies have clearly identified macular edema, particularly CME, as one of the most severe long-term complications of chronic uveitis.

According to several series, CME is observed in 26%-33% of all uveitis patients and it occurs in 9%-11% of anterior uveitis, 41%-60% of intermediate uveitis, 28%-34% of posterior uveitis, and 53%-66% of panuveitis. CME accounts for 29% of affected blind eyes and for 41% of severely visually impaired eyes in the uveitis population. CME causes severe visual impairment in 59% of patients with panuveitis and in 85% of patients with intermediate uveitis.

## III. Mechanisms

### A. Inflammation

Intraocular inflammation alters (1) the inner (retinal capillary endothelial cell tight junctions), (2) the outer (retinal pigment epithelium [RPE] cell tight junctions) blood-retinal barrier, and (3) the pumping function of RPE cells.

During intraocular inflammation, numerous molecules (prostaglandins, leukotrienes, protein kinase C, nitric oxide, and various cytokines such as vascular endothelial growth factor [VEGF], tumor necrosis factor α, interferon γ and interleukins such as IL2, IL6, and IL12) may induce hyperpermeability of the retinal blood vessels, particularly of the retinal capillaries, leading to extravasation and accumulation of fluid, proteins, and macromolecules into the retinal interstitium. Leukostasis mediated by nitric oxide, adhesion molecules, and other inflammatory mediators can cause endothelial damage, contributing to vascular leakage. Leakage of fluid is exacerbated by factors that increase retinal blood flow, such as vasodilation, increased intraluminal pressure, and increased blood volume.

Disruption of the outer retinal barrier and/or pumping mechanism, caused mainly by choroidal inflammation, can lead to chronic serous macular detachment and secondary CME, such as in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. RPE function may be impaired in focal or generalized intraocular inflammation.

### B. Mechanical

Perifoveal vitreous traction or epiretinal membrane can cause distortion and thickening of the macula and cystoid space formation, with or without traction-induced leakage of macular capillaries.

Vitreous traction at the macula through vitreous fibers connecting to the Müller cells represents a possible mechanism of CME. Thus, uveitic eyes with complete posterior vitreous detachment have fewer macular changes and better visual acuities than those with partial posterior vitreous detachment.

### C. Optic nerve head leakage

Macular edema may develop during long-standing inflammation of the optic disc causing hyperpermeability of capillaries in the optic nerve head, with fluid leakage leading to macular edema (ie, neuroretinitis, optic disc swelling in sarcoidosis).
Section IV: Aftermath—Rebuilding After the Fire

IV. Diagnosis

A. Clinical

1. Symptoms such as micropsia, metamorphopsia, and visual loss are late manifestations of macular edema.

2. Fundus biomicroscopy: Can detect only advanced macular edema and is not sensitive enough for diagnosing early retinal accumulation of fluid. One should therefore not rely on visual acuity or clinical examination for the diagnosis and the monitoring of the disease because prolonged macular edema will induce permanent irreversible structural damage, leading to severe visual impairment and blindness.

B. Imaging

1. Fluorescein angiography:

   FA is more sensitive than clinical examination. In numerous cases, macular edema can be demonstrated only on FA and is not suspected clinically. It detects leakage from retinal blood vessels, particularly from perifoveal capillaries causing diffuse or cystoid macular edema.

   The accumulation of fluorescein in the macular region is seen as an increasing hyperfluorescence of the perifoveal retina, progressively increasing during the angiographic sequence and demonstrating a diffuse macular edema often sparing the foveola itself. During the course of the disease, the development of a cystoid macular edema is seen as the accumulation of fluorescein in the macular cysts, giving, at the late stages of the angiogram (5-0 minutes), a petaloid pattern that is often incomplete. It is important to note the possible presence of a central cyst reflecting the severity of the intraocular inflammation and a poorer prognosis. Staining of the optic disc and leakage from the preapillary capillaries is often present. (See Table 1.)

2. OCT, enhanced depth OCT (EDI-OCT), swept source OCT (SS-OCT):

   OCT is a noninvasive technique and can be performed even in the presence of a poor pupil dilation, which may be the case in uveitis patients. It is as sensitive as FA in identifying macular edema in uveitis. It has the advantages of easily localizing the axial distribution of fluid within the macular area and of detecting subretinal fluid accumulation, both of which have a practical impact on the therapeutic management and on the prognosis. OCT easily allows accurate serial macular thickness measurements and consequently a good monitoring of the course of the disease with or without treatment, although there is a controversial correlation between the macular thickness measured by OCT and the visual acuity.

   Recent EDI-OCT studies noted that eyes with uveitic macular edema appear to have thinner measured choroid than eyes without uveitic macular edema, suggesting a possible role of ischemia in the pathogenesis of inflammatory macular edema. (See Table 2)

Table 1. Fluorescein Angiographic Grading System for Macular Edema (LA Yannuzzi)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No leakage, absence of perifoveal hyperfluorescence</td>
</tr>
<tr>
<td>1</td>
<td>Less than perifoveal edema, incomplete perifoveal hyperfluorescence</td>
</tr>
<tr>
<td>2</td>
<td>Minimal perifoveal edema, mild 360° hyperfluorescence</td>
</tr>
<tr>
<td>3</td>
<td>Moderate perifoveal edema, moderate 360° hyperfluorescence of 1 disc diameter</td>
</tr>
<tr>
<td>4</td>
<td>Severe perifoveal edema, severe 360° hyperfluorescence &gt; 1.5 disc diameter</td>
</tr>
</tbody>
</table>

Table 2. OCT Classification of the Macular Edema Pattern

A. Diffuse macular edema (DME): Sponge-like or diffuse macular edema; diffuse, ill-defined hyporeflective area of thickening in the outer retinal layer

B. Cystoid macular edema (CME): cystic hyporeflective spaces with high signal elements bridging the retinal layers. CME was classified depending on the location into:

1. external cystoid edema when the cysts were localized to the outer retinal layers
2. internal cystoid edema when the cysts were situated in the inner retinal layers
3. external and internal cystoid edema when the cysts involved all the retinal layers

C. The presence of serous retinal detachment (SRD) was diagnosed as separation of neurosensory retina from the highly reflective retinal pigment epithelium / choriocapillaris band.

D. Presence of a vitreomacular traction, of an epiretinal membrane (ERM)
3. Several studies reported the rates of the tomographic patterns of macular edema at initial presentation:
   a. DME (26%-37.5%-60.7%)
   b. CME (39.3%-50.8%-60%)
   c. SRD (11%-14%-20.2%)
   d. ERM (12%-21%)
   e. Vitromacular traction (4%-4.7%)
   The occurrence of inner retinal cysts seems to be correlated to the presence of an ERM.

C. Multifocal ERG (MfERG) combined with OCT is useful to evaluate objectively and quantitatively the alterations of morphology and of local retinal function of the macula.

V. Etiology
   A. Anatomical type of uveitis
      1. Anterior: 11%
      2. Intermediate: 60%
      3. Posterior: 34%
      4. Panuveitis: 66%
   B. Main causes of macular uveitis
      1. HLA-B27 associated: 12%
      2. Sarcoidosis: 59%
      3. Behçet’s disease: 63%
      4. Acute retinal necrosis: 100%
      5. Juvenile idiopathic arthritis: 60%
      6. Infectious uveitis (tuberculosis, Lyme disease, syphilis . . . ): 40%
   An adequate and thorough workup is always indicated in the presence of a sight-threatening and recurrent uveitis, particularly in the presence of CME. It must exclude definitely an infection and a masquerade syndrome such as a malignant disease.
   C. Practical approach: Exclude an infectious origin, particularly when unilateral.

VI. Close Monitoring2,9,11,14,15,19-21
   A. Combine several criteria for evaluating disease activity:
      1. Visual acuity, although not reliable (Do not rely on visual acuity +++)
      2. Clinical (AC flare, vitreous haze)
      3. Laser flare meter
      4. Visual fields (Humphrey, Goldmann)
      5. SD-OCT, EDI-OCT, SS-OCT
      6. Electrophysiology (30 Hz flicker implicit times, mfERG)
      7. FA/ICG-A
   B. Clinical judgment is not reliable most of the time!!
   It is not surprising that visual acuity correlates poorly with macular thickness measured by OCT or with macular leakage seen on FA because visual acuity depends on many other factors, such as duration of edema, location of cystic spaces, photoreceptor loss and impairment, perfusion of macular capillaries and ischemia, RPE dysfunction, and media opacities. Nevertheless, quantitative assessment of macular thickening by OCT may still be useful in predicting the response to treatment of all types of macular edema by evaluating the degree of improvement 1 month after initiation of treatment.

In uveitic macular edema, there is a moderate agreement between macular thickening measured by OCT and macular leakage seen on FA. OCT may be the preferred initial test for evaluation of uveitic macular edema because it is safer, easier, and quicker to perform than FA. However, macular leakage cannot be excluded if macular thickening is absent and vice versa. Therefore, it is necessary to eventually perform both examinations in addition to other ancillary tests cited above. Visual fields
and electrophysiology are of utmost importance in evaluating the treatment efficiency in long-standing uveitis and thereby in preventing severe visual loss and blindness.

VII. Prognosis\textsuperscript{1,8,5,15,17,19-21}

A. A better visual prognosis is associated with:
   1. A better visual acuity at baseline
   2. Younger patients
   3. Initiation of treatment at early stages of CME.

   Improved visual acuity 1 month after the therapeutic intervention is usually indicative of the final functional outcome.

B. Poor visual outcome is related to:
   1. Advanced age of the patients
   2. Prolonged duration of CME and chronic inflammation
   3. Incomplete posterior vitreous detachment
   4. A large foveal avascular zone on angiography
   5. Macular retinal atrophy
   6. Foveola central cyst
   7. Inner CME (There is a correlation between inner retinal cysts and ERM.)

   The socioeconomic impact of the visual impairment related to CME should not be underestimated.

VIII. Treatment\textsuperscript{1,3,6,8,9,11,17-21}

There is no consensus on the symptomatic treatment of uveitic macular edema.

In any case, we stress the importance of not following the usual recommendation found in the literature: one must never wait for a decrease of the visual acuity below 20/40 to initiate an aggressive treatment because it represents a lost chance for the patient. A better prognosis depends on the level of the initial visual acuity.

The treatment of CME consists of causal treatment of the underlying disease and symptomatic treatment of CME.

Restoration of the blood-retina barrier can be obtained by various combinations of systemic and local treatments.

A. Means: Local

1. Local treatments are utilized in predominantly unilateral diseases (topical, subconjunctival, or parabulbar routes).

   a. Intravitreal administration of corticosteroids is now often indicated. Repeated intravitreal injections can be replaced by an intravitreal implant (6- to 36-month duration) or by an intravitreal device (2- to 3-year duration), according to the chronicity of the inflammation.

   b. The main drawbacks are the need for repeated procedures in long-standing diseases and the frequent rise in IOP, often necessitating glaucoma and cataract surgery.

   c. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) combined with low-dose oral carbonic anhydrase inhibitors represent an adjunctive treatment during the tapering of the induction therapy. It should not be used as a monotherapy.

2. Local corticosteroids

   a. Topical (anterior uveitis)

   b. Periocular (subconjunctival injections for anterior uveitis, parabulbar injections for posterior uveitis)

   c. In posterior uveitis:

      i. Intravitreal (IVT) corticosteroids

         (a) repeated IVT injections

         (b) Retisert intravitreal fluocinolone implant (need surgery)

         (c) intravitreal dexamethasone implant injection: Ozurdex(DXM)

      ii. IVT of anti-VEGF agents, of immunosuppressive drugs (infliximab, adalimumab, sirolimus)

B. Means: Systemic

1. Anti-infectious therapy in uveitis with an infectious origin

2. Corticosteroid treatment remains the mainstay for treatment of noninfectious uveitis.

IX. Therapeutic Strategy

A. The treatment decision depends upon the presentation and the course of the uveitic macular edema.

1. When the disease is bilateral, one should favor a systemic treatment, particularly if extraocular manifestations are present.

2. In case of severe acute ocular attacks, anti-TNF agents are indicated when IV pulse methylprednisolone administration or high-dose oral corticosteroids are insufficient. The main contraindication is an underlying infection, especially tuberculosis.

3. During chronic stages:

   a. Taper to a minimal oral corticosteroids, less than 10 mg of prednisone/day as monotherapy if possible.

   b. Or use an adjunctive strategy with a corticosteroid-sparing agent, following a stepladder process in order to decrease the corticosteroid dosage to an acceptable level below 7-10 mg/day. (See Figure 2.)
Section IV: Aftermath—Rebuilding After the Fire

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B. Practical approach according to the anatomic location (see Figures 3 and 4).

C. Corticosteroid responses (see Figure 5).

**UVEITIS**

Severe Acute Attacks

Unilateral or Bilateral Sight threatening

**EMERGENCY+++**

- Pulse IV, methylprednisolone (500mg - 1000mg/day x 3 days) followed by 0.5-1.0 mg/kg/d oral prednisone.
- High dose oral corticosteroids (1.2-1.5 mg/kg/d)
- anti-TNF (Infliximab, Adalimumab)
- Possible combined Local Rx

**Corticosteroids remain the mainstay and the first line of treatment.**

D. Current recommendations for very long lasting diseases with subclinical inflammatory activity (Birdshot, VKH):

1. Early introduction of immunomodulatory therapy (IMT) after / along with corticosteroids initiation

2. Allows tapering of corticosteroids to an acceptable dosage (less than 10 mg/kg/d)

3. IMT is often maintained for a long period (2 to 5 years) because a low dose of corticosteroid monotherapy is usually inefficient to control a creeping inflammation.

E. Bilateral disease

1. Systemic corticosteroids and corticosteroid-sparing agents
   a. One can use conventional drugs such as antimetabolites or T cell inhibitors (AZA, MMF, CSA, MTX).
   b. Nowadays, alkylating agents are rarely indicated. Cyclophosphamide may be considered essentially by IV route.
   c. Interferon alpha 2a therapy has been shown to be effective, particularly in uveitic CME. It is a safe corticosteroid-sparing agent that can also be administered as a first line of treatment in definite entities.
   d. If none of the above is effective, anti-TNF agents (infliximab - chimeric, IV; adalimumab - humanized, subC; golimumab - humanized, subcutaneous) can be administered with the customary precautions. They appear very efficient but are more costly. As stated above, anti-TNF agents are sometimes indicated early during the course of the disease when the vision is heavily threatened, either as an initial monotherapy or soon after the absence of efficacy of high doses of corticosteroids.
Some other biologics have been used or are still under evaluation:

i. Daclizumab: humanized mAb against IL2 receptor of T cells (alpha subunit), no longer available
ii. Campath: chimeric anti-CD52
iii. Anakinra: anti-IL1 receptor
iv. Canakimumab: anti-IL1 beta
v. Tocilizumab: anti-IL6 receptor
vi. Abatacept: fusion protein, CTLA-4
vii. Rituximab: anti-CD20 targeting B cells
viii. And others to come

Bilateral disease and indications for a local treatment.

a. Adjunction of a local treatment (topical, periocular injections, intraocular route) may be useful.

b. In case of flare-ups during the maintenance therapeutic adjustment phase in order to increase only moderately the systemic treatment dosage.

Unilateral disease

1. In any doubt, repeat a complete workup to exclude again an infection and a masquerade syndrome before initiating any anti-inflammatory / immunosuppressive treatment without an anti-infectious treatment coverage. A latent involvement of the fellow eye must be excluded (flare, ICG-A).

2. Local treatment (topical, periocular injections, intraocular route) will be favored if there is no associated systemic disease.

3. The addition of a systemic treatment is indicated when:

a. The local treatment is insufficient to control the inflammation.

b. There is an associated systemic disease with extraocular manifestations.

c. The involvement of the fellow eye occurs during the initiation of the local therapy.

Indications for combination of routes or drugs: emergency, flare-up, ineffective monotherapy

1. Several routes of administration: systemic routes (oral, IV) + local routes (topical, periocular, intraocular)

2. Several immunosuppressive drugs

   a. CSA+AZA combination

   b. CSA+MMF combination

H. Alternative therapeutic options:

To treat uveitic macular edema, we do not use pars plana vitrectomy (unless there is a vitreous traction, an epiretinal membrane impairing the vision, or a concomitant rhegmatogenous retinal detachment), laser photocoagulation, hyperbaric oxygen, or cryo-application.

Conclusion

Cystoid macular edema is a major cause of visual loss in patients with uveitis. The treatment of uveitic macular edema is often unsatisfactory and is not standardized. Despite aggressive treatment, the progression of UCME with accompanying visual loss is common.

The key points are:

A. A rigorous workup utilizing new molecular diagnostic tools

B. Need to rule out masquerade syndromes

C. Give a specific anti-infectious treatment if indicated.

D. Consider new therapeutic approaches, either medical (IFN, TNF blockers in refractory cases, other promising biologics) or surgical (intravitreal implants, Retisert, Ozurdex). Intraocular therapy (injections, implants) is effective and represents a good adjunctive treatment in specific indications (unilateral, acute attacks, flare ups) but cannot be considered as a long-term maintenance treatment because:

1. It has a transient action and is difficult to adjust.

2. Of ocular side effects (glaucoma, cataract, retinal atrophy)

3. It acts downstream on the inflammatory response.

4. It does not address the possible associated systemic manifestations of the disease.

E. The evaluation of cancer risks with long-term use of biologics is necessary.

F. Early and aggressive treatment for improving uveitic macular edema with a very early introduction of immunomodulatory agents in some specific sight-threatening entities is important.

Provided those recommendations, satisfactory long-term results for the majority of patients suffering from uveitis macular edema are attainable.

References


Viral Uveitis: Anterior and Posterior

Quan Dong Nguyen MD

I. Introduction
Estimated prevalence and incidence

II. Significance of viral infection in uveitis and ocular inflammatory diseases
Anterior Uveitis: Suspicion, Diagnosis, and Management
A. Herpes simplex
B. Cytomegalovirus
C. Others

III. Posterior Uveitis: Suspicion, Diagnosis, and Management
A. Herpes simplex
B. Varicella zoster
C. Cytomegalovirus
D. Human immunodeficiency virus
E. Others

IV. Pathologic Evaluation in Uveitis: Indications and Approaches
A. Anterior chamber paracentesis
B. Iris biopsy
C. Vitreous biopsy
D. Retinal/chorioretinal biopsy
E. Fine needle aspiration biopsy (FNAB)

V. Advances in Diagnosis
A. Immunohistochemistry
B. Polymerase chain reaction
   1. Advantages
   2. Disadvantages

VI. Summary and Clinical Pearls
Toxoplasmosis

Rubens Belfort Jr MD PhD

In the last 20 years, many papers emerged changing classic concepts in ocular toxoplasmosis; some of these changes are presented in Table 1.

*Toxoplasma gondii* exists in several forms: the oocyst; the tachyzoite; and the cyst. Oocysts are shed in cat feces. Tachyzoites are the obligate intracellular form of the parasite and are able to invade nearly all host tissues. Tachyzoites change into bradyzoites and form tissue cysts that contain hundreds of thousands of bradyzoites that will continue to replicate slowly and may persist for life.

**Table 1. Changed Points in Ocular Toxoplasmosis**

- All cases congenital
- Must present retinochoroiditis
- Vertical transmission (pregnancy) only once
- Cats and meat are the sources
- Nothing to prevent ocular form
- No treatment to avoid recurrences
- Recurrences related only to local retinal cysts

**Epidemiology**

*T. gondii* infects up to a third of the world's population. Prevalence is highest in tropical areas. In some areas of Latin America, the South Pacific, and Western Europe, seropositivity rates exceed 90% by the fourth decade of life.

Ocular toxoplasmosis is the most common cause of posterior uveitis in many countries. The prevalence of ocular toxoplasmosis ranges from almost zero to over 30%, and the correlation between the percentage of patients with antibodies against *T. gondii* and the occurrence of ocular lesions is not always strong.

Human beings can be infected by ingestion or handling of undercooked or raw meat (mainly pork or lamb) containing cysts and food containing oocysts excreted in cat feces but also by drinking water.

Transplacental transmission of *T. gondii* to the fetus occurs when infection is acquired during or just before pregnancy. Rarely, the mother could transmit the disease in more than 1 pregnancy.

In HIV-infected patients, toxoplasmosis causes encephalitis and uveitis.

**Ocular Disease**

The symptoms include floaters, blurring, and decreased vision. Patients may also develop painful, red eyes from the associated anterior segment inflammatory reaction. Recurrent toxoplasmic retinochoroiditis is usually not associated with systemic disease but may also be preceded by flu-like symptoms.

The retina is the primary site of *T. gondii* infection in the eye, but the choroid is usually also inflamed and may play a role in recurrences. The hallmark is a necrotizing focal retinochoroiditis, and this have the same basic characteristics whether resulting from congenital or acquired infections. Congenitally infected patients have a tendency to develop bilateral retinal lesions. These are usually white, with overlying vitreous inflammatory haze, and the severe vitritis will have the classic “headlight in the fog” appearance. A secondary iridocyclitis and vasculitis, often subclinical, may also be present. Often patients develop new lesions satellite to hyperpigmented retinal scars.

**Course of Disease**

In most cases toxoplasmic retinochoroiditis is a self-limited disease, and untreated lesions generally begin to heal after few weeks to many months.

The frequency of recurrent inflammation attacks varies widely and cannot be predicted. Classically it was considered as caused by the rupture of toxoplasma cyst in the retina. Circulating monocytes carrying toxoplasma antigens and DNA from organisms liberated by the rupture of cysts outside the eye may also explain the disease recurrence.

In immunosuppressed patients (HIV, biologics, cancer, or organ transplant recipients), lesions will continue to enlarge if left untreated. In most reported cases of ocular toxoplasmosis in immunosuppressed patients, there have not been pre-existing scars.

**Diagnostic Tests**

The presence of anti-*T. gondii* IgG antibodies cannot confirm the ocular diagnosis but admits this possibility.

Parasites can be detected by polymerase chain reaction in the aqueous and in the vitreous. Chorioretinal biopsy is associated with serious risks that hinder its routine use.

The identification of parasite strains has provided new insights into the pathogenesis of Toxoplasmosis, and genotyping ultimately is becoming an important diagnostic and prognostic tool. The majority of strains identified in Europe and North America are classified into 3 distinct genotypes (types I, II, and III). All of them can cause disease in humans. Type I strains are considered to be more often associated with postnatal acquired ocular infections, and type II strains are more associated with congenital infections and toxoplasmic encephalitis. Atypical strains as well as mixed infections have been identified in many parts of the world and seem to be common. It suggests that the genetic makeup of *T. gondii* is more complex than previously recognized, and unique or divergent genotypes may contribute to different clinical outcomes of toxoplasmosis in different localities.

**Treatment of Ocular Toxoplasmosis**

Treatment is proposed for the majority of *T. gondii* infections with the objective of decreasing inflammation severity and avoiding the risk of worsening of the infection. Antitoxoplasmic drugs should be used in association with systemic steroids.
**Antimicrobial Agents**

The combination of pyrimethamine and sulfadiazine, which is considered classic or specific therapy for ocular toxoplasmosis, has been replaced in many situations by the use of trimethoprim / sulfamethoxazole, which presents many advantages, such as high compliance and low side effects. Other drugs (such as clindamycin, spiramycin, etc.) have been used, but their relative efficacies remain uncertain. Short-term treatments of active toxoplasmic retinochoroiditis lesions do not prevent subsequent recurrences, but prophylactic intermittent treatment with the association of trimethoprim / sulfamethoxazole can reduce the recurrence rate of toxoplasmic retinochoroiditis. Recent information, though, suggests this protective effect may tend to disappear after months of the treatment discontinuation.

**Corticosteroids**

Corticosteroids decrease complications associated with inflammation, such as macular edema, vitreous inflammatory reaction, and retinal vasculitis, and are especially important for lesions that threaten the macula or optic disc.

Intravitreal injection of clindamycin in association with dexamethasone may be indicated in cases where patients have contraindication of systemic therapy specific for toxoplasmosis.

**Selected Readings**


Pro and Con—Toxoplasmosis Therapy: Triple Therapy Is Superior to Other Options

Gary N Holland MD, Glenn J Jaffe MD

There has been no consensus among uveitis specialists regarding the best treatment for recurrent toxoplasmic retinochoroiditis.

Numerous drugs, drug combinations, and routes of drug administration have been described for treatment of ocular toxoplasmosis. A 2002 survey of American Uveitis Society (AUS) members found that 9 different antimicrobial drugs (or commercially available drug combinations) were being used in 24 different regimens to treat ocular toxoplasmosis. Some, but not all, clinicians administer oral corticosteroids with antimicrobial drugs.

These treatments have never been compared head-to-head in well-designed, prospective, clinical trials. In the 2002 AUS survey, “classic therapy,” first described in the 1950s and consisting of oral pyrimethamine, sulfadiazine, and prednisone, was used most often by uveitis specialists for treatment of ocular toxoplasmosis, but there is evidence that alternative treatments have gained increased popularity among clinicians in recent years.

In the absence of results from a randomized clinical trial, decisions about treatment must be based on a number of factors, including:

- In vitro studies of drug sensitivities,
- Animal studies of treatment effects,
- An understanding of the pathophysiology of toxoplasmic retinochoroiditis,
- Descriptive case series that report outcomes associated with various treatments, and
- Expert opinion.

Drs. Holland and Jaffe, both experts with extensive experience in the management of ocular toxoplasmosis, who have each published on various treatments for the disease, will present arguments both in favor of (Dr. Holland) and against (Dr. Jaffe) the following recommendation:

In the absence of medical contraindications (eg, drug allergies), the treatment of choice for recurrent, active toxoplasmic retinochoroiditis in an immunocompetent adult man or non-pregnant adult woman is the oral administration of triple therapy, consisting of a dihydrofolate reductase inhibitor, a sulfonamide antibiotic, and prednisone.

References

Ocular tuberculosis is an important form of extrapulmonary tuberculosis. It presents with diverse clinical manifestations, and in spite of recent revolutionary advances in diagnostic technologies, diagnosis and treatment remain a challenge.

The hematogenous spread of *Mycobacterium tuberculosis* from pulmonary or extrapulmonary sites may result in necrotizing scleritis, posterior scleritis, granulomatous uveitis, ciliary body tuberculosis, choroiditis, chorioretinitis, subretinal abscess, choroidal granuloma, optic disc granuloma, panuveitis, and serpiginous-like choroiditis (SLC). Tubercular uveitis is either unilateral or asymmetrically bilateral, characterized by granulomatous presentation, insidious onset, and chronic course. Specific clinical signs include mutton fat keratic precipitates or anterior chamber granulomas, broad-based posterior synechiae, and isolated or multiple grayish-white or creme-colored choroidal granulomas with defined edges. Multifocal chorioretinitis with pigmented scars and exudative retinal periphlebitis with retinal hemorrhages often indicate a tubercular etiology. Healed periphlebitis results in sclerosed venules and perivascular healed chorioretinal scars.

**Laboratory Workup**

A complete systemic history taking and examination might reveal evidence of pulmonary and other extrapulmonary tuberculosis. Isolation of *M. tuberculosis* by culture remains the cornerstone for diagnosis. Histopathological analysis of iris or retinochoroidal tissue can also be done. However, the absence of acid-fast bacilli or of caseating necrosis in the biopsy specimen cannot rule out tuberculosis. Recent advances in diagnostic tools for tuberculous infection, including molecular biology techniques, interferon-gamma release assays, and radiodiagnostics, are also used in the diagnosis. However, suboptimal specificity and sensitivity of existing diagnostic tools delay the diagnosis and treatment of active ocular infection.

Positive reaction after an intradermal injection of tuberculin purified protein derivative (PPD) indicates a successful cellular immune response by the patient. However, a negative test alone cannot rule out TB; in a study on histopathologically proven ocular tuberculosis, 40% of patients had negative TST results. To study the immune response, a novel in vitro test, interferon-gamma release assay (IGRA), has been developed using specific tubercular antigens ESAT-6 and CFP-10. However, IGRAIs perform differently in high-burden than in low-burden countries. Because of the low prevalence of TB in the United States, the low pretest probability and low positive predictive value, IGRAIs may not be useful as a standard part of the uveitis workup. The QFT result, together with the TST, may increase the sensitivity. However, lack of a gold standard for the diagnosis of TB prevents an effective and interpretable comparison of the IGRAIs and the TST in ocular tuberculosis. High-resolution computed tomography of the chest is found to be a useful tool in the diagnosis of granulomatous uveitis. Some centers further recommend use of positron emission tomography/CT-guided lymph node identification for biopsy diagnosis of TB-associated uveitis. Diagnosis based on detection of mycobacterial DNA through polymerase chain reaction (PCR) and real-time PCR are becoming method of choice because of rapid test results and the ability to test in a very small sample.

**Treatment**

Antitubercular therapy is highly effective in reducing the recurrence of uveitis in patients with manifest TB. The World Health Organization recommends that new patients with both pulmonary TB and extrapulmonary TB to be treated with a 4-drug regimen (isoniazid, 5 mg/kg/day; rifampicin, 10 mg/kg/day; ethambutol, 15 mg/kg/day; and pyrazinamide, 20-25 mg/kg/day). Ethambutol and pyrazinamide are stopped after 2 months. Isoniazid and rifampicin are continued for 4-6 months. Corticosteroids seem to have a potential benefit in patients with tubercular pericarditis and meningitis, similarly; steroids are used in ocular TB as well. More evidence is required on the dose and duration of corticosteroids in ocular infections. Antibiotic sensitivity tests and minimum inhibitory concentration of drug in ocular TB are not studied well. In patients with coexisting HIV and systemic TB, initiation of concomitant antitubercular and antiretroviral therapy may result in exacerbation of inflammation and clinical deterioration. Either addition of corticosteroids or delaying the administration of highly active antiretroviral therapy (HAART) for the first 2 months of antituberculosis treatment is advised.

**Drug-Resistant TB**

The possibility of drug-resistant TB is not always considered in ocular TB. Detection of drug resistance is not attempted because drug susceptibility testing is possible only in culture isolates. Difficulties in isolating the organisms from ocular TB make this assay difficult. This has serious implications specifically in uveitis; when a trial of antitubercular treatment fails in presumed ocular TB, there is a very high possibility for the uveitis specialist to assume a nontubercular etiology and to start corticosteroids or immunosuppressive treatment to control inflammation.

Drug susceptibility testing can be performed on all positive mycobacterial cultures by 1% proportional method on Middlebrook 7H10 agar for all antitubercular drugs. Conventional methods for mycobacteria culture and drug susceptibility testing (DST) are elaborate and time consuming. In such situations, molecular diagnostic studies to rule out drug resistance may be of help.

Drug-resistant strains have evolved mainly due to incomplete or improper treatment of TB patients. Multidrug-resistant (MDR)-TB and extensively drug-resistant tuberculosis (XDR-TB) have been reported in 45 countries, and they are considered as a global threat. Most cases are missed due to insufficient laboratory infrastructure for diagnosis. MDR- and XDR-TB are generally thought to have high mortality rates. At present, MDR-TB is treated by a combination of 8 to 10 drugs with therapies lasting up to 18-24 months; only 4 of these drugs were actually developed to treat TB. With the correct combination and rational use of available antituberculosis drugs, better prognosis can be obtained.
Nontuberculous Mycobacterial (NTM) Infections

Microbiological tests like smear and culture of NTM infections such as *Mycobacterium chelonae* and *Mycobacterium abscessus* can closely mimic *M. tuberculosis*. Biochemical analysis and molecular diagnostics can pinpoint the diagnosis. They are reported to result in severe and progressive postoperative endophthalmitis, often misdiagnosed as *Propionibacterium acnes* or Nocardial or fungal endophthalmitis. NTM infections are resistant to most conventional antimycobacterial drugs but are sensitive to a variety of other antibiotics like amikacin, moxifloxacin, and to a lesser extent levofloxacin and ciprofloxacin. Large gaps still exist in our knowledge of ocular NTM infection. Accurate biomarkers to predict exposure, latency, relapse, and resistant disease are still on research and are not yet available for application.

Selected Readings

Syphilis

Lourdes Arellanes-García MD

I. Introduction: History

II. Epidemiology
   A. Etiology
   B. Prevalence

III. Disease Natural History
   A. Primary stage
   B. Secondary stage
   C. Latent stage
   D. Tertiary stage

IV. Congenital Syphilis

V. Syphilis in the HIV Patient

VI. Clinical Manifestations
   A. Systemic
   B. Ophthalmic
      1. Eyelids
         a. Chancre
         b. Madarosis
      2. Conjunctiva
         a. Chancre
         b. Conjunctivitis
      3. Sclera: episcleritis/scleritis
      4. Cornea: interstitial keratitis
      5. Lens: cataract (congenital)
      6. Uveal tract
         a. Iris nodules
         b. Iris roséola
         c. Iritis
      7. Retina
         a. Retinitis
         b. Retinal vasculitis
         c. Acute syphilitic posterior placoid chorioretinitis
     8. Optic nerve: papillitis
     9. IOP: inflammatory ocular hypertension syndrome
    10. Pupils: Argyll Robertson pupil
    11. Extraocular motility
   C. By stage

VII. Testing
   A. Treponemal tests
   B. Nontreponemal tests
   C. Lumbar puncture
   D. HIV test

VIII. Treatment

Selected Readings

Is It Infectious, Autoimmune or Malignant? The Importance of Diagnostic Surgery

Henry J Kaplan MD

I. Indications for Diagnostic Surgery

A. Sight-threatening lesion
B. Atypical intraocular inflammation
C. Failure to respond to empirical therapy
D. Suspicion of a neoplastic process

II. Patient Evaluation Prior to Diagnostic Vitrectomy: Patient-Directed Diagnostic Approach

A. Exclusion of systemic infectious disease
   1. Syphilis: serology for T palladium
   2. Tuberculosis: QuantiFERON-TB Gold, chest imaging (x-ray, CT scan)
   3. Infectious pathogens implicated by history (eg, Bartonella henselae – catscratch disease, Borrelia burgdorferi – Lyme disease)
B. Exclusion of systemic autoimmune disease
C. Negative chest imaging for sarcoidosis
D. Exclusion of intraocular or systemic malignancy if suggested by ocular examination or medical history (eg, bone marrow dysfunction – leukemia, non-Hodgkin lymphoma)
E. Unresponsiveness to high-dose oral prednisone for noninfectious disease; ≥ 0.75 mg/kg body weight for a minimum of 2 weeks, with slow tapering over the ensuing 4-8 weeks

III. Diagnostic Surgery Techniques

A. For vitreous fluid only: 3-port pars plana vitrectomy
   1. 23- or 25-gauge transconjunctival sutureless vitrectomy for vitrectomy only
   2. Manual aspiration of 1.0 cc of undiluted vitreous in a 3.0-cc syringe, with infusion of air to prevent hypotony
B. For chorioretinal biopsy tissue
   1. Fine needle biopsy for evaluation / suspicion of neoplasm
   2. 20-gauge vitrectomy
      a. Intraocular diathermy
      b. Endolaser photocoagulation
      c. Automated vertical vitrectomy scissors
      d. Pneumatic tamponade
C. Testing of intraocular specimens
   1. Suspected infection
      a. PCR for bacterial 16S rRNA, fungal 18S/28S rRNA, or specific primers (eg, Toxoplasma, herpes viruses – HSV1, HSV2, VZV, EBV, CMV, HHV6)
      b. Goldmann-Witmer coefficient (GCW): intraocular antibody production
      c. Standard microbiologic culture for bacteria and fungi
      d. Standard cytologic analysis
   2. Suspected neoplasia
      a. Cell block for cytomorphology (eg, atypical lymphoid cells)
      b. Monoclonality: immunohistology or flow cytometry for B cells (κ or λ light chains) or T cells (CD3)
      c. Molecular analysis, using microdissection. Gene rearrangement - IgH in B cell tumors; TCR in T cell tumors
      d. Cytokine analysis (IL-10/IL-6)
   3. Examples of laboratory test results
      a. Genomic DNA of ocular infectious pathogens – Sugita
      b. Posterior segment inflammation (intermediate uveitis, posterior uveitis) – Kitiratschky

IV. Potential Complications of Diagnostic Surgery

A. Most common complication: Cataract formation
   1. Cataract required surgery if not pseudophakic at time of surgery
   2. Correlated with age of patients (> 60 years)
B. Other significant complication: Retinal detachment
   1. Tractional RD at time of surgery (eg, Candida albicans)
   2. Retinal necrosis (eg, ARN secondary to VZV)
      Patients with ARN are at a greater risk of RD with prophylactic vxt.
   3. Chorioretinal biopsy
V. Summary
A. Diagnostic surgery is a relatively safe procedure.
B. Viral testing on vitreous fluid should probably be performed in patients with idiopathic uveitis who don’t respond to empiric therapy because of the frequent identification of a viral etiology.
C. The positive predictive value for vitreal and choroidal lymphoma is improved but remains low despite our newer diagnostic testing.
D. Long-lasting intraocular tamponade should be considered in all patients undergoing vitrectomy with necrotic retina or chorioretinal biopsy.

References
Current Best Practices for Timely Diagnosis of Intraocular Malignancy

Bahram Bodaghi MD PhD

I. General Introduction
A. Background
B. Implications

II. Definitions: Masquerade Syndromes
A. Malignant ocular infiltrations
   1. Intraocular malignancy in children
      a. Diffuse infiltrating retinoblastoma
      b. Metastatic tumors
   2. Intraocular malignancy in adults
      a. Primary vitreoretinal lymphoma
         i. B cell lymphoma
         ii. T cell lymphoma
         iii. NK cell lymphoma
      b. Intravascular lymphoma
      c. Metastatic tumors
   B. Paraneoplastic syndromes
      1. CAR (cancer-associated retinopathy) syndrome
      2. MAR (melanoma-associated retinopathy) syndrome
      3. BDUMP (bilateral diffuse uveal melanocytic proliferation)

III. Epidemiology

IV. Mean Diagnostic Delay
   Sight and life-threatening consequences

V. Clinical Findings
A. Ocular symptoms
   1. Anterior segment
   2. IOP
   3. Vitreous
   4. Retina
   5. Choroid
   6. Optic disc
B. CNS symptoms
C. Other malignancies

VI. Differential Diagnosis
A. Infectious
   1. Bacterial
      a. Syphilis
      b. Lyme disease
      c. Tuberculosis
      d. Nocardiosis
   2. Viral
      a. Herpes simplex virus
      b. Varicella zoster virus
      c. Cytomegalovirus
      d. Epstein-Barr virus
      e. HTLV-1
      f. Rubella virus: atypical Fuchs uveitis
   3. Parasitic: toxoplasmosis
B. Autoimmune
   1. White dot syndromes
   2. Sarcoidosis
   3. Birdshot retinochoroiditis
   5. Langerhans cell histiocytosis

VII. Diagnostic Evaluation
A. Imaging techniques
   1. B-mode ultrasound scan
   2. OCT
   3. Autofluorescence
   4. Fluorescein angiography
   5. Indocyanine green angiography
   6. MRI (CNS)
B. Fluids and tissue analysis
   1. Anterior chamber paracentesis: indications and limitations
   2. Vitreous biopsy
   3. Retinal biopsy
   4. Enucleation
Section VI: The Fire That Won’t Die—Treatment-Resistant Disease

C. Processing of ocular fluids or tissues and application of diagnostic tools
   1. Optimization of diagnostic analysis (importance of specialized laboratories)
   2. Cytokine analysis (IL-6/IL-10)
   3. Cytology
   4. FACS analysis
   5. Histopathology
   6. Gene rearrangement
   7. Diagnosis of clonality

References
Autoimmune Retinopathy: A Diagnostic and Therapeutic Puzzle

Hatice N Sen MD

Introduction and Definition
Autoimmune retinopathy (AIR) is an autoantibody retinopathy characterized by vision loss, scotomas, visual field deficits, and photoreceptor dysfunction. The critical feature of AIR is the presence of circulating autoantibodies against retinal antigens. It is believed to result from an immunologic attack on the retina by antiretinal autoantibodies, but the mechanisms by which these antibodies cause retinal dysfunction are not entirely understood. AIR can be studied in 2 groups: paraneoplastic and nonparaneoplastic. Paraneoplastic AIR was described by Sawyer et al in 1976, and the term “paraneoplastic retinopathy” was first used by Klingele et al in 1984. This presentation will focus on nonparaneoplastic form of AIR.

Evidence from paraneoplastic retinopathies suggests that molecular mimicry between retinal proteins and tumor antigens plays an important role. Thus, it is plausible that nonparaneoplastic AIR may be triggered by a molecular mimicry between presumed viral or bacterial proteins and retinal antigens. Multiple retinal proteins have been found to be antigenic; some of these are retina-specific (recoverin) and others are not (enolase). Among these, recoverin and enolase are the most extensively studied antigens in AIR. These antiretinal antibodies can target any retinal cell type, including photoreceptor cells, ganglion cells, or bipolar cells. However, the presence of antiretinal antibodies alone is not sufficient for the diagnosis of this ill-defined ocular disorder.

Although it is believed to be rare, the prevalence of AIR is currently unknown. The overlap of clinical features with other degenerative retinal disorders and the lack of standardized diagnostic criteria, clinical and laboratory, may be contributing to underestimation of its prevalence.

Clinical Findings
Patients with AIR typically present with subacute vision loss, scotomas, photopsias, nyctalopia or photoaversion, and dyschromatopsia. Despite the heterogeneity in their circulating antiretinal antibodies, common clinical features in AIR patients include retinal vascular attenuation, diffuse retinal atrophy, retinal pigment epithelial (RPE) changes, and waxy disc pallor. AIR is usually bilateral, but it can be asymmetric. There is usually minimal or no clinically detectable intraocular inflammation. Fundus may appear unremarkable in some patients. Visual field testing shows constricted visual fields and central or paracentral scotomas, and ERG can show abnormalities in rods, cones, or bipolar cell responses or a combination of these. Visual acuity, particularly in the earlier stages, may be deceivingly good. Ancillary testing with fluorescein angiography (FA) or OCT may show mild retinal vascular staining or leakage, or cystoid macular edema (CME) in some cases.

Diagnosis and Differential Diagnosis
Diagnosis of AIR is a challenge because there are no standardized diagnostic criteria. Most AIR patients may have been diagnosed with retinitis pigmentosa (RP) prior to presentation. Absence of malignancy and family history of RP and the presence of antiretinal antibodies in the setting of appropriate clinical findings as outlined above are critical to diagnosing nonparaneoplastic AIR. A family or a personal history of systemic autoimmune disease can be common among patients with nonparaneoplastic AIR. There is a female preponderance (63%-66%), and average age at diagnosis appears to range from 51 years to 56 years (8-11).

The seemingly most important factor in diagnosis, antiretinal antibody detection, has its own limitations. First of all, the techniques used to detect these antibodies are not highly sensitive or specific, and secondly, their presence does not always indicate pathogenicity. Some of these antiretinal antibodies can be found in multiple autoimmune diseases, other ocular diseases, and even in healthy subjects. Regardless of its caveats, western blot (WB) and immunohistochemistry (IHC) are the more commonly performed techniques.

Differential diagnosis of AIR includes paraneoplastic AIR (eg, CAR, MAR), white-dot syndrome spectrum disorders, particularly acute zonal occult outer retinopathy (AZOOR), retinal degenerative disorders such as RP, cone-rod dystrophy, and noninfectious and infectious uveitis syndromes. Because of significant implications, it is important to differentiate paraneoplastic AIR from nonparaneoplastic AIR. RP patients can have very similar clinical features to AIR, and some demonstrate antiretinal antibodies, which makes differentiating these 2 entities with overlapping features very difficult. Some uveitis syndromes can also demonstrate antiretinal antibodies, but most of these syndromes have typical fundus findings that help differentiate them from AIR.

Treatment
Because of the presumed autoimmune nature of AIR, various forms of immunomodulatory approaches have been tried. However, the ambiguity in diagnosis creates an enormous challenge in the management of AIR. Because of limitations in diagnostic testing and our lack of understanding of the underlying mechanisms, immunomodulatory therapy can be considered empiric at this time. Most of the knowledge regarding therapy comes from paraneoplastic retinopathy. Common approaches include systemic or local corticosteroids, intravenous immunoglobulin (IVIG) or plasmapheresis, antimetabolites such as mycophenolate mofetil, azathioprine, and T-cell inhibitors such as cyclosporine. Less frequently, targeted B-cell therapy, such as anti-CD20 monoclonal antibody (rituximab), has also been used in the treatment of AIR.

The benefit of immunosuppressive therapy in AIR is unclear at this time, and adding to the challenges in the management is the lack of parameters to guide treatment. There are no prognostic indicators, and whether timing of therapy is important or whether autoantibodies can be used to guide therapy is still unclear. Long-term treatment is usually needed in most cases, and therapy is not helpful once widespread retinal degeneration occurs. Early treatment attempts would require establishing
a clear diagnosis, using sensitive and specific assays and more definitive clinical criteria that can only be achieved with a better understanding of the disease.

References


Late Breaking News

Andrea Birnbaum MD PhD
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<td><strong>Robert B Nussenblatt MD</strong></td>
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<td><strong>Sumru Onal MD</strong></td>
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<tr>
<td><strong>Emil Mitchel Opremcak MD</strong></td>
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S R Rathinam MBBS PhD  
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Matthews Family Foundation: S  
Research to Prevent Blindness: S

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National Eye Institute: S  
National Health & Medical Research Council: S  
Ophthalmic Research Institute Australia: S  
Teva Pharmaceutical Industries, Ltd.: C

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Abbvie: C,S  
Bristol-Myers Squibb: S  
Clearside Biomedical: C  
Eleven Biotherapeutics: C  
EyeGate: S  
Genentech: S  
Xoma: C,S

Howard H Tessler MD  
Allergan, Inc.: O

Jennifer E Thorne MD PhD  
Abbott Medical Optics, Inc.: C  
AbbVie: S  
Allergan: S  
Gilead Sciences: C  
National Eye Institute: S  
Xoma: C,S

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