ACADEMY MOC ESSENTIALS®



PRACTICING OPHTHALMOLOGISTS CURRICULUM 2014-2016

# Uveitis

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# Practicing Ophthalmologists Curriculum Authors and Financial Disclosures

The Practicing Ophthalmologists Curriculum was developed by a group of dedicated ophthalmologists reflecting a diversity of background, training, practice type and geographic distribution.

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The Academy gratefully acknowledges the contributions of the American Uveitis Society.

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#### **Background on Maintenance of Certification (MOC)**

Developed according to standards established by the American Board of Medical Specialties (ABMS), the umbrella organization of 24 medical specialty boards, Maintenance of Certification (MOC) is designed as a series of requirements for practicing ophthalmologists to complete over a 10-year period. MOC is currently open to all Board Certified ophthalmologists on a voluntary basis; time-limited certificate holders (ophthalmologists who were Board Certified after July 1, 1992) are required to participate in this process. All medical specialties participate in a similar process.

The roles of the American Board of Ophthalmology (ABO) and the American Academy of Ophthalmology relative to MOC follow their respective missions.

The mission of the American Board of Ophthalmology is to serve the public by improving the quality of ophthalmic practice through a process of certification and maintenance of certification that fosters excellence and encourages continual learning.

The mission of the American Academy of Ophthalmology is to advance the lifelong learning and professional interests of ophthalmologists to ensure that the public can obtain the best possible eye care.

The role of the ABO in the MOC process is to evaluate and to certify. The role of the Academy in this process is to provide resources and to educate.

#### Background on the Practicing Ophthalmologists Curriculum (POC)

At the request of the ABO, the Academy developed the Practicing Ophthalmologists Curriculum (POC), a knowledge base that identifies and defines areas of knowledge important to the delivery of quality eye care as a basis for the content of examinations for the MOC process. The content in the POC is comprised of the information deemed as the most relevant clinical information for a practicing ophthalmologist.

The ABO has agreed that their Periodic Ophthalmic Review Test (PORT) and closed-book Demonstration of Ophthalmic Cognitive Knowledge (DOCK) examinations will be based on the POC. The ABO is solely responsible for creating the PORT and DOCK exams and for certifying MOC candidates. The Academy has developed study tools based on the POC to assist doctors preparing to meet these MOC requirements.

#### **Organization of the POC**

The Practicing Ophthalmologists Curriculum comprises 10 practice emphasis areas (PEA), plus Core Ophthalmic Knowledge. The ABO has designated the following as practice emphasis areas:

- Comprehensive Ophthalmology
- Cataract/Anterior Segment
- Cornea/External Disease
- Glaucoma
- Neuro-Ophthalmology and Orbit
- Oculoplastics and Orbit
- Pediatric Ophthalmology/Strabismus
- Refractive Management/Intervention
- Retina/Vitreous
- Uveitis

In addition to two practice emphasis areas of choice, every diplomate sitting for the DOCK examination will be tested on Core Ophthalmic Knowledge. Core Ophthalmic Knowledge is defined as the fundamental knowledge every practicing ophthalmologist must have whatever their area of practice.

Each PEA is categorized into topics presented in an outline format for easier reading and understanding of the relevant information points by the reader. These outlines are based on a standard clinical diagnosis and treatment approach found in the Academy's Preferred Practice Patterns.

For each topic, there are Additional Resources that may contain journal citations and reference to textbooks. These resources are supplemental to the topic outline, and should not be necessary for MOC exam preparation purposes.

#### **Creation of the POC**

The POC was developed by panels of practicing ophthalmologists in each of the ten practice emphasis areas. The panels reflect a diversity of background, training, practice type and geographic distribution, with more than 90 percent of the panel members being time-limited certificate holders.

The panels ranked clinical topics (diseases and procedures) in terms of clinical relevance to the subspecialist or comprehensive ophthalmologist. The panelists created outlines for the topics deemed Most Relevant, based on what an ophthalmologist in a specific practice emphasis area needs to know to provide competent, quality eye care (i.e., directly related to patient care). These outlines were reviewed by subspecialty societies and the American Board of Ophthalmology.

#### **Revision Process**

The POC is intended to be revised every three years. The POC panels will consider new evidence in the peer-reviewed literature, as well as input from the subspecialty societies, the American Board of Ophthalmology and the Academy's Self-Assessment Committee, in revising and updating the POC.

Prior to a scheduled review the POC may be changed only under the following circumstances:

- A Level I (highest level of scientific evidence) randomized controlled trial indicates a major new therapeutic strategy
- The FDA issues a drug/device warning
- Industry issues a warning

# Uveitis

# **Basic concepts in immunology**

### Basic concepts in immunology

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### Complications of uveitis and their management

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# Basic concepts in immunology: effector cells and the innate immune response

# I. Definitions

#### A. Immune response

- 1. Sequence of cellular and molecular events designed to rid the host of an offending pathogenic organism, toxic substance, cellular debris, or neoplastic cell
  - a. Adaptive (or acquired) responses are directed against unique antigens with an immunologic response specific for that antigen
  - b. Innate immune responses, or natural immunity, require no prior contact with the stimulus against which they are directed

# II. Cellular components of the immune system

#### A. Leukocytes

- 1. Nucleated cells that can be distinguished from one another by the shape of their nuclei and the presence or absence of granules/ various histologic stains
  - a. Polymorphonuclear leukocytes
  - b. Eosinophils
  - c. Basophils
  - d. Mast cells
  - e. Monocytes and macrophages
  - f. Lymphocytes

# III. Innate immunity triggers

#### A. Bacteria-derived molecules

- 1. Bacterial lipopolysaccharide
- 2. Other bacterial cell wall components
- 3. Exotoxins and other secretory products
- B. Traumatic or toxic stimuli within ocular sites can trigger innate immunity.

# IV. Mediator systems that amplify immune responses

#### A. Plasma-derived enzyme systems

- 1. Complement factors
- 2. Fibrin and other plasma factors

3. Histamine

#### B. Lipid mediators

- 1. Eicosanoids
  - a. The cyclooxygenase (COX) pathway, which produces prostaglandins, thromboxanes, and prostacyclins
  - b. The 5-lipoxygenase pathway, which produces hydroxyeicosatetraenoic acid, lipoxins, and leukotrienes
  - c. COX-derived products can either up-regulate or down-regulate the production of cytokines, enzyme systems, and oxygen metabolites
  - d. 5-lipoxygenase pathway
    - Leukotrienes probably contribute significantly to inflammatory infiltration. Leukotriene
       B<sub>4</sub>, a potent chemotactic factor that also causes lysosomal enzyme release and
       reactive oxygen radical production by granulocytes
    - ii. Leukotrienes may have 1000 times the effect of histamine on vascular permeability

#### C. Platelet-activating factors

#### D. Cytokines

- 1. Soluble polypeptide mediators
- 2. Synthesized and released by cells for intercellular signaling and communication
- 3. To signal neighboring cells at the site (paracrine action)
- 4. To stimulate a receptor on its own surface (autocrine action)
- 5. To act on a distant site by release into the blood (endocrine action)
- 6. Growth factors, interleukins, lymphokines, interferons, monokines, and chemokine
- E. Reactive oxygen intermediates
- F. Reactive nitrogen products
- G. Neutrophil-derived granule products

# V. Adaptive immunity

- A. Interaction between antigen and the adaptive immune system at a site such as the skin can be subdivided into 3 phases
  - 1. Afferent phase
    - a. Recognition, transport, and presentation of antigenic substances to the adaptive immune system
  - 2. Processing phase
    - a. Conversion of the antigenic stimulus into an immunologic response
    - b. Priming of naive B and T lymphocytes

- c. Within the lymph nodes and spleen
- d. Also called activation, or sensitization, of lymphocytes
- 3. Effector phase
  - a. The elimination of offending foreign antigen physically carried out
  - b. Antigen-specific effectors exist in 2 major subsets
    - i. T lymphocytes
    - ii. B lymphocytes plus their antibodies
      - i) Antibodies, or immunoglobulins, are soluble antigen-specific effector molecules
      - ii) After appropriate antigenic stimulation with T-lymphocyte help
      - iii) B lymphocytes secrete IgM antibodies
      - iv) Later, other isotypes, into the efferent lymph fluid draining into the venous circulation
      - v) Mediate a variety of immune effector activities by combining with antigen in the blood or in tissues

#### B. Normal function of HLA molecules

- 1. All animals with white blood cells express major histocompatibility complex (MHC) proteins, in humans, termed human leukocyte antigen (HLA) molecules
  - a. 3 MHC class I
    - i. HLA-A, -B, -C
  - b. 3 MHC class II
    - i. HLA-DR, -DP, -DQ
- 2. Allelic variation
  - a. Polymorphic variants of each of the 6 HLA types exist
  - b. 25 alleles for HLA-A
  - c. 50 for HLA-B
  - d. 10 for HLA-C
  - e. 100 for HLA-DR
- 3. Disease associations
  - a. Defined as the statistically increased frequency of an HLA haplotype in persons with that disease as compared to the frequency in a disease-free population
  - b. The ratio of these 2 frequencies is called relative risk
  - c. The HLA association identifies individuals at risk, but it is not a diagnostic marker
  - d. The association is only as strong as the clinical diagnosis
  - e. Testing for HLA can provide supportive evidence for a particular diagnosis

- f. Cannot make a definitive diagnosis
- g. 8% of the white American population is HLA-A29 positive, but fewer than 1 in 10,000 Americans have birdshot choroiditis
- h. The vast majority of individuals who are HLA-A29 positive will never have birdshot chorioretinopathy

#### C. Theories on the role of HLA in uveitis

- 1. HLA molecules act as peptide-binding molecules for etiologic antigens or infectious agents
- 2. molecular mimicry between bacterial antigens and an epitope of an HLA molecule
- 3. T-lymphocyte antigen receptor (gene) is really the true susceptibility factor
- 4. Specific T-lymphocyte receptor uses a specific HLA haplotype
- 5. A strong correlation would exist between an HLA and the T-lymphocyte antigen receptor repertoire

#### Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

# Lab testing in uveitis

# I. Indications and contraindications

#### A. Indications

- 1. Anterior uveitis
  - a. Chronic, persistent, or recurrent disease
  - b. Presence of hypopyon
  - c. Bilateral disease
  - d. Granulomatous disease
  - e. Diagnostic testing not indicated in initial episode of unilateral (non-granulomatous) anterior uveitis with no pertinent findings on thorough history and review of systems
- 2. Intermediate uveitis
- 3. Posterior uveitis
- 4. Panuveitis
- 5. Scleritis
- 6. Retinal vasculitis
- 7. HIV screening required if AIDS defining ocular opportunistic infection is present
- 8. Suspicion of infectious uveitis
- 9. Suspicion of neoplastic masquerade syndrome
- 10. Suspicion of other masquerade syndrome (e.g. amyloidosis)

# II. Describe the pre-procedure evaluation

- A. History, physical examination, review of systems and formulation of a working differential diagnosis are essential cornerstones of the work-up of a uveitis patient and should precede any laboratory testing
- B. History thorough review of
  - 1. Ocular history
  - 2. Medical history
  - 3. Social History, especially sexual history, travel history, history of incarceration, drug use, smoking history, and occupational history
  - 4. Family History
  - 5. Response to previous therapy
- C. Review of systems

1. While helpful as a starting point, a questionnaire alone is insufficient unless the examiner probes into details of patient responses

#### D. Thorough ophthalmologic examination

- 1. Must include every part of the exam avoid commonly missed areas such as
  - a. Lids e.g. cutaneous nodules
  - b. Conjunctiva e.g. nodules/granuloma
  - c. Lacrimal gland inspect for granulomatous inflammation (lumpy, bumpy appearance)
  - d. Cornea diminished sensation in suspected herpetic uveitis
  - e. Anterior segment slit lamp examination including vitreous
  - f. Gonioscopy especially in chronic disease or if IOP is elevated, and in unilateral uveitis to rule out possible foreign body in angle
  - g. Dilated fundus examination

#### E. Thorough physical examination based upon pertinent positives in review of systems e.g.

- 1. Examine oral aphthae
- 2. Cutaneous rashes
- 3. Joint deformities and abnormalities in range of motion
- 4. Lymph nodes, glandular enlargement
- 5. Genital ulcers and rashes
- F. Working differential diagnosis based on these elements of history and physical. Almost always must include
  - 1. Sarcoidosis
  - 2. Syphilis
  - 3. Tuberculosis

#### III. List the alternatives to the procedure

- A. Radiologic procedures (Chest CT, MRI of head and orbits)
- B. Tissue biopsy -skin, conjunctiva, retina/choroid, extraocular (e.g. lung/mediastinum)
- C. Ophthalmic imaging procedures
  - 1. Fundus autofluorescence
  - 2. Fluorescein angiography
  - 3. ICG Angiography
  - 4. OCT

# IV. Describe instrumentations and technique

#### Uveitis

- A. Venipuncture to obtain blood for serologic testing
- B. CSF tap for VDRL, cytology
- C. If the vitreous is involved, either
  - 1. Vitreous tap
    - a. May not yield sufficient material for cytology but may be sufficient for culture or polymerase chain reaction (PCR) examinations
  - 2. Vitrectomy: standard techniques except first samples should be obtained before diluted by infusion if possible

#### D. If aqueous is involved, then anterior chamber tap

- 1. Useful for PCR, Goldmann-Witmer coefficient testing (not readily available); may be enough material for cytology
- 2. Sterile technique is important.
- 3. Avoid contact with the crystalline lens in phakic individual

# V. List the complications of the procedure, their prevention and management

- A. Vitrectomy
  - 1. As for any vitrectomy, infection, bleeding, retinal detachment, cataract formation
  - 2. Failure to obtain a diagnosis

#### B. Anterior chamber tap

- 1. Infection, bleeding, cataract formation, wound leak, pain
- 2. Failure to obtain a diagnosis
- C. CSF Tap
  - 1. CSF leak
  - 2. Headache
- D. False positive results may cause unwarranted anxiety for patients

# VI. Describe the considerations in interpretation - specific tests

- A. List of all laboratory tests and indications
- B. Flowchart for evaluation of uveitis Patients
- C. Syphilis tests
  - 1. Serologic tests are divided into nontreponemal and treponemal tests
    - a. Nontreponemal (indirect) tests may be negative in latent and tertiary stages of syphilis. Therefore, a negative result does not rule out infection.
      - i. Rapid plasma regain (RPR) detects antibodies against cardiolipin, released by cells

damaged by T. pallidum

- ii. Venereal disease research laboratory test (VDRL) is a microflocculation assay using nontreponemal antigen, cardiolipin
- b. Treponemal (direct) tests should be ordered on all patients requiring laboratory testing for ocular inflammation
  - i. FTA-ABS and the microhemagglutination assay (MHA-TP) test reactive sera for antibodies specific for *T. pallidum* antigens
  - ii. Western blot assay (WB) uses extracts of *T. pallidum*
- 2. Serologic testing for syphilis has limitations
  - a. False-positive results in RPR and VDRL testing
    - i. Systemic lupus erythematosus
    - ii. HIV
    - iii. Pregnancy
    - iv. Lyme disease
  - b. False-positive results in FTA-ABS testing
    - i. Systemic lupus erythematosus
    - ii. Rheumatoid arthritis
    - iii. HIV
      - i) FTA-ABS false-positive rate can be as high as 10% among AIDS patients
  - c. False-negative results in latent syphilis, the most common form of ocular syphilis
    - i. VDRL testing is falsely negative in 30%
    - ii. FTA-ABS is falsely negative in 1-2% of the cases
- 3. Serum titers correlate with disease activity but not severity
  - a. Nontreponemal antibody titers (RPR,VDRL) are positive in primary and secondary syphilis and decline in the latent stage and after treatment
- 4. Treponemal antibody titers (FTA-ABS) become positive during secondary syphilis and usually remain positive. All uveitis patients potentially have ocular syphilis. Although uncommon, ocular syphilis is treatable and the consequences of missed diagnosis may be serious ocular structural and neurologic damage
- 5. Obtain both nontreponemal tests (RPR or VDRL) and treponemal test (FTA-ABS, MHA-TP or other treponemal test) as recommended by the CDC. A negative nontreponemal test does not rule out the diagnosis of syphilis, particularly latent and tertiary syphilis
- 6. HIV testing should performed if treponemal tests are positive, as recommended by the CDC
- D. TB testing Tuberculin skin test (TST, also known as purified protein derivative (PPD) test)
  - 1. Background

- a. Test for latent TB infection (LTBI)
- b. Not a test for active infection
- c. In ophthalmology, used as indirect evidence, along with clinical signs, of possible TB ocular infection
- d. A positive TST is indicative of prior exposure to TB but not necessarily of active systemic infection
- 2. Dosage
  - a. Purified protein derivative (PPD) simple protein precipitate of old tuberculin
  - b. 5-tuberculin unit (TU) dose of PPD
- 3. Technical aspects
  - a. Intracutaneous injection of 5 TU of PPD in 0.1 mL of solution, typically on the volar aspect of the forearm
  - b. Use a short, beveled 26 or 27- gauge needle
  - c. Injection should produce a raised, blanched wheal
  - d. Deeper injections may be washed out by vascular flow
  - e. Read reaction in 48 to 72 hours
  - f. Positive test defined by diameter of induration, not erythema
  - g. In the United States, PPD is considered positive requiring intervention if
    - i. Induration of >5 mm in
      - i) Patients with human immunodeficiency virus HIV
      - ii) Patients with contacts with active TB
      - iii) Radiographs consistent with healed TB lesions
    - ii. Induration of > 10 mm in
      - i) Patients with diabetes mellitus
      - ii) Patients with renal failure
      - iii) Patients using immunosuppressive agents
      - iv) Health care workers
      - v) Recent immigrants from high prevalence countries
    - iii. Induration is > 15 mm in patients with no known risk factors
  - h. False-negative skin testing occurs at a rate of 25%
    - i. Profound acute illness
    - ii. Immunosuppression
    - iii. Corticosteroid use

- iv. Advanced age
- v. Poor nutrition
- vi. Sarcoidosis
- i. False-positive skin testing
  - i. Individuals infected with atypical mycobacteria
  - ii. Prior immunization with bacillus Calmette-Guerin (BCG), especially children who develop weak reactions
  - iii. Prior treatment with intra-luminal BCG injections for bladder carcinoma
  - iv. Booster effect TST may become positive if two tests are repeated within a short interval, such as a week. A negative test followed by a positive test in 1 week is considered non-reactive
- 4. Indications for testing
  - a. Center for Disease Control and Prevention (CDC) & American Thoracic Society recommendations for TST testing
    - i. No specific recommendations for testing in uveitis patients, but many recommend that all uveitis patients undergo TB testing
  - b. Any patient who may require systemic immunosuppression for uveitis of other etiologies who has not had testing for tuberculosis as part of their diagnostic evaluation.

#### E. TB testing: Interferon-gamma (IFN-g) assays for latent TB infection

- 1. T-cell based *in vitro* assays that detect interferon-gamma (IFN-g) released by T cells after stimulation by *Mycobacterium tuberculosis* antigens. The principle of the assay is that T cells of individuals previously sensitized with tuberculous antigens will produce interferon-gamma when they re-encounter mycobacterial antigens
  - a. Early assays used PPD as the stimulating antigen
  - b. Newer assays use antigens specific to *M. Tuberculosis*, RD1 antigens. These antigens are not shared with BCG or most nontuberculous Mycobacterium species
- 2. Two IFN-g assays are currently available
  - a. QuantiFERON-TB Gold (Cellestis Ltd., Carnegie, Australia) assay
    - i. Uses whole blood
    - ii. Enzyme-linked immunoabsorbent assay (ELISA)-based test
  - b. T SPOT-TB (Oxford Immunonotec, Oxford, UK)
    - i. Uses peripheral blood mononuclear cells
    - ii. ELISPOT technology
- 3. Current evidence suggests
  - a. IFN-g assays have higher specificity than TST (95-100% vs 70-95%)
  - b. IFN-g assays seem to be at least as sensitive as the PPD-based TST in active TB (80-95%

vs 75-90%)

- c. IFN-g assays have less cross-reactivity due to BCG vaccination than the TST
- 4. Recommendation
  - a. United States CDC recommended that the Quanti-FERON-TB Gold assay be used in all circumstances in which the TST is currently used

#### F. Human leukocyte antigen (HLA) testing in uveitis

- 1. Use of HLA testing in uveitis
  - a. No HLA type is sufficiently sensitive or specific to make the diagnosis of any disease
  - b. The results must be considered in the context of the clinical picture

#### 2. HLA-A29

- a. HLA-29 is present in 95-97% of patients with birdshot chorioretinopathy (BCR)
  - i. The relative risk of the presence of HLA-A29 for BCR has been estimated to be over 200, and the sensitivity and specificity over 90%
- b. About 7-9% of Caucasians are HLA-A29+
  - i. Therefore as many as 7-9% of Caucasians with other forms of uveitis that are not class I HLA associated may be expected to be HLA-A29 +
  - ii. HLA-A29 + individuals with sarcoidosis with a picture mimicking BCR have been reported
- 3. HLA-B27
  - a. HLA-B27 is present in 50-75% of Caucasian individuals with unilateral acute anterior uveitis (See Acute anterior uveitis)
    - i. Other clinical pictures, including chronic anterior uveitis, bilateral anterior uveitis and vitritis may be seen in HLA-B27 + individuals, but less commonly
  - b. About 7-9% of the Caucasian population is HLA-B27+
    - i. Therefore as many as 7-9% of Caucasians with other forms of uveitis that are not class I HLA associated may be expected to be HLA-B27+.
  - c. The relative risk for AAU in HLA-B27 + individuals has been estimated to be 10
  - d. The association of AAU with ankylosing spondylitis and reactive arthropathies may be higher in HLA-B27 + individuals with AAU than HLA-B27 individuals with AAU
  - e. AAU may be more severe in HLA-B27+ individuals than in HLA-B27- individuals with AAU
- 4. Other HLA Associations
  - a. HLA-B51 in Behçet disease (See Behçet disease)
    - i. Relative risk only about 5; the diagnosis should be made on clinical grounds

#### G. Urine $\beta$ -2 microglobulin

1. Used for screening patients with bilateral acute anterior uveitis

- 2. Elevated in up to 60% of patients with tubulointerstitial nephritis and uveitis syndrome (TINU)
- 3. Confirmatory biopsy necessary to make diagnosis of TINU

#### H. Antinuclear antibodies (ANA) testing in uveitis

- 1. Definition
  - a. ANAs: antibodies detectable in blood that have the capability of binding to certain structures within the nucleus of cells
  - b. ANAs are found in multiple autoimmune diseases and indicate possible presence of autoimmunity
- 2. Design of the ANA Test and its indications
  - a. Fluorescence techniques are frequently used to actually detect the antibodies in the cells, thus ANA testing is sometimes referred to as fluorescent antinuclear antibody test (FANA)
  - b. ANAs can be found in patients with a number of different autoimmune diseases
    - i. Systemic lupus erythematosus
    - ii. Sjögren syndrome
    - iii. Rheumatoid arthritis
    - iv. Polymyositis
    - v. Scleroderma
    - vi. Hashimoto thyroiditis
  - c. ANAs can also be found in patients with conditions that are not considered "classic" autoimmune diseases, such as chronic infections, cancer, and medications
  - d. The presence of ANA alone should not be used to establish a specific disease diagnosis
- 3. Implications of the presence of ANA
  - a. Patterns of ANA fluorescence: certain conditions can more frequently be associated with one pattern or another
  - b. ANAs can be found in approximately 5% of the normal population, usually in low titers. These persons usually have no disease
    - i. Titers of lower than 1:80 are less likely to be significant
    - ii. ANA titers of less than or equal to 1:40 are considered negative
    - iii. Even higher titers are often insignificant in patients > 60 years of age
  - c. ANA result must be interpreted in the specific context of an individual patient's symptoms and other test results. It may or may not be significant in a given individual
- 4. ANA testing in ocular inflammatory disease
  - a. Screening all patients with uveitis for ANA would result in approximately 100 false positive results for every one positive test in an individual with SLE. Therefore, to increase pretest likelihood of diagnosing a condition (e.g. SLE), disease-specific testing should be performed only in those in whom the clinical suspicion is high

- i. E.g., chronic iridocyclitis in a child with juvenile idiopathic arthritis (JIA) (See Juvenile idiopathic arthritis)
- ii. Retinal vasculitis (SLE) (See Systemic vasculitis intraocular manifestations)
- iii. Scleritis (See Scleritis associated with systemic autoimmune diseases)

#### I. Antineutrophil cytoplasmic autoantibody (ANCA)

- 1. Introduction
  - a. ANCA tests are most valuable when selectively ordered in clinical situations where some form of ANCA-associated vasculitis is a serious consideration
  - b. ANCA should not be used a screening test (i.e. if clinical suspicion is low)
  - c. Three patterns of neutrophil staining possible
    - i. c-ANCA: cytoplasmic staining
    - ii. p-ANCA: perinuclear staining
    - iii. Atypical patterns
- 2. Association with ANCA and active vasculitis
  - a. Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) 70-80% have positive c-ANCA, <10% have positive p-ANCA
  - b. Polyarteritis nodosa 60% have positive p-ANCA, 30% have positive c-ANCA
  - c. Microscopic polyangiitis c-ANCA or p-ANCA may be positive
  - d. Churg-Strauss syndrome 50-80% have positive p-ANCA, c-ANCA rarely positive
  - e. Idiopathic pauci-immune necrotizing vasculitis 50-80% have positive p-ANCA, c-ANCA rarely positive
- 3. ANCA detection methods
  - a. ANCA reacts with neutrophil cytoplasmic antigens that were previously shielded
  - b. Detection methods
    - i. Indirect immunofluorescence microscopy (IFM) is the most sensitive widely used method for ANCA detection
  - c. C-ANCA: characterized by finely granular staining of neutrophil cytoplasm with central accentuation between the nuclear lobes
    - i. Antigenic specificity of c-ANCA has been identified as a 29 kDA neutral serine protease, proteinase 3 (PR-3)
  - d. P-ANCA: characterized by staining of the perinuclear area
    - i. Autoantibodies against myeloperoxidase (MPO-ANCA)
- 4. Interpretation
  - a. ANCA tests should not be used as a screening test in non-selected patient groups (i.e. when no scleritis or vasculitis)

- b. ANCA tests are valuable when ordered in clinical situations when some form of ANCA-associated vasculitis is a serious consideration
- c. ANCA may be negative in patients with associated disease, particularly in patients on prednisone or other systemic anti-inflammatory agents
- d. C-ANCA in granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) is considered highly sensitive in signaling active systemic disease
- e. P-ANCA on IFM is nonspecific and needs to be tested in ELISA for MPO-ANCA
- f. Rise in ANCA titer is considered a risk factor for a flare but medications should not be adjusted based on this test
- g. Treatment decisions should not be based on only a positive or a negative ANCA
- 5. Indications for ANCA testing in ocular inflammatory disease
  - a. Scleritis especially necrotizing scleritis
  - b. Peripheral ulcerative keratitis
  - c. Retinal vasculitis

#### J. Serum angiotensin converting enzyme (ACE) level

- 1. Indications
  - a. Suspected underlying systemic sarcoidosis
  - b. Any anterior, intermediate, posterior or panuveitis that necessitates work-up
- 2. ACE detections methods
  - a. Serum ACE activity is measured by kinetic spectrophotometry of furylacryloyl-phenylalanylglycyl-glycine hydrolysis
- 3. Interpretation
  - a. Sensitivity 70%
  - b. Specificity 80%
    - i. Higher if
      - i) ACE levels are >2SD above mean
      - ii) Combined with chest radiograph or chest CT
  - c. Predictive value is low less than 50% (even if values are high)
  - d. Usefulness of ACE is improved with chest radiograph, chest CT, and positive gallium scan
  - e. Gold standard for diagnosis of sarcoidosis tissue biopsy
- 4. False negatives common
  - a. ACE activity inhibited by Anti-hypertensive ACE inhibitors
  - b. Hyperthyroidism
  - c. Cystic fibrosis

- d. COPD
- e. Systemic corticosteroids
- f. Lung cancer
- g. Hyperlipidemia
- 5. False positives
  - a. Tuberculosis
  - b. Leprosy
  - c. Hyperthyroidism
  - d. Pulmonary histoplasmosis
  - e. Alcoholic cirrhosis
  - f. Diabetes mellitus

#### K. HIV testing

- 1. Serologic tests divided into screening assays and confirmatory tests
  - a. Screening assays
    - i. Enzyme-linked immunoabsorbent assay (ELISA) tests
    - ii. Results considered reactive or nonreactive
  - b. Confirmatory tests
    - i. Western blot or immunofluorescence assays
    - ii. Results are termed positive, negative or indeterminate
  - c. U.S. Preventive Services Task Force currently recommends screening the following patients:
    - i. One of more individual risk factors
      - i) Men having sex with men
      - ii) Men and women having unprotected sex with multiple partners
      - iii) Past or present injection drug users
      - iv) Men and women who exchange sex for money or drugs or have sex partners who do
      - v) Persons whose past or present sex partners were human immunodeficiency virus (HIV)-infected, bisexual, or injection drug users
      - vi) Persons with a history of blood transfusion between 1978 and 1985
      - vii) Persons who request an HIV test despite reporting no individual risk factors
      - viii) People who report no individual risk factors but are seen in high-risk or high-prevalence clinical settings
    - ii. Ophthalmologists should strongly consider testing patients if an HIV-associated

diagnosis is suspected -

- i) CMV retinitis
- ii) Atypical or extensive toxoplasma retinochoroiditis
- iii) Some forms of necrotizing herpetic retinitis
- iv) Infectious multifocal choroiditis
- v) Syphilis
- vi) (See Ocular manifestations of acquired immune deficiency syndrome)
- iii. Pre and post-test counseling is mandatory
- iv. Syphilis Serology should be obtained if HIV suspected
- v. Informed consent mandatory
- vi. Occasionally T-cell subsets may be performed if a person presents with possible CMV retinitis and HIV is suspected if social situation warrants
- 2. Screening test
  - a. ELISA test
    - i. Most sensitive test for HIV infection (> 99.5% sensitive)
    - ii. False positives may be significant (1-10%)
    - iii. Positive tests are confirmed with a more specific test (W) -ELISA captures HIV antibody using immobilized HIV antigens
    - iv. Detecting HIV infection during the HIV-1 seroconversion period
      - i) During window period (period between exposure and seroconversion), the antibody levels may be below the limit of detection
      - ii) Newer generation ELISA tests have combined the standard test with a p24 antigen detection assay
      - iii) This improves detection of viral antigen (p24) during early virus infection
  - b. Western blot confirmatory
    - i. Specific method to detect the presence of serologic reactivity to individual viral antigens
    - ii. Specificity > 99%
    - iii. Gold standard confirmatory test for HIV infection

#### L. Chest imaging in uveitis: chest radiograph

- 1. Indications
  - a. Tuberculosis suspect
  - b. Sarcoidosis suspect 90% sensitivity in active sarcoidosis
- 2. List the alternatives to this procedure

- a. Computed tomography (CT) scan higher sensitivity in inactive sarcoidosis and in Caucasian women over 50 years of age
- 3. Describe the considerations in interpretation of this diagnostic procedure
  - a. Tuberculosis
    - i. Multinodular infiltrates and cavitation in one or both upper lobes of the lungs
    - ii. Multiple infiltrates are suggestive of tuberculosis.
    - iii. Pleural effusion
  - b. Sarcoidosis
    - i. Bilateral hilar adenopathy
    - ii. Right paratracheal adenopathy
    - iii. Symmetrical diffuse ground-glass appearance, fine reticular or miliary lesions, large nodular lesions, or multiple large confluent infiltrates
    - iv. Pulmonary fibrosis may produce contraction and distortion

#### M. Chest imaging in uveitis: chest computed tomography (CT)

- 1. Indications
  - a. High resolution contrast CT scans provide improved anatomic lung detail and are more sensitive than plain chest radiographs in delineating parenchymal, mediastinal, and hilar structures
  - b. Sarcoidosis. May be useful in making diagnosis of sarcoidosis in patient with normal or non-diagnostic chest x-ray, especially if sarcoid pulmonary disease is inactive, and the clinical suspicion, based on ocular findings, is high
  - c. Tuberculosis
- 2. Describe the pre-procedure evaluation
  - a. Check blood urea nitrogen level (BUN), creatinine prior to contrast
- 3. List the alternatives to this procedure
  - a. Chest x-ray (less sensitive)
- 4. Describe the considerations in interpretation of this diagnostic procedure
  - a. Sarcoidosis
    - i. It can show parenchymal infiltrates, mediastinal or hilar adenopathy
    - ii. Enlarged lymph nodes are often observed in paratracheal, pretracheal, para-aortic, internal mammary, subcarinal, or axillary regions, which are not appreciated on chest radiographs
  - b. Tuberculosis
    - i. Active pulmonary tuberculosis
      - i) Centrilobular nodules and branching linear structures (tree-in-bud appearance)

- ii) Lobular consolidation
- iii) Cavitation
- iv) Bronchial wall thickening
- ii. Inactive pulmonary tuberculosis
  - i) Calcified nodules or consolidation
  - ii) Irregular linear opacity
  - iii) Parenchymal bands
  - iv) Pericicatricial emphysema

#### N. Nuclear medicine and positron emission tomography

- 1. Nuclear medicine
  - a. Gallium scan for sarcoidosis may be considered Low sensitivity and specificity
  - b. May demonstrate uptake in the lacrimal and salivary glands and variably in lungs if granulomatous inflammation present
  - c. Rarely performed and expensive
- 2. Positron emission computed tomography PET scan
  - a. PET scan using 18F labeled fluorodeoxyglucose for suspected sarcoidosis
    - i. Functional imaging modality
    - ii. Based on increased glucose metabolism in metabolically active sites of sarcoid inflammation
    - iii. Useful in the diagnosis of pulmonary and extrapulmonary sarcoidosis
      - i) Even when anatomic radiographic studies such as CT scans appear normal
  - b. Expensive and not widely available
    - i. Does not typically alter therapy

#### O. Examination of intraocular fluids

- 1. PCR
  - a. A false negative result may occur. Many commercial laboratories are not experienced in handling specimens, and PCR primers are not available or standardized for all infectious agents
  - b. A false positive result may occur. PCR is very sensitive and if the sensitivity of the standards is too low, any contamination or viral DNA from leukocytes may be recovered.
  - c. PCR can be done to identify the following
    - i. HSV I&II, VZV, CMV, EBV
    - ii. Toxoplasma gondii
    - iii. Mycobacterium tuberculosis (65 kDA sAg )

- iv. Borrelia burgdorferi (41 kda flagellin gene )
- v. Propionibacterium (Pa1, rPa2, rPa3 antigens)
- vi. Fungi (28S rRNA gene)
- vii. Tropheryma whipplei and other bacteria (16S rRNA gene)
- viii. Intraocular lymphoma (IgH gene)
- 2. Cultures
  - a. Culture vitreous or anterior chamber fluid specimens to culture plates or culture tubes directly when possible
  - b. Check with the laboratory that will do the cultures for their preferred media
  - c. Separate media may be required for aerobic, anaerobic and acid fast bacilli, as well as for fungal and viral organisms
  - d. Prompt transport to the laboratory is critical
  - e. Give sufficient time for cultures of slow growing or fastidious organisms; these may take longer to incubate
- 3. Cytology
  - a. It is very important to get a sufficient specimen
  - b. It is very important that the specimen is handled properly. Consult with the pathologist (who may want to be there when the specimen is obtained)
  - c. False negatives can occur if insufficient material, material not handled properly or preparation delayed, or if treatment has altered the cellular material

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular and Inflammation and Uveitis, 2013-2014.
- 2. Nahid P, Pai M, Hopewell P. Advances in the Diagnosis and Treatment of Tuberculosis. Proc Am Thorac Soc 2006;3:103-110.
- 3. Guidelines for Using the QuantiFERON-TB Gold Test for Detecting Mycobacterium tuberculosis infection. MMWR 2005 December 16.
- 4. McPherson and Pincus. Henry's Clinical Diagnosis and Management by Laboratory Methods. 21st ed. W.B. Saunders Company; 2006.
- 5. Mandell, Bennett & Dolin. Principles and Practice of Infectious Diseases. 6th ed. Churchill Livingstone (Elsevier); 2005.
- U. S. Preventive Services Task Force. "Screening for HIV: Recommendation Statement." American Academy of Family Physicians, 2005.
- Branson BM, Handsfield HH, Lampe MA, et al; Centers for Disease Control and Prevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006 Sep 22;55(RR-14):1-17.

- Bénéteau-Burnat B, Baudin B. Angiotensin-converting enzyme: clinical applications and laboratory investigations on serum and other biological fluids. Crit Rev Clin Lab Sci. 1991;28(5-6):337-56.Lynch DA, Webb WR, Gamsu G, et al. Computed tomography in pulmonary sarcoidosis. J Comput Assist Tomogr 1989;13:405-410.
- 9. Lee, J. Y., K. S. Lee, et al. Pulmonary tuberculosis: CT and pathologic correlation. J Comput Assist Tomogr 2000;24:691-8.
- 10. Kaiser PK, Lowder CY, et al. (2002). Chest computerized tomography in the evaluation of uveitis in elderly women. Am J Ophthalmol 2002;133:499.

# Optical coherence tomography (OCT) - in uveitis

# I. Underlying physical principles

- A. Interferometric technique- reflected light is analyzed to produce a cross section of tissue
- B. Requires optically clear media (different from ultrasonography)
- C. Provides real-time, in situ, "optical biopsy"
- D. Resolution depends on equipment
  - 1. Time-domain OCT ~ 18  $\mu$ m
  - 2. Spectral-domain OCT ~ 8 μm
  - 3. Ultra high resolution OCT ~ 2  $\mu$ m

# II. List the indications/contraindications

### A. Indications

- 1. Macular diseases OCT may be of value in the evaluation of
  - a. Uveitic macular edema
  - b. Vitreoretinal interface disorders such as
    - i. Macular edema
      - i) Vitreomacular traction syndrome
    - ii. Macular hole
    - iii. Epiretinal membrane
  - c. Chorioretinitis
    - i. White dot syndrome
    - ii. Toxoplasmosis
  - d. Macular atrophy
  - e. Atrophy of retinal pigment epithelium (RPE)
  - f. Subretinal fluid
    - i. Central serous chorioretinopathy (CSCR)
    - ii. Vogt Koyanagi Harada (VKH) (fluid, septae)
    - iii. Choroidal neovascular membranes
      - i) Assess treatment

- iv. Macular granuloma
- g. Choroidal/retinal folds
  - i. VKH
  - ii. Posterior scleritis
  - iii. Sarcoidosis
  - iv. Sympathetic ophthalmia
- 2. Optic nerve diseases OCT may be of value in
  - a. Glaucomatous optic neuropathy
  - b. Optic atrophy
  - c. Optic nerve pits
- 3. Choroidal disease using "enhanced depth imaging"
  - a. VKH and SO- loss of focal hyperreflectivity of inner choroid
  - b. Posterior scleritis choroidal thickening
  - c. Anterior segment OCT

#### B. Contraindications

1. No absolute contraindications, but cloudy media, poor pupil dilation and poor co-operation may limit usefulness of test

#### C. OCT clinical utilities in uveitis

- 1. Explanation of reduced visual acuity
  - a. Macular edema
  - b. Macular atrophy
  - c. Epiretinal membrane
  - d. Macular hole
  - e. Subtle subretinal fluid
  - f. Optic atrophy
  - g. Glaucoma
- 2. Assessment of response to treatment of macular edema (uveitic, cystoid), macular granuloma, choroidal neovascularization, or serous retinal detachments (VKH, sympathetic ophthalmia)

# III. Describe the pre-procedure evaluation

- A. Explain procedure
- B. Pupillary dilation required for optimal imaging
  - 1. A scan can be obtained through undilated pupils, but the resulting image may lack clarity or be

truncated

- C. Media clarity required for optimal imaging
  - 1. A scan obtained through hazy media may be of poor quality

### D. Adequate patient fixation is required

1. Poor patient cooperation may limit the scan quality

# IV. List the alternatives to this procedure

- A. Macular contact lens examination at the slit-lamp
- B. Fluorescein angiography
- C. Indocyanine green angiography
- D. Confocal scanning laser ophthalmoscopy
- E. B-scan for choroidal thickening

# V. Describe the technique

- A. Dilate the pupils
- B. Comfortably position the patient in front of the machine; properly align the scanning module
- C. Optimize the scan image
- D. Select the scan acquisition protocol
- E. Select the scan analysis protocol
- F. Archive and/or print the scan results

# VI. Describe considerations in interpretation of this procedure

#### A. Acquisition of a good quality OCT scan

- 1. Adequate pupillary dilation may be problematic if posterior synechiae present
- 2. Clear ocular media problematic if corneal, lenticular, or vitreous opacities
- 3. Steady patient fixation problematic if poor vision
- 4. Proper scanning module alignment
- 5. Appropriate scan image optimization

#### B. Accurate OCT scan interpretation - qualitative information

- 1. Identification of morphological changes in tissue layers atrophy, thickening, distortion
- 2. Interpretation of changes in the relative reflectivity of tissue layers hyporeflectivity, hyperreflectivity
- 3. Correct identification of common artifacts

#### C. Accurate OCT scan interpretation - quantitative information

- 1. Retinal thickness/volume measurement
- 2. Retinal thickness map
- 3. Retinal nerve fiber layer thickness/volume measurement
- 4. Retinal nerve fiber layer thickness map
- 5. Serial analysis

#### D. Disease specific findings

- 1. Uveitic macular edema
  - a. Focal rare pattern
  - b. Diffuse Poor correlation of central thickness to vision
  - c. Cystoid Good correlation of central thickness to vision
  - d. Cystoid with serous retinal detachment
    - i. Intermediate correlation with vision
    - ii. Presence of serous detachment does not correlate with visual recovery
  - e. Used to quantitatively follow treatment efficacy
- 2. White dot syndromes (Inflammatory chorioretinopathies of unknown etiology)
  - a. Loss of the Inner segment outer segment band common to most inflammatory chorioretinopathies
  - b. Multifocal choroiditis and panuveitis
    - i. Transretinal reflectivity of active lesions
  - c. Serpiginous choroiditis
    - i. Hyper-reflectivity of outer retina
    - ii. "Waterfall effect" in choriocapillaris due to lymphocytic infiltration of choroid and choriocapillaris
- 3. VKH syndrome and sympathetic ophthalmia
  - a. Acute phase
    - i. Hypo reflective collections of subretinal and occasionally intraretinal fluid
    - ii. Serous retinal detachments with fibrin bridges
      - i) Can be used to quantitatively follow treatment efficacy
    - iii. Disruption of photoreceptor outer segments
  - b. Chronic phase
    - i. Retinal disorganization and thinning atrophy
- 4. Vitreomacular traction (VMT) syndrome usually found in idiopathic panuveitis

- a. Focal versus broad based hyaloidal traction on fovea
- b. Results in tractional macular edema

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 12: Retina and Vitreous, 2013-2014.
- 2. Carl Zeiss Ophthalmic Systems, Inc. Optical Coherence Tomographer Model 3000, User manual. Germany, 2002.
- 3. Schuman JS, Puliafito CA, Fujimoto JG. Optical Coherence Tomography of Ocular Disease. 2nd ed. Slack Incorporated; 2004.
- 4. Massin P, Girach A, Erginay A, et al. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. Acta Ophthalmol Scand 2006;84:466-474.
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- 7. Tran THC, deSmet MD, Bodaghi B, Fardeau C, Cassoux N, Lehoang P. Uveitic macular oedema: correlation between optical coherence tomography patterns with visual acuity and fluorescein angiography. Br J Ophthalmol. 2008;92(7):922-7.

# Posterior segment angiography: fluorescein angiography (FA)

# I. List indications and contraindications

#### A. Indications

- 1. Choroidal neovascularization
- 2. Retinal neovascularization
- 3. Chorioretinal inflammatory conditions
- 4. Subretinal fluid accumulation
- 5. Retinal perfusion abnormalities
- 6. Macular edema
- 7. Other retinal vascular leakage, such as retinal vasculitis

#### B. Contraindications (relative)

- 1. Prior urticarial reaction (1%) increases the risk of a similar reaction
- 2. Pregnancy (although teratogenic effects have not been identified)

# II. Describe the pre-procedure evaluation

A. Fundoscopic examination to establish a correct indication

# III. List the alternatives to this procedure

- A. Optic coherence tomography (OCT) in some diseases (cystoid macular edema, epiretinal membranes, choroidal neovascularization, macular atrophy)
  - 1. Discrepancies exist between OCT and FA
- B. Indocyanine green angiography (ICG) in select conditions such as birdshot chorioretinopathy and multifocal evanescent white dot syndrome as an adjunct procedure to view the choroid. (See Posterior segment angiography: indocyanine green angiography (ICG))
- C. Autofluoresence photography

# IV. Describe the instrumentation and technique

- A. Pupillary dilation
- B. Intravenous dye injection (5 cc of a 10% solution in adults followed by a flush of saline)
- C. Oral administration of fluorescein (mixed with orange juice or chocolate milk) for those without vein access
- D. Start timer with dye injection and measure arm to eye time and monitor transit phase in eye of
greater clinical interest

- E. Capture photographs at frequent intervals immediately following the injection of the dye until the dye disappears form the blood vessels (late phases, typically > 10 minutes after injection)
- F. Consider late photos of periphery to scan for peripheral choroiditis and vasculitis

# V. List the complications of the procedure, their prevention and management

- A. Nausea, vomiting or vasovagal reactions: 10% of injections
- B. Severe vasovagal reactions: bradycardia, hypotension, shock, and syncope: rare
- C. Extravasation of dye with subcutaneous granuloma, local tissue necrosis
- D. Urticarial reactions (1%)
- E. Anaphylactic reactions (cardiovascular shock): less than 1 in 100000 injections
- F. Death extremely rare usually due to anaphylactic shock or MI

# VI. Describe the considerations in interpretation of this diagnostic procedure

- A. Capillary non-perfusion must scan periphery occlusive retinal vasculitis
- B. Optic nerve head leakage indicative of active uveitis
- C. Petaloid pattern of leakage in macula Cystoid macular edema
- D. Retinal vascular staining must scan periphery retinal vasculitis, birdshot retinochoroiditis
- E. Multiple pinpoint areas of leakage: marked increase in fluorescence through the study with greatest intensity in the late phases VKH, sympathetic ophthalmia, posterior scleritis
- F. Early hypofluorescence and late hyperfluorescence of multiple lesions seen in APMPPE, active areas of choroiditis
- G. Early hyperfluorescence and diffuse leakage associated with retinal neovascularization (NVD, NVE) must scan periphery with attention to junction of nonperfused retina
- H. Early hyperfluorescence with late leakage associated with choroidal neovascularization ( commonly seen in POHS, MCP, PIC, SFU)

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Ophthalmology Monograph 5. Fluorescein angiography: technique and interpretation. Berkow J, Orth DH, Kelley JS.

# Posterior segment angiography: indocyanine green angiography (ICG)

# I. List indications and contraindications

# A. Indications

- 1. Choroidal neovascularization blocked by pigment, blood, fluid or lipid
- 2. Choroidal inflammatory conditions
  - a. Serpiginous choroidopathy
  - b. Birdshot retinochoroidopathy
  - c. Acute multifocal placoid pigment epitheliopathy
  - d. Multiple evanescent white dot syndrome
  - e. Multifocal choroiditis
    - i. Multifocal choroiditis and panuveitis (MCP)
    - ii. Punctate inner choroidopathy (PIC)
  - f. Vogt Koyanagi Harada syndrome
  - g. Sympathetic ophthalmia

# B. Contraindications (relative)

1. Allergies to iodides and shellfish (ICG contains 5% iodide)

# II. Describe the pre-procedure evaluation

A. Funduscopic examination to establish a correct indication

# III. List the alternatives to this procedure

- A. Biomicroscopic examination of fundus
- B. Optic coherence tomography
- C. Fluorescein angiography

# IV. Describe the instrumentation and technique

- A. Pupillary dilation
- B. Intravenous dye injection (25 mg of ICG dissolved in 5 ml solvent)
- C. ICG fluoresces in the near-infrared range. It can be detected with specialized infrared video

# V. List the complications of the procedure, their prevention and management

- A. Nausea and vomiting are rare (less than 1%)
- B. Anaphylaxis (very rare)

# VI. Describe the considerations in interpretation of this diagnostic procedure

#### A. Choroidal neovascularization: is seen as a focal "hot spot", plaque, or combination of both

- B. Serpiginous choroiditis
  - 1. Hypofluorescence throughout the study
  - 2. Better seen than clinically or on fluorescein angiography
  - 3. Due to
    - a. Choroidal perfusion abnormalities
    - b. Blockage by inflammatory exudative material
    - c. Edema of the retinal pigment epithelium (RPE) and outer retina

# C. Acute multifocal placoid pigment epitheliopathy (APMPPE):

- 1. Hypofluorescent in both early and late phase of the study
- 2. Due to a partial choroidal vascular occlusive vasculitis

#### D. Multiple evanescent white dot syndrome (MEWDS)

- 1. Hypofluorescent spots throughout the posterior pole and peripheral retina
  - a. Appear about 10 minutes after dye injection and persist throughout the remainder of the study
  - b. Abnormality in choroidal circulation
- 2. Larger and greater in number than the white dots seen clinically

#### E. Birdshot retinochoroidopathy

- 1. Multiple hypofluorescent lesions
- 2. Correspond to the clinical creamy lesions
- 3. May help in diagnosis when spots not visible clinically

#### F. Multifocal choroiditis

1. Active and inactive atrophic lesions block fluorescence

#### G. Vogt Koyanagi Harada Syndrome

- 1. Delay in choroidal perfusion
- 2. Multiple hypofluorescent spots (foci of lymphocytic infiltration)

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Hope-Ross M, Yannuzzi LA, et al. Adverse reactions due to indocyanine green. Ophthalmology 1994;101(3):529-33.
- 3. Ryan. Chorioretinal Inflammatory Diseases. Mosby (online book).

# Conjunctival biopsy/pathology

# I. List the indications/contraindications

# A. Indications

- 1. Granulomatous disease sarcoidosis
- 2. Mucosa-associated lymphatic tissue (MALT) tumor/Conjunctival tumor (masquerading as follicular conjunctivitis or granulomatous disease)
  - a. Conjunctival lymphoma
  - b. Kaposi sarcoma
  - c. Molluscum contagiosum
- 3. Acquired immune deficiency syndrome (AIDS) related disease
- 4. Ocular mucous membrane pemphigoid
- 5. Differentiation of conjunctival sebaceous cell carcinoma from an inflammatory lesion
- 6. Exclude other infectious etiologies

# B. Contraindications

- 1. Prior history of ligneous conjunctivitis
- 2. Evident, active conjunctival infection

# II. Describe the pre-procedure evaluation

# A. In suspected sarcoidosis

- 1. Search for skin lesions consistent with sarcoidosis that might give a higher diagnostic yield
- 2. Purified protein derivative (PPD) or interferon gamma release assay (IGRA) for tuberculosis
- 3. Chest x-ray or chest computed tomography (CT) scan to evaluate for pulmonary involvement
- 4. Serum angiotensin converting enzyme (ACE) and lysozyme levels as well as gallium scan have low sensitivity and specificity
- 5. Avoid topical corticosteroids prior to biopsy, as nodules will dissolve
- B. Evaluation for systemic lymphoma in suspected conjunctival lymphoma
- C. Bartonella henselae Immunoglobulin (Ig)G and IgM in suspected cat scratch disease
- D. Evaluation for additional sites of mucous membrane pemphigoid.

# III. List the alternatives to this procedure

A. Suspected sarcoid

1. Biopsy of other involved tissue such as skin, lung, parotid or lacrimal or minor salivary gland

#### B. Mucous membrane pemphigoid

- 1. Conjunctival biopsy may cause exacerbation of disease
- 2. Consider oral biopsy or skin biopsy

# IV. Describe the instrumentation and technique

- A. Identify an appropriate lesion potentially consistent with conjunctival sarcoid (blind biopsy of conjunctiva has very low diagnostic yield communication with examining pathologist essential to ensure thorough tissue evaluation and increase yield)
- B. Excisional biopsy preferred (incisional biopsy reserved for large lesions)
- C. Gentle handling of tissue to prevent crush artifact
- D. Place specimen flat (to avoid rolling of conjunctiva) on a substance like filter paper
- E. Light microscopy pathology studies (formalin-fixed tissue)
  - 1. Hematoxylin and eosin
  - 2. Periodic Acid Schiff
  - 3. Acid-fast bacillus & fungal staining
- F. Examination of the section under polarized light microscope in granulomatous disease to rule out other causes, since sarcoid is a diagnosis of exclusion
  - 1. Warthin-Starry staining to rule-out cat-scratch (*Bartonella henselae*) disease
- G. Immunohistochemistry, cytology and flow cytometry (fresh tissue) in suspected lymphoma
- H. Immunofluorescence
- I. Cultures and polymerase chain reaction may be indicated

# V. List the complications of the procedure, their prevention & management

- A. Subconjunctival hemorrhage prevention includes avoiding anti-platelet agents pre-operatively
- B. Symblepharon
- C. Ligneous reaction
- D. Infection sterile technique

# VI. Describe the considerations in interpretation of this diagnostic procedure

#### A. Granulomatous disease

1. Must rule out foreign body, mycobacterium, fungal diseases (as sarcoid is a diagnosis of exclusion)

#### B. Suspected conjunctival lymphoma

1. Need a large enough biopsy of fresh tissue for clonality testing (flow cytometry / cytogenetics)

#### C. Cat scratch disease

- 1. Requires special stain for organism Warthin-Starry
- D. Blind conjunctival biopsies without a visible lesion have a low diagnostic yield

# VII. Describe the follow-up care

#### A. Sarcoidosis

1. Internal medicine or pulmonary consultation

#### B. Conjunctival lymphoma

- 1. Systemic work-up by the oncologist (usually negative)
- 2. Usually followed by local irradiation

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- Shields CL, Shields JA, Carvalho C, Rundle P, Smith AF. Conjunctival lymphoid tumors: clinical analysis of 117 cases and relationship to systemic lymphoma. Ophthalmology. 2001 May;108(5):979-84.

# Diagnostic vitreoretinal procedures in uveitis: vitreous biopsy

# I. List the indications/contraindications

# A. Indications

- 1. Uveitis where neoplastic or infectious disease are suspected (either due to the clinical appearance or to failure to respond to conventional therapy)
  - a. Primary intraocular (CNS) Lymphoma
  - b. Viral infection (Herpes simplex, herpes zoster, cytomegalovirus, Epstein Barr, human herpesvirus-6)
  - c. Toxoplasmosis
  - d. Mycobacterium tuberculosis
  - e. Whipple disease
- 2. Microbiologic evaluation of endophthalmitis

# II. Describe the pre-procedure evaluation

- A. Magnetic resonance imaging (MRI) of the brain and lumbar puncture for cerebrospinal fluid cytology may be done if there is a strong suspicion of central nervous system lymphoma
- B. Other diagnostic evaluations for uveitis if appropriate (e.g., blood cultures for bacteria and fungi, serology for syphilis, chest X-ray)
- C. Preparation for distribution of samples
  - 1. Involve the pathologist before collecting the specimen to be sure of proper specimen handling and delivery
  - 2. Contact laboratory if planning PCR some laboratories will not accept small samples for quantitative PCR

# III. List the alternatives to this procedure

- A. If lymphoma is suspected, lumbar puncture with cerebrospinal fluid cytology, MRI and brain biopsy may be other options
- B. Polymerase chain reaction (PCR) analysis of aqueous humor via paracentesis is a reasonable option in the management of herpetic eye disease

# IV. Describe the instrumentation and technique

A. Standard 3-port pars plana vitrectomy to obtain 1.5 cc to 2.0 cc of undiluted vitreous

- B. Once the pure vitreous aspirate has been obtained, syringe is capped and should be given immediately to the pathologist (who should be informed of the procedure and the differential diagnosis being considered). Undiluted vitreous specimen may be aliquoted for
  - 1. Cytopathology to determine if malignant lymphoma cells are present.
    - a. The cells in these vitreous specimens are particularly susceptible to rapid degradation and death. Thus, immediate processing by a cytopathologist is essential. Choice of tissue culture media should be left to the cytopathologist
    - b. Clear communication must exist between the cytopathologist and ophthalmologist regarding the differential diagnosis being considered
  - 2. Immunohistochemistry and flow cytometry to determine monoclonality and diagnosis of primary intraocular lymphoma
  - 3. Molecular studies for gene rearrangement for diagnosis of lymphoma (IgH gene rearrangement) (must request in advance to be certain that laboratories can perform studies requested)
  - 4. Culture and staining for bacteria and fungi
  - 5. Polymerase chain reaction (PCR) for specific infections (especially HSV1, HSV2, VZV, CMV, and Toxoplasmosis)
- C. Subsequently, pars plana vitrectomy is completed. At the end of the procedure, the vitreous cassette containing diluted vitreous may be sent to be centrifuged for additional flow cytometry, cultures, and PCR studies

# V. List the complications of the procedure, their prevention and management

- A. Vitreous or suprachoroidal hemorrhage
- B. Retinal tear or detachment
- C. Cataract
- D. Endophthalmitis

# VI. Describe the considerations in interpretation of this diagnostic procedure

- A. Recognition of limitations in cytology
- B. Pre-procedure clinical suspicion impacts selection of tests and ultimate diagnostic yield
- C. Decreased diagnostic yield with prior treatment
  - 1. Corticosteroids may be lympholytic to lymphoma cells
  - 2. Antimicrobial or antiviral therapy in infectious cases
- D. Repeat biopsy may be performed if there is sufficient suspicion for particular processes such as primary intraocular lymphoma, and initial biopsy is inconclusive

# VII. Describe the follow-up care

A. If the biopsy reveals lymphoma, refer to oncologist for management

B. If the biopsy reveals infectious agent, the patient should be treated for the infection May require infectious disease expert in cases of systemic infection (i.e. endogenous endophthalmitis)

# VIII. Describe appropriate patient instructions

- A. Emphasize follow-up examinations and care by oncologist for the lymphoma
- B. Procedure may not yield diagnosis in some cases
- C. Procedure may lead to complications and loss of vision

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- Han DP, Wisniewski SR, Kelsey SF, et al. Microbiologic yields and complication rates of vitreous needle aspiration versus mechanized vitreous biopsy in the Endophthalmitis Vitrectomy Study. Retina 1999;19:98-102.
- 3. AAO, Focal Points: Intraocular Lymphoma, Module #12, 2005.

# Diagnostic vitreoretinal procedures in uveitis: chorioretinal biopsy

# I. List the indications/contraindications

# A. Indications

- 1. Intraocular lymphoma mostly confined to the subretinal space
- 2. Site-threatening chorioretinitis of unknown etiology involving one eye or both eyes
  - a. Biopsy is performed in eye with worse visual potential
  - b. Includes cases with an atypical presentation, inconclusive system work up, inadequate response to conventional therapy
  - c. Useful to distinguish between cases of suspected infection or malignancy in which the biopsy has the potential to alter management
- 3. Suspected intraocular malignancy mostly confined to the subretinal space

# B. Contraindications

- 1. Disease in which there is a reasonable expectation that vitreous biopsy would provide sufficient material for cytologic examination
- 2. Chorioretinitis in which there is reasonable expectation that culture, or polymerase chain reaction analysis or antibody determinations of ocular fluid would be sufficient to make the diagnosis
- 3. Possible retinoblastoma in which intraocular biopsy may worsen the systemic prognosis

# II. Describe the pre-procedure evaluation

A. Usually, prior attempt at intraocular diagnosis with analysis of vitreous humor obtained by pars plana vitrectomy (unless subretinal material can be easily obtained by aspiration) or aqueous humor obtained by anterior chamber paracentesis

# B. Systemic evaluations

- 1. Suspected lymphoma
  - a. Magnetic resonance imaging (MRI) of brain
  - b. Lumbar puncture
- 2. Suspected chorioretinitis
  - a. Chest x-ray or computed tomography (CT)
  - b. Blood and urine cultures
  - c. Skin test or tuberculin skin test (TST), interferon-gamma release assay (IGRA), such as QuantiFERON-TB Gold
  - d. Additional testing as appropriate for clinical presentation

#### C. Ocular evaluations

- 1. B-scan ultrasonography to evaluate extent of chorioretinal involvement prior to biopsy
- 2. Subretinal aspirations, retinal biopsy or retinal-choroidal biopsy, *ab interno* 
  - a. Evaluate for surgical site that is easy to access and contains sufficient tissue
    - i. Ideal location
      - i) Outside the arcades, posterior to equator, superior hemisphere (for easier tamponade)
  - b. Create plan for repairing retinal defect (pars plana vitrectomy, endolaser, internal tamponade (long-acting gas, silicone oil in cases of severe retinopathy, possible scleral buckle))
  - c. Preoperative laser to surround site may be useful
  - d. Plan for cautery to blood vessels contained within the biopsy site
  - e. VERY IMPORTANT: Pathologic consultation should be done prior to procedures to discuss biopsy site, proper handling and fixation of tissue, and appropriate evaluation of specimens
- 3. Chorioretinal biopsies, ab externo
  - a. This procedure was performed in the past, but is very rarely done today due to advanced vitreoretinal techniques

# III. List the alternatives to this procedure

- A. Analysis of another involved tissue, such as skin, lung, cerebral spinal fluid, or brain if more appropriate in cases where there are systemic involvements
- B. Analysis of ocular fluid with vitreous biopsy or anterior chamber paracentesis
- C. Analysis of other ocular tissue (e.g., conjunctiva)

# **IV.** Describe the instrumentation and technique

- A. Ab interno subretinal aspiration
- B. Ab interno retinal-choroidal biopsy
- C. Ab externo chorioretinal biopsy
- D. Pathologic examination
  - 1. Histopathology
    - a. Tissue is fixed
    - b. Light and electron microscopy
    - c. Stain for suspected organisms
  - 2. Immunohistochemistry
    - a. Frozen tissue

- b. Polymerase chain reaction (PCR)
- c. Specific stains for lymphoma
- 3. Culture if infection suspected

# V. List the complications of this procedure

- A. Retinal detachment
- B. Cataract
- C. Vitreous hemorrhage
- D. Decreased or lost vision from surgical complications
- E. Choroidal hemorrhage
- F. Subretinal hemorrhage
- G. Infection

# VI. Describe the considerations in interpretation of this diagnostic procedure

- A. Lymphoma cells may be sparse, necrotic and difficult to interpret
  - 1. Patients should be off from therapy with corticosteroids or immunosuppressive medications prior to having biopsy to maximize yield of pathologic cells
- B. Retinal biopsies are often small, difficult to partition and may contain necrotic tissue only
- C. Some eyes will have no acceptable biopsy site
- D. Chorioretinal biopsy can separate during fixation making the relationship of the various layers difficult to interpret
- E. Proper orientation of biopsy specimen should be maintained when submitting to pathology

# VII. Describe the follow-up care

- A. Usual postoperative care for vitreoretinal procedures
- B. Head positioning to tamponade the site of biopsy

# VIII. Describe appropriate patient instructions

- A. Procedure may not lead to diagnosis
- B. Procedure may lead to sight-threatening complications

# Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

2. AAO, Focal Points: Intraocular Lymphoma, Module #12, 2005.

# Acute anterior uveitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of the disease

- 1. Etiology (see differential diagnosis)
  - a. Idiopathic (up to 50% of cases, depending on practice pattern)
  - b. Autoimmune and commonly associated with seronegative (absence of Rf-factor) spondyloarthropathies
  - c. Other causes in differential diagnosis
- 2. Genetic risk factor
  - a. Human leukocyte antigen (HLA)-B27 approx. 8% population + for HLA-B27, only 1/5 will develop arthritis

#### B. Describe the relevant aspects of the epidemiology of the disease

- 1. Peak incidence in young adults but wide age range
- 2. Worldwide
- 3. Male predominance

#### C. List the pertinent elements of the history

- 1. Sudden onset
- 2. Pain, redness, photophobia
- 3. May have decreased vision
- 4. Patterns
  - a. Typically acute, unilateral, recurrent in the same eye or contralateral eye. Periods of disease quiescence off treatment are typically longer duration than episodes of acute disease consider herpes viruses as an etiology
    - i. inquire about cutaneous manifestations of Herpes infections
  - b. Uncommonly, cases may be bilateral, simultaneous
    - i. TINU
    - ii. History of recent infections/pharyngitis

#### D. Describe the pertinent clinical features

- 1. Mild ptosis
- 2. Tearing
- 3. Ciliary flush or bulbar conjunctival injection with quiet palpebral conjunctival surfaces
- 4. Anterior chamber flare and cells

- 5. Fibrinous anterior chamber exudates and hypopyon with severe episodes . HLA B-27 associated uveitis is the most common cause of hypopyon iridocyclitis
- 6. Posterior synechiae are common and often fully resolve with appropriate treatment
- 7. Anterior vitreous cells
- 8. Secondary CME and optic nerve hyperemia common with severe episodes of inflammation
- 9. Intraocular pressure commonly several mm Hg lower in the involved eye

#### E. Describe the appropriate testing and evaluation for establishing the diagnosis

- 1. History review of systems with particular attention to
  - a. Joint pain, redness or swelling. Particularly low-back, occurring at night or on awakening, Hip, knee, heel pain; swelling or deformity of distal digits of hands or feet
  - b. Skin rashes, particularly psoriasis, rash on palms or soles, nail bed abnormalities, genital skin abnormalities
  - c. Mucus membrane lesions of mouth or genitalia
  - d. Episodes of abdominal pain, blood in stool, history of "colitis" or bowel inflammation
  - e. Urinary tract symptoms
  - f. As with all uveitis patients, general health problems, drug ingestion (prescription and otherwise), habits, pets, travel history, occupational history, and review of other systems (particularly neurologic and pulmonary) may be relevant
- 2. Physical examination easily performed components
  - a. Inspection of hands
  - b. Inspection of skin for rashes, hair loss or abnormality
  - c. Spine flexibility
  - d. Inspection for oral lesions
- 3. Laboratory evaluation
  - a. HLA-B27
  - b. FTA-abs or MHATP
  - c. Urinalysis and serum creatinine in acute bilateral cases in young women
  - d. Urine for Beta 2 microglobulin

# II. List the differential diagnosis

- A. Systemic diseases associated with the HLA B-27 genetic marker
  - 1. Ankylosing spondylitis
  - 2. Reactive arthritis (Reiter syndrome)
  - 3. Inflammatory bowel disease

- 4. Psoriatic arthritis
- B. Behçet disease (See Behçet disease)
- C. Sarcoidosis (See Sarcoidosis panuveitis)
- D. Infection
  - 1. Viral
    - a. Herpesvirus family (See Herpetic anterior uveitis)
    - b. Numerous other viral agents
  - 2. Syphilis (See Syphilitic panuveitis)
  - 3. Leptospirosis
  - 4. Endophthalmitis
- E. Post-traumatic iritis

# F. Drug-related uveitis

- 1. Rifabutin
- 2. Cidofovir

# G. Tubulointerstitial nephritis uveitis (TINU)

- 1. Bilateral disease typical
- 2. Abnormal serum creatinine and urinalysis
  - a. Elevated Beta-2 microglobulin levels in Urine and HLA-DR\*101

# III. Describe patient management in terms of treatment and follow-up

# A. Describe medical therapy options for ocular disease

- 1. Topical corticosteroids
- 2. Cycloplegia
- 3. Adjunctive therapy for severe attacks
  - a. Periocular corticosteroid injections
  - b. Oral corticosteroids
  - c. Intravenous pulse corticosteroid
- 4. Immunomodulatory therapy, especially but by no means exclusively in patients with an underlying systemic disease, including use of anti tumor necrosis factor (TNF) alpha agents (See Biologic response modifiers)
- 5. Sulfasalazine prophylaxis for highly frequent recurrent bouts of HLA-B27 related disease

#### B. Describe surgical therapy options

1. Rare patients with 360 degree posterior synechiae and iris bombé may require laser iridotomy, and some, with brown irides, may even require surgical iridectomy

2. Selected patients may require cataract surgery, conducted after eye free of inflammation for at least 3 months

# IV. List the complications of treatment, their prevention and management

# A. Complications of topical corticosteroids

- 1. Elevated intraocular pressure
- 2. Cataracts
- B. Complications of oral steroid
  - 1. (See Corticosteroids)

# C. Complications of immunomodulatory therapy

1. (See Biologic response modifiers)

# V. Describe ocular disease-related complications

# A. Posterior synechiae and pupillary seclusion

- 1. Prophylactic PIs not indicated in absence of bombé
- B. Peripheral anterior synechiae
- C. Glaucoma
- D. Cataracts
- E. Cystoid macular edema
- F. Epiretinal membrane formation

# VI. Describe appropriate patient instructions

- A. Medication instructions
  - 1. Discuss side effects
- B. Follow-up instructions
- C. Discussion of natural history of the disease
- D. Appropriate rheumatologic consultation

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.6.
- 3. D'Alessandro LP, Forester DJ, Rao NA. Anterior uveitis and hypopyon. Am J Ophthalmology; 1991;112:317-321.

- 4. Rodriguez A, Akova YA, Pedroza-Seres M, et al. Posterior segment ocular manifestations in patients with HLA-B27-associated uveitis. Ophthalmology. 1994;101:1267-1274.
- 5. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol 2005; 50:364-88.
- 6. Mackensen F, Billing H. Tubulointerstitial nephritis and uveitis syndrome. <u>Curr Opin Ophthalmol.</u> 2009 Nov;20(6):525-31.

# Lens-associated uveitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Immune reaction to lens material
  - a. Phacoantigenic rupture of the lens capsule
  - b. Phacolytic leakage of lens protein through an intact capsule
    - i. Lens protein and swollen macrophages block the trabecular meshwork

# B. Define the relevant aspects of epidemiology of this disease

- 1. Phacoantigenic
  - a. Rupture of the lens capsule following trauma or surgery
  - b. Retained lens fragments after cataract extraction
- 2. Phacolytic
  - a. Occurs in setting of mature or hypermature cataract

# C. List the pertinent elements of the history

- 1. Phacoantigenic
  - a. History of trauma or intraocular surgery
  - b. Sudden or insidious onset of decreased vision, pain, redness, photophobia
- 2. Phacolytic
  - a. Progressive loss of vision due to gradually worsening cataract
  - b. Sudden or insidious onset of decreased vision, pain, redness, photophobia

# D. Describe pertinent clinical features

- 1. Phacoantigenic
  - a. Anterior uveitis
    - i. Granulomatous or nongranulomatous
    - ii. Mild to severe
    - iii. Keratic precipitates; small, punctate, or mutton-fat
    - iv. Posterior synechiae
    - v. Hypopyon in some
  - b. Retained lens material in anterior chamber possible
  - c. Elevated intraocular pressure
  - d. Vitreous cells often present

- 2. Phacolytic
  - a. Large, refractile cells in the aqueous (lipid containing macrophages)
  - b. Elevated intraocular pressure
  - c. Corneal edema possible
  - d. Lens capsule may appear wrinkled
  - e. Keratic precipitates rare
  - f. Posterior synechiae rare

# E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Phacoantigenic
  - a. History and clinical exam paramount
  - b. B-scan ultrasonography
    - i. Useful if lens material located in vitreous
  - c. Histopathology of lens material
    - i. Zonal granulomatous inflammation centered about the site of injury. Neutrophils with the lens material surrounded by lymphocytes, plasma cells, epithelioid cells, macrophages
- 2. Phacolytic
  - a. Anterior chamber paracentesis may be considered
    - i. Aqueous cytology may reveal swollen macrophages

# II. Define the risk factors

- A. Trauma
- B. Cataract or glaucoma surgery
- C. Advancing age, dense cataract

# III. List the differential diagnosis

- A. Sympathetic ophthalmia
- B. Postoperative endophthalmitis
- C. Traumatic iritis
- D. Anterior uveitis
- E. Intermediate uveitis
- F. Posner-Schlossman syndrome (phacolytic)

# IV. Describe patient management in terms of treatment and follow up

#### A. Describe medical therapy options

- 1. Phacoantigenic
  - a. Corticosteroids
    - i. Topical or regional. Severe cases may require systemic therapy
  - b. Cycloplegics
  - c. Aqueous suppressants to control intraocular pressure
- 2. Phacolytic
  - a. Aqueous suppressants to control intraocular pressure
    - i. Additional topical and/or systemic therapy may be required to lower the intraocular pressure
  - b. Topical corticosteroids

#### B. Describe surgical therapy options

- 1. Phacoantigenic
  - a. Cataract extraction is typically curative and should be performed as soon as possible
  - b. In cases with retained lens material
    - i. Removal of all residual lens material in most cases, consider vitrectomy for cases of lens material in posterior segment
    - ii. Patients with very small amounts of lens material may improve with corticosteroid therapy alone
- 2. Phacolytic
  - a. Cataract extraction as soon as possible

# V. Describe the complications of treatment, their prevention, and management

- A. Medical (See Corticosteroids)
- B. Surgical (See Cataract extraction for uveitis patients)

# VI. Describe disease-related complications

- A. Pupillary membrane
- B. Glaucoma
- C. Corneal edema and decompensation
- D. Cystoid macular edema

# VII. Describe appropriate patient instructions

- A. Use medications as prescribed
- B. Adhere to postoperative instructions
- C. Report changes in vision and/or pain immediately

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Michel SS, Foster CS. Lens-Induced Uveitis. In: Foster CS, Vitale AT, eds. Diagnosis and Treatment of Uveitis. Philadelphia: W.B. Saunders; 2002:817-21.

# Persistent (chronic) iridocyclitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. See differential diagnosis below
- 2. Often idiopathic
- B. List the pertinent elements of the history
  - 1. Onset is usually insidious
  - 2. Duration is at least 3 months
  - 3. Blurred vision
  - 4. Floaters
  - 5. May be asymptomatic
  - 6. Pain, redness and photophobia are rare, although may occur at onset or intermittently

# C. Describe pertinent clinical features

- 1. Keratic precipitates (KP)
  - a. Often medium or large and "mutton fat"
  - b. May be inactive, crenellated "ghost" KP
  - c. Anterior chamber (AC) cell
  - d. AC flare, may be significant, even with few cells
  - e. Anterior vitreous cells
  - f. Iris nodules
  - g. Koeppe
    - i. At pupillary border
    - ii. Not pathognomonic of granulomatous disease
  - h. Busacca
  - i. In iris stroma, pathognomonic of granulomatous disease

#### D. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Detailed history, review of systems is paramount
- 2. Chest x-ray (CXR)
- 3. In adults, consider high resolution computed tomography of chest with and without contrast or similar imaging, such as gallium scanning
- 4. Angiotensin converting enzyme, lysozyme

- a. Not very sensitive or specific for sarcoid, but suggestive of granulomatous disease
- 5. Purified protein derivative (PPD) if appropriate or QuantiFERON testing
- 6. Specific treponemal test, such as fluorescent treponemal antibody absorption test or micro hemagglutination assay Treponema pallidum
- 7. Rest of work-up guided by history/age of patient e.g., antinuclear antibodies looking for juvenile idiopathic arthritis (JIA) in pediatric age group

# II. Define the risk factors

A. Systemic inflammatory disease such as sarcoidosis

# III. List the differential diagnosis

#### A. Local eye disease - e.g.

- 1. Fuchs heterochromic iridocyclitis (See Fuchs heterochromic iridocyclitis)
- 2. Viruses such as herpes simplex, zoster as well as rubella and cytomegalovirus may cause recurrent or chronic anterior uveitis in immunocompetent individuals
- 3. Intermediate or posterior uveitis with anterior segment inflammation

#### B. Associated with systemic disease - e.g.

- 1. Multiple sclerosis
- 2. Sarcoidosis
- 3. Tuberculosis
- 4. Syphilis
- 5. Inflammatory bowel disease
- 6. JIA

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Topical corticosteroids
  - a. Less frequently than for acute disease
  - b. Prednisolone acetate 1% twice a day to 4 times a day
  - c. Check intraocular pressure (IOP) at every visit, even patient with normal IOP for years on topical corticosteroids may develop corticosteroid response and high IOP
- 2. Dilating drops
  - a. May be required indefinitely, especially in patient with posterior synechiae and chronic flare

- b. E.g., homatropine 5% or atropine 1%
- 3. Local injection (off-label use) (See Corticosteroids)
  - a. Corticosteroids
    - i. Anterior Sub-Tenons for anterior chamber reaction
    - ii. Posterior Sub-Tenons for cystoid macular edema (CME)
    - iii. Orbital floor injection for CME
    - iv. Triamcinolone acetonide can be used
    - v. Intravitreal injection triamcinolone acetonide for CME (off-label use)
  - b. Intravitreal injection of anti-VEGF agents (off-label use) for CME
  - c. Watch IOP
- 4. Systemic therapy
  - a. Oral prednisone (See Corticosteroids)
    - Avoid long term; remember that bone metabolism negative effects are seen as early as 3 months of therapy with prednisone as low as 5 mg a day. Baseline DEXA scan for anyone in whom corticosteroid therapy beyond 3 months is anticipated
    - ii. If require more than 5 mg/day prednisone after 3 6 months, consider steroid-sparing immunomodulatory treatment (IMT)
  - b. Corticosteroid-sparing agents (See Corticosteroids)
    - i. Methotrexate
    - ii. Azathioprine
    - iii. Cyclosporine
    - iv. Tacrolimus
    - v. Mycophenolate mofetil
    - vi. TNF inhibitors (not etanercept)
- 5. Internal medicine consultation for systemic disease, if appropriate, e.g., for pulmonary tests, chest X-ray
- B. Describe surgical therapy options (See Cataract extraction for uveitis patients) (See Glaucoma surgery for uveitis patients)

# V. List the complications of treatment, their prevention and management

- A. Topical corticosteroids: cataract, glaucoma, ptosis
- B. Depot corticosteroid injection: as above, plus inadvertent perforation of globe
- C. Systemic therapy (See Corticosteroids)

# VI. Describe disease related complications

- A. Posterior synechiae are frequent
- B. Anterior synechiae (peripheral anterior synechia (PAS))

# C. Ocular hypertension/glaucoma

- 1. Frequent
- 2. Open angle
  - a. Cells and debris in meshwork
  - b. "Corticosteroid response"
- 3. Closed angle
  - a. Progressive PAS
  - b. Pupillary block secondary to posterior synechiae

#### D. Hypotony

- 1. More difficult to treat than glaucoma
- 2. Atrophy of ciliary processes
- 3. Inflammation of ciliary processes
  - a. Treat with anti-inflammatory drugs
- 4. Ciliary body detachment
  - a. Due to cyclitic membranes
  - b. Diagnose with ultrasound biomicroscopy
  - c. May be able to treat surgically
- E. Iris atrophy
- F. Epiretinal membrane
- G. CME
  - 1. Frequent cause of decreased vision
- H. Cataract is frequent, both because of underlying inflammatory disease and corticosteroid use
- I. Band keratopathy
  - 1. Much more common in children

# VII. Describe appropriate patient instructions

- A. Nature of chronic disease, i.e., we may not be able to cure the disease, and patient may not be able to be tapered off of drops
- B. Necessity of using drops even in absence of symptoms
- C. Requirement for follow-up, even in absence of symptoms

1. For example, may develop asymptomatic glaucoma secondary to corticosteroid drops

#### Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

# Juvenile idiopathic arthritis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of the uveitis

1. Usually associated with oligoarticular juvenile idiopathic arthritis (JIA) (previously known as juvenile rheumatoid arthritis - JRA), but may also occur in those children with polyarticular onset form of the disease

#### B. Describe the relevant aspects of the epidemiology of juvenile arthritis

- 1. Systemic onset JIA
  - a. Any number of joints
  - b. Onset <5 years and no sex predilection
  - c. 10 20% cases
  - d. Antinuclear antibodies (ANA) usually negative (10% positive)
  - e. Uveitis is rare
- 2. Polyarticular rheumatoid factor positive
  - a. Older onset than typical JIA patients
  - b. Female predominance
  - c. Behave like adult rheumatoid arthritis
  - d. Uveitis may occur
  - e. May develop scleritis
- 3. Oligoarticular onset JIA most common chronic form of arthritis in children in North America/Europe
  - a. Four or fewer joints (within 6 months of presentation)
  - b. Female: male 5:1
  - c. Onset of age 2-8 years
  - d. 50 60 % of cases
  - e. ANA + in 85%, RF Negative
  - f. Uveitis frequent up to 30% will develop AU in first 4 years of disease
- 4. Polyarticular, rheumatoid factor negative onset JIA
  - a. More than 4 joints
  - b. Female: male 3:1
  - c. Bimodal age of onset <5, teenager

- d. ANA + in 40%
- e. Intermediate risk of uveitis up to 10% will develop AU
- 5. Juvenile human leukocyte antigen (HLA) B27 associated enthesitis
  - a. Recurrent acute iritis, one eye at a time
  - b. More common in boys
- 6. Psoriatic arthritis
  - a. Resembles Oligoarthritis or RF negative Polyarthritis and 2 of the following
    - i. Nail pitting or onycholysis, dactylitis or history of psoriasis in a 1st degree relative
  - b. Up to 10% will develop AU

#### C. List the pertinent elements of the history

- 1. For uveitis associated with pauciarticular JIA
  - a. Asymptomatic
  - b. Painless loss of vision
  - c. For uveitis associated with HLA-B27 (See Acute anterior uveitis)

#### D. Describe the pertinent clinical features of JIA uveitis

- 1. Bilateral
- 2. Non-granulomatous iridocyclitis
- 3. Quiet conjunctiva

#### E. Describe the diagnostic procedures

- 1. ANA
- 2. Rheumatology consult if necessary

# II. Define the risk factors

- A. Oligoarticular onset JIA
- B. Female sex
- C. ANA +
- D. Arthritis onset between 2 and 5 years of age
- E. Highest risk is within 2 years of onset of arthritis
- F. 90% have arthritis first, but uveitis may precede arthritis diagnosis
- G. Describe the factors associated with poorer visual outcome
  - 1. More severe ocular involvement at presentation
  - 2. Longer duration of uveitis
  - 3. Longer delay from onset to employment of steroid-sparing immunomodulatory therapy

- 4. Female sex
- 5. Younger age at onset of uveitis
- 6. Uveitis diagnosis prior to arthritis diagnosis
- 7. Severity of arthritis not related
- 8. Titer of ANA not related

# III. List the differential diagnosis

- A. Sarcoidosis (juvenile onset)
- B. Juvenile reactive arthritis (Reiter syndrome), ankylosing spondylitis, psoriatic arthritis related uveitis
- C. Inflammatory bowel disease associated uveitis
- D. Herpetic uveitis (unilateral)
- E. Lyme disease
- F. Tubulointerstitial nephritis and uveitis

# IV. Describe patient management in terms of treatment and follow-up

#### A. Mild disease

- 1. Topical corticosteroids
- 2. Mydriatics

#### B. Moderate disease severity

- 1. Consider adding periocular corticosteroids
- 2. Consider adding oral non-steroidal anti-inflammatory drugs (NSAIDs)
- 3. Consider corticosteroid-sparing immunomodulatory therapy (IMT) such as methotrexate, azathioprine, cyclosporine

#### C. More severe disease

- 1. Short term oral corticosteroids
- 2. Immunomodulatory therapy (e.g., methotrexate, azathioprine or cyclosporine; in rare instances, chlorambucil)
- 3. Biologic inhibitors
  - a. Anti-tumor necrosis factor agents
    - i. Etanercept little or no help for uveitis though helps joints
    - ii. Both infliximab and adalimumab appear efficacious for the uveitis
  - b. Other biologic inhibitors such as anti-CD20 (rituximab),T-cell activation inhibitors (abatacept)(Daclizumab)

#### D. Ethylene diamine tetra acetate chelation of band keratopathy

#### E. Cataract surgery

- 1. Lensectomy, vitrectomy, no intraocular lens (IOL) is most commonly utilized approach
- 2. Consider phacoemulsification/posterior chamber IOL in selected favorable circumstances, with strict inflammatory control
  - a. Controversial
- 3. Quiet eye for three months pre-op
- 4. Anti-inflammatory coverage
- 5. Cataract surgery is problematic enough that minimization of steroid exposure through the use of systemic steroid-sparing agents is very strongly advocated BEFORE cataract formation begins

# V. List the complications of treatment, their prevention and management

#### A. Topical corticosteroid therapy

- 1. Cataract
- 2. Glaucoma
- 3. Ptosis

#### B. Periocular corticosteroid therapy

- 1. Cataract
- 2. Glaucoma
- 3. Ptosis
- 4. Inadvertent perforation
- C. Systemic corticosteroids and immunosuppressive therapy (See Corticosteroids) (See Methotrexate) (See Cyclosporine)

# VI. Describe disease related complications

- A. Band keratopathy
- B. Posterior synechiae very frequent
- C. Cataract
- D. Glaucoma
- E. Hypotony
- F. Macular edema
- G. Amblyopia

# VII. Describe appropriate patient instructions

#### A. Patients without uveitis but with JIA require screening

- 1. Low risk e.g., systemic onset ANA negative: yearly until 4 years after onset of arthritis at <7 years of age and for 7 years after onset at >7 years of age
- Intermediate risk ANA negative every 6 months until 4 years after onset of arthritis at <7 years and for 7 years after onset at >7 years of age
- 3. High risk ANA positive: every three months for 7 years if onset of arthritis < 7 years and every 6 months for 4 years if onset of arthritis > 7 years; if diagnosed before age 7, screen every 6 months if ANA negative; ANA positive, screen every 3-4 months and if after 4 years no uveitis, then screen every 6 months; if diagnosed at 7 years or greater, screen every 6 months whether ANA negative or positive; after 7 years of screening then ophthalmologic examination should be yearly

# B. Patients with uveitis

- 1. Follow-up based on severity of disease
- 2. Need for treatment even without symptoms
- C. Summary of screening guidelines

# VIII. Describe "chronic iridocyclitis of young girls"

- A. Uveitis resembles that seen in JIA
- B. No joint disease
- C. ANA may be positive or negative
- D. Some of these patients, particularly with positive ANA, may go on to develop bona fide JIA

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# Fuchs heterochromic iridocyclitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Evidence for an association with rubella, cytomegalovirus, Toxoplasmosis, infection
- 2. Heterochromia, abnormal vessels, links to sympathetic disorders, and electron microscope studies suggest theory of decreased adrenergic innervation
- 3. Immunoglobulin deposit in iris vessel walls may be related to formation of disease

# B. List the pertinent elements of the history

- 1. No pain, redness and photophobia
- 2. Often found on routine exam
- 3. Decreased vision, usually caused by cataract
- 4. Floaters

#### C. Describe pertinent clinical features

- 1. Usually unilateral, but bilateral in 7 15%
- 2. Heterochromia
  - a. Not required for diagnosis
  - b. May be hard to discern in dark irides
  - c. Affected eye usually lighter
  - d. Affected eye may be darker late in disease in blue-eyed patient with extensive loss of stroma (increased visibility of posterior iris pigment epithelium)
- 3. Keratic precipitates (KP)
  - a. Small
  - b. Stellate
  - c. Distributed throughout the whole cornea, rather than in Arlt triangle
- 4. Iris atrophy
  - a. Diffuse, involving anterior iris stroma and loss of crypts
  - b. Transillumination defects rare
- 5. Koeppe nodules may be present, but does not form posterior synechiae in absence of surgery
- 6. Anterior chamber cells and flare
- 7. Anterior vitreous cells
- 8. No posterior synechiae (rare exceptions)

- 9. Cataract
  - a. Usually posterior subcapsular cataract
  - b. In approximately 70%
- 10. Elevated intraocular pressure/glaucoma
  - a. Up to 50%
  - b. Open-angle
- 11. Abnormal angle vessels
  - a. Do not grow or fibrose like rubeotic vessels
  - b. Do not cause angle closure
  - c. Amsler sign
    - i. Bleeding after anterior chamber paracentesis (not done as diagnostic test. May be seen, e.g., at time of anterior chamber paracentesis or at cataract surgery)

# II. List the differential diagnosis

- A. Herpetic uveitis
- B. Sarcoid uveitis or other chronic anterior uveitis
- C. Other causes of heterochromia e.g., congenital Horner syndrome, iridocorneal endothelial syndrome, diffuse iris melanoma
- D. Prostaglandin analogue therapy for glaucoma (no stellate KP or vitreous cells)
- E. Syphilis

# III. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Inflammation does not tend to require treatment
- 2. Some patients see better if the keratic precipitates are cleared with topical corticosteroids
- 3. Treatment of glaucoma
  - a. May be resistant to medical therapy
  - b. May require trabeculectomy or shunt procedures
- 4. Treatment for confirmed infectious causes
  - a. Anti-viral
    - i. Ganciclovir
  - b. Antibiotic
    - i. Toxoplasmosis
#### B. Describe surgical therapy options

- 1. Cataract
  - a. Do well with standard phacoemulsification surgery for cataract
  - b. Increased risk of intraoperative or postoperative hyphema (because of abnormal angle vessels)
- 2. Glaucoma
  - a. May require filter or shunt if medical therapy ineffective
- 3. Vitreous opacities
  - a. Pars plana vitrectomy can be visually beneficial

# IV. List the complications of treatment, their prevention and management

- A. Rarely need corticosteroid therapy
- B. Avoid over-treatment
- C. Treat patient symptoms only and not the amount of cells in the eye

#### V. Describe disease related complications

- A. Glaucoma
- B. Cataract
- C. Vitreous opacification

# VI. Describe appropriate patient instructions

A. Need follow-up because of risk for glaucoma

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.4-5.
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# Intermediate uveitis, including pars planitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Pars planitis
  - a. Idiopathic by definition
- 2. Associated with systemic inflammatory or infectious disease
  - a. Multiple sclerosis (MS)
  - b. Sarcoidosis
  - c. Inflammatory bowel disease
  - d. Infections
    - i. Lyme disease
    - ii. Whipple disease (older patient)
    - iii. Rarely primary acquired toxoplasmosis (retinal lesions may present after vitritis)
    - iv. Toxocara
    - v. Syphilis
    - vi. HTLV
    - vii. If dense vitritis must consider other infections with focus of retinitis not seen
  - e. Tubulointerstitial nephritis and uveitis
  - f. Masquerade (central nervous system (CNS) lymphoma)

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Pars planitis
  - a. Disease of children and young adults
  - b. Bimodal age distribution
    - i. 5 15 years
    - ii. 25 35 years

#### C. List the pertinent elements of the history

- 1. Floaters
- 2. Decreased vision
- 3. Pain and photophobia are very rare (more common in young children)
- 4. Onset is usually insidious
- 5. Long duration (chronic)

#### D. Describe pertinent clinical features

- 1. Anterior chamber reaction
  - a. Absent or very mild in adults
  - b. May be more severe in children
- 2. Vitreous cell always present in active disease
- 3. Snowballs
  - a. White or yellowish aggregates of inflammatory cells
    - i. More common inferiorly
- 4. Snowbanks
  - a. Seen in pars planitis
  - b. Pars plana/ora serrata
  - c. Usually inferior, may extend 360 degrees
  - d. Coalesced exudates or in late stages fibroglial mass
  - e. May be vascularized
- 5. Periphlebitis is common
- 6. Periarteritis is not typical of pars planitis
- 7. Pars planitis is bilateral at presentation in 70-80%
- E. Describe appropriate testing and evaluation for establishing the diagnosis
  - 1. MS (history suggestive of MS)
    - a. Neurologic exam
    - b. Magnetic resonance imaging (MRI)
    - c. Human leukocyte antigen (HLA)-DR2
  - 2. Sarcoid
    - a. Chest x-ray and angiotensin converting enzyme/lysozyme
      - i. Low sensitivity and specificity
    - b. If sarcoidosis is considered in an adult patient, high resolution chest CT (or similar imaging) should be considered
  - 3. Lyme disease
    - a. Serology (western blot if ELISA positive or equivocal)
    - b. History suggestive of exposure or Lyme disease
  - 4. Masquerade syndrome (e.g. Lymphoma)
    - a. Diagnostic vitrectomy with cytology and flow cytometry
    - b. MRI of the brain

- c. Lumbar puncture
- 5. Other infections (e.g. Whipple disease, toxoplasmosis, toxocariasis)
  - a. Serologies (e.g. toxoplasmosis IgM and IgG, specific anti-treponemal serology)
  - b. Cultures and PCR of vitreous

# II. List the differential diagnosis

- A. Pars planitis idiopathic
- B. Infections
  - 1. Toxocariasis unilateral, look for granuloma
  - 2. Lyme disease
  - 3. Whipple disease older patient
  - 4. Toxoplasmosis
- C. Sarcoidosis
- D. Intraocular lymphoma older patient
- E. Inflammatory bowel disease
- F. Intermediate uveitis associated with MS

# III. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. May not need therapy, if vision is good and there is no cystoid macular edema
- 2. Offer treatment if there is cystoid macular edema (CME), even if good vision
- 3. Local corticosteroids
  - a. Sub-Tenon corticosteroid injection
  - b. Intravitreal triamcinolone acetonide
  - c. Fluocinolone implant (Retisert®)
  - d. Dexamethasone pellet (Ozurdex®) ()
- 4. Oral corticosteroids
  - a. Avoid long-term high dose
- 5. Corticosteroid sparing agents
  - a. Methotrexate
  - b. Azathioprine
  - c. Cyclosporine

- d. Mycophenolate mofetil
- e. TNF inhibitors; contraindicated if any question of masquerade syndrome, infection or demyelinating disease

#### B. Describe surgical therapy options

- 1. Cryotherapy to snowbank
- 2. Laser application posterior to the snowbank
- 3. Vitrectomy

# IV. List the complications of treatment, their prevention and management

#### A. Cryotherapy

- 1. Increased inflammation
- 2. Increased risk of rhegmatogenous retinal detachments

#### B. Vitrectomy

- 1. Increased risk of cataract
- 2. Increased risk of proliferative vitreoretinopathy
- 3. Increased risk of retinal detachment
- 4. Potentially, increased risk for flare-up in the immediate postoperative period
- C. Periocular/intraocular corticosteroid injection (off-label) or slow release device implantation
  - 1. Cataract
  - 2. Glaucoma
  - 3. Ptosis with periocular injection
  - 4. Perforation with periocular injection-very rare
  - 5. Endophthalmitis with intravitreal injection

# V. Describe disease related complications

#### A. Cystoid macular edema

- 1. Most frequent cause of decreased vision
- B. Vitreous hemorrhage
  - 1. More common in children
  - 2. Usually clears spontaneously

#### C. Optic disc edema is frequent

- D. Neovascularization of the disc
  - 1. Rare
- E. Band keratopathy

- F. Cataract
- G. Glaucoma or hypotony
- H. Epiretinal membrane
- I. Retinal detachment
  - 1. Rhegmatogenous
  - 2. Coats-like reaction
    - a. Rare

## VI. Describe appropriate patient instructions

- A. Chronic nature of the disease
- B. In pars planitis, 2/3 of <u>treated</u> patients maintain visual acuity of 20/40 or better in at least one eye

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Pars Planitis, Module #11, 1993.
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# Acute posterior multifocal placoid pigment epitheliopathy

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Etiology is unknown
- 2. Many cases have been reported following viral syndromes
- 3. Sporadic cases reported in association with other systemic illnesses, including cerebral vasculitis, which may be fatal

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Usually in young, healthy adults
- 2. Although it is a well known type of posterior uveitis, it is infrequent

#### C. List the pertinent elements of the history

- 1. Sudden onset of bilateral disturbance in vision
- 2. No photopsias
- 3. May be asymmetric with complaints involving only one eye
- 4. Review of systems
  - a. Patient should be queried for
    - i. Recent viral illnesses
    - ii. Neurological (to uncover a systemic/central nervous system vasculitis) and other symptoms
    - iii. Review of system may be negative

#### D. Describe pertinent clinical features

- 1. Creamy yellow to gray white, flat, subretinal lesions at the level of the retinal pigment epithelium (RPE)
- 2. Central or paracentral scotomas
- 3. No isolated enlargement of the blind spot
- 4. Rapid resolution of the lesions, with varying degree of residual RPE disturbance which may limit vision
- 5. Good return of vision in most cases is expected, though potentially less in ampiginous version
  - a. May be associated with episcleritis, vein occlusion, or optic nerve edema
  - b. Mild vitreous reaction may be present, but iritis would be very unusual
  - c. Subretinal fluid collections are sometimes seen

#### E. Describe appropriate testing and evaluation to establish the diagnosis

- 1. Fundus photography
- 2. Fluorescein angiography may be the most characteristic finding of the disease
  - a. In acute disease, the visible lesions block early and stain late with fluorescein
  - b. Window defects are present on angiography in later stages of disease, due to damage to the RPE

## II. List the differential diagnosis

- A. Serpiginous choroidopathy
- B. Syphilitic chorioretinitis
- C. Punctate outer retinal toxoplasmosis if unilateral
- D. Multifocal choroiditis
- E. Punctate inner choroidopathy
- F. Birdshot chorioretinopathy
- G. Viral retinitis
- H. Diffuse unilateral subacute neuroretinitis
- I. Cerebral vasculitis with ocular manifestations
- J. Primary CNS lymphoma/Intraocular lymphoma

#### III. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Oral corticosteroids have been recommended to speed resolution, especially in cases with extensive macular or foveal involvement
  - a. However, its efficacy has not been proven
  - b. High dose corticosteroid treatment suggested if cerebral vasculitis is present

#### IV. Describe disease-related complications

- A. Choroidal neovascularization
- B. Persistent scotomata/reduced vision, especially if foveal involvement
- C. Permanent reduction in vision due to RPE scarring or choroidal neovascular membrane

# V. Describe appropriate patient instructions

A. Reassurance that resolution of symptoms is likely to occur with return of normal or near normal vision

- B. Improvement in vision occurs over a period of months
- C. Periodic ophthalmologic examinations are needed to document changes as disease resolves and check for complications
- D. Corticosteroid treatment is optional and unproven, but some feel that it might shorten the time to resolution or improve outcomes
- E. Headache or neurologic symptoms should be reported promptly

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: White Dot Syndrome, Module #4, 2007.

# Birdshot retinochoroidopathy

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

1. Etiology unknown

#### B. Define the relevant aspects of the epidemiology of this disease

- 1. People of Northern European extraction with HLA-A29 genetic background
- 2. Mean age at presentation 53 years
- 3. Slight female predominance

#### C. List the pertinent elements of the history

- 1. Visual loss
- 2. Floaters
- 3. Nyctalopia

#### D. Describe pertinent clinical features

- 1. Spots: cream to pale orange, 200-600 microns in diameter, indistinct borders, choroidal, most prominent nasally. They may assume a configuration that seems to radiate from the disc
- 2. Minimal or no anterior chamber inflammation
- 3. Mild vitreous inflammation
- 4. Fluorescein Angiography (FA) is useful as it may show retinal venular leakage, disc leakage, and cystoid macular edema. Birdshot lesions show up on FA depending on the stage of the disease.
- 5. Cystoid macular edema,
- 6. Narrowed arterioles
- 7. Indocyanine green angiography will show the spots as hypofluorescent, and there may more spots or larger spots than are seen ophthalmoscopically or on FA

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. The diagnosis is clinical; not established unequivocally by any test
- The presence of Human leukocyte antigen (HLA) -A29 is considered strong evidence in the appropriate clinical setting, as this gene is strongly associated with Birdshot; however, HLA-29 is not diagnostic. Some practitioners consider the diagnosis problematic in the absence of this cell surface marker, however

# II. Define the risk factors

- A. Northern European ancestry
- B. Presence of HLA-A29

# III. List the differential diagnosis

- A. Sarcoidosis
- B. Intraocular lymphoma
- C. Syphilitic chorioretinitis
- D. Multifocal choroiditis
- E. Multiple evanescent white dot syndrome (MEWDS)
- F. Tuberculosis

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Corticosteroids systemically, by intravitreal or periocular injection (not drops), or by intraocular corticosteroid implant
  - a. Typically for acute control of disease at diagnosis or with exacerbation; control of cystoid macular edema
  - b. Due to typical bilateral and chronic nature, local therapy may not be a viable long term option, though it may be useful for control of cystoid macular edema in the short term
- 2. Immunomodulatory medications
  - a. May be needed in most patients (some clinicians treat all patients regardless of visual status due to generally poor long term prognosis)
    - i. May help slow down the rate of progression of disease, but may not provide durable remission of disease
- 3. Some patients with very mild disease with normal ERG, and visual fields may be followed without treatment (Controversial, see IV.A.2.a above)

#### B. Describe follow-up options

- 1. FA is useful to follow clinical activity by detecting vasculitis or disc leakage
  - a. Retinal vascular leakage typically ceases in advanced disease yet vision loss may continue
  - b. FA in advanced disease may demonstrate poor perfusion with early loss of visible dye in vessels at 1 to 2 minutes post injection
- 2. Visual fields, either computerized or Goldmann, to measure retinal sensitivity and map blind spots
  - a. Pericentral scotomas and perineural scotomas common even in early disease
  - b. Peripheral vision loss common in advanced disease
- 3. ERG to evaluate for photoreceptor dysfunction in advanced disease
  - a. Reduction of rod B wave amplitude correlates with nyctalopia
  - b. Cone 30 Hz flicker B wave implicit time correlates with overall disease activity

4. Visual field and ERG abnormalities may improve in patients on IMT

# V. List the complications of treatment, their prevention and management

- A. Corticosteroid (See Corticosteroids)
- B. Immunomodulatory therapy (IMT) should be considered at the outset for symptomatic disease and possibly for all disease
- C. Disease progression may ensue despite IMT

## VI. Describe disease-related complications

- A. Cystoid macular edema
- B. Epiretinal membranes
- C. Moderate to severe vision loss from retinal degeneration (over many years)
- D. Optic atrophy
- E. Subretinal neovascularization
- F. Night blindness
- G. Reduced contrast sensitivity, color perception
- H. Visual field loss
- I. Apparent increased risk of normal tension glaucoma related to choroidal thinning and ischemia

# VII. Prognosis

- A. Some studies have suggested that some patients with birdshot (15-20%) have a favorable prognosis, however, the largest studies with long-term follow up suggest that the prognosis is poor without treatment and that this is a function of disease duration and independent of systemic corticosteroid use
- Two large cohorts show about a 20%, 5-year cumulative incidence of visual acuity of worse than 20/200
- C. Systemic corticosteroids are ineffective as monotherapy
- D. Preservation of visual function, with a reduction of inflammation, reduced risk of macular edema, and preservation of global retinal integrity as measured by VF and ERG, as well as the induction of long-term remission is possible in patients with birdshot managed with IMT

# VIII. Describe appropriate patient instructions

- A. Medication should be taken as instructed
- B. Disease may be chronic or spontaneously remit in 20%. Treatment for 2 to 4 years may increase the chances of remission
- C. Risk of long-term visual disability
- D. Familial cases of birdshot retinochoroidopathy rare, despite HLA-A29 association

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
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- 6. AAO, Focal Points: White Dot Syndrome, Module #4, 2007.

# Multiple evanescent white dot syndrome (MEWDS)

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Unknown
- 2. MEWDS may represent a spectrum of disease from an acute idiopathic blind spot to multi focal choroiditis

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Most common in young, healthy women
- 2. May follow a viral syndrome
- C. List the pertinent elements of the history
  - 1. Sudden onset of blurred vision in one eye associated with photopsias and paracentral scotomata
  - 2. May be aware of a shadow in the temporal field of vision (enlarged blind spot)

#### D. Describe pertinent clinical features

- 1. Ocular features depend on the time of examination following onset.
  - a. In early stages, gray-white, poorly demarcated, patchy outer retinal lesions are present along and outside the arcades, usually 200 to 500 microns
    - i. They may not be visible in all quadrants
    - ii. They fade rapidly
    - iii. Acute lesions are hyperfluorescent
  - b. Orange, granular pigmentation of the fovea as the acute lesions resolve
  - c. Vitreous cellular reaction (mild, if present)
  - d. May have a prominent sectoral field defect in the area most involved with the white dots
  - e. Subtle clinical signs may be present in absence of symptoms
- 2. Rapid resolution of retinal lesions and usually a return to normal vision
- 3. Slower resolution of granular macular pigmentation
- 4. Retinal pigment epithelium scarring infrequently occurs but when it does may be associated with permanent field defects
- 5. Describe appropriate testing and evaluation for establishing the diagnosis
- 6. Fluorescein angiography may demonstrate the typical "wreath-like" collections of punctate hyperfluorescence at the site of the white lesions
- 7. Indocyanine green angiography (ICG) may show multiple hypocyanescent spots, more numerous

than on exam, in the posterior pole and typically clustered around the optic nerve

- 8. Although MEWDS is nominally unilateral, ICG angiography usually shows a few subtle lesions in the fellow, asymptomatic eye
- 9. Visual fields may reveal enlarged blind spot (possibly explained by peripapillary location of lesions on ICG described in I.D.7. above.

#### II. Define the risk factors

- A. Female sex
- B. Young adult age

## III. List the differential diagnosis

- A. Acute idiopathic enlarged blind spot syndrome
- B. Acute zonal occult outer retinopathy (AZOOR)
- C. Multifocal choroiditis
- D. Syphilitic retinitis

## IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. None recommended
- 2. Corticosteroids used in some cases with optic nerve edema and reduced vision

#### V. Describe disease-related complications

- A. Permanent scotomata or sectoral field defects (rare)
- B. Development of a more permanent posterior uveitis such as AZOOR

#### VI. Describe appropriate patient instructions

- A. Disorder is usually self-resolving within several weeks
- B. Return of vision is usually excellent
- C. Follow-up is needed to document resolution
- D. This can be the first sign of a very rare, permanent condition (AZOOR)
- E. Very rarely, MEWDS has been reported to recur or to symptomatically affect the fellow eye

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: White Dot Syndrome, Module #4, 2007.

# Multifocal choroiditis with panuveitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Unknown
  - a. By definition, this condition is idiopathic. If a specific associated disease is diagnosed, then the condition is named based on that disease, such as "sarcoid choroiditis"

#### B. Define the relevant aspects of epidemiology of the disease

1. Generally younger individuals, including children

#### C. List the pertinent elements of the history

- 1. Visual disturbance; vitreous floaters; scintillating scotomata, enlarged blind spot
- 2. Query regarding residence in regions where histoplasmosis is endemic

#### D. Describe pertinent clinical features

- 1. Small (200 to 1500 micron) lesions at the level of the inner choroid
  - a. Active lesions are creamy white with hazy, less distinct borders
  - b. Healed lesions have variable degrees of retinal pigment epithelium (RPE) atrophy (centrally) or hyperpigmented discrete, sometimes granular borders
- 2. Lesions usually in different stages of evolution with several lesions of the same "age" or pigmentation, often clumped
- 3. Peripapillary predilection
- 4. Variable vitreous and anterior chamber reaction
- 5. Unilateral or bilateral
- 6. Variable subretinal fibrosis

# II. Describe appropriate testing and evaluation for establishing the diagnosis

A. The diagnosis is clinical; no ancillary testing establishes the diagnosis, though a work up should be performed to rule out other identifiable causes, especially infectious

#### B. Imaging

- 1. FA shows early blockage, late staining of active lesions. CNVM, CME show characteristic staining patterns
- 2. ICG shows mid-phase hypocyanescence, greater number of lesions than evident on FA, frequently confluent around optic nerve
- 3. OCT shows IS/OS junction disruption

# III. List the differential diagnosis

- A. Sarcoid choroiditis
- B. Secondary underlying choroidal scarring from toxoplasmic retinitis
- C. Vogt-Koyanagi-Harada disease
- D. Serpiginous choroidopathy
- E. Acute posterior multifocal placoid pigment epitheliopathy
- F. Diffuse unilateral subacute neuroretinitis (unilateral cases)
- G. Birdshot choroidopathy (this disease has much less vitreous cell and does not involve the inner choroid)
- H. Multiple evanescent white dot syndrome (MEWDS, similar initially, with a different clinical course because MEWDS resolves)
- I. Presumed Ocular Histoplasmosis Syndrome (POHS) (absolute absence of cell)
- J. Punctate Inner Choroidopathy (PIC)
- K. West Nile Virus chorioretinitis
- L. Syphilis
- M. Tuberculous uveitis
- N. Primary intraocular/CNS lymphoma
- O. Dengue fever

#### IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Systemic or periocular corticosteroids for acute disease
- 2. Corticosteroid sparing immunomodulatory therapy for chronic disease, especially with presence of subretinal fibrosis
- 3. Observation for recurrence or choroidal neovascularization

#### B. Describe surgical therapy options

- 1. Anti-vascular endothelial growth factor (VEGF) agents should be considered for choroidal neovascular membranes
- 2. Visual results from laser photocoagulation with thermal laser surgery or photodynamic therapy are often limited by fibrotic scarring even if the neovascular vessels are successfully closed
- 3. Surgical therapy to remove subretinal neovascularization has been an approach in the past, but has largely been supplanted by anti-VEGF agents and photodynamic therapy
- 4. Corticosteroid implant for unilateral or asymmetrical disease

# V. List the complications of treatment, their prevention and management

A. Refer to topics on specific agents in Medical Therapy section e.g. Corticosteroids

## VI. Describe disease-related complications

- A. Choroidal neovascularization
- B. Scotomata, enlargement of the blind spot, visual impairment, or blindness
- C. Progressive subretinal fibrosis
- D. Cytoid macular edema

# VII. Describe appropriate patient instructions

- A. Report changes in vision
- B. Follow Amsler grid if lesions present in posterior pole to detect signs of choroidal neovascularization
- C. Regular eye examinations to detect progression of disease

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: White Dot Chorioretinal Inflammatory Syndromes, Module #11, 1990, p.4-5.

# Serpiginous choroidopathy

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Unknown
- 2. Recently, recognition of the association of tuberculosis with a form of posterior uveitis that is similar in appearance to serpiginous has led to attempts to differentiate these two conditions. The term "Tuberculous Serpiginouslike Choroiditis" is now proposed in reference to the form associated with tuberculosis and should be considered a separate, infectious entity. This condition presents with significant vitreitis, multifocal lesions, and in individuals from endemic TB areas, in contrast to classic serpiginous choroidopathy

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Rare <5% of all posterior uveitis
- 2. Men > Women
- 3. Onset in 4th or 5th decades
- 4. Eventually bilateral (may be asymmetric at onset)
- 5. Usually no associated systemic diseases
  - a. Rarely can occur in Crohn disease, sarcoidosis, and periarteritis nodosa
  - b. Reports of an association with varicella zoster reactivation
  - c. Tuberculosis is the cause of tuberculous serpiginous-like choroiditis, as detailed above

#### C. List the pertinent elements of the history

- 1. Sudden onset of
  - a. Decreased vision
  - b. Scotoma
  - c. Metamorphopsia
- 2. Two-thirds of patients may present with scars in fellow eye with similar visual history
- 3. Relapsing and remitting disease
  - a. Intervals between activity variable (weeks to years)

#### D. Describe pertinent clinical features

- 1. Three distinct entities
  - a. Classic peripapillary geographic choroiditis (80%)
  - b. Macular serpiginous choroiditis (10%)
  - c. Ampiginous choroiditis (relentless placoid chorioretinitis) (<10%)

- 2. Classic peripapillary geographic choroiditis
  - a. Choroid
    - i. Grayish areas of active choroiditis that spread centrifugally from the optic disc with pseudopodal extensions
    - ii. Serpentine like progression toward macula
    - iii. Symptomatic as the disease approaches macula
    - iv. Natural history
      - i) Lesions heal over 6-8 weeks
      - ii) Atrophic choriocapillaris and RPE
      - iii) Recurrences develop at edges of old lesions
        - (i) Skip lesions may occur
        - (ii) Periphery may be involved
      - iv) Each recurrence increases area of atrophy in a serpentine or pseudopodal fashion
      - v) Choroidal neovascularization (CNV)
        - (i) Occurs in up to 35%
        - (ii) Peripapillary or at edge of atrophy
      - vi) Subretinal fibrosis in up to 25%
  - b. Retina
    - i. Thickened and opacified over areas of active choroiditis
    - ii. Subretinal fluid may be present
    - iii. Subretinal hemorrhage may be present
  - c. Vitreous minimal cellular reaction
  - d. Macular serpiginous choroiditis
  - e. Less common (10%)
  - f. Typical serpentine, chorioretinal lesions involving macula without continuity with edge of the optic disc
  - g. Poorer visual prognosis due to greater likelihood of foveal involvement
- 3. Ampiginous choroiditis (relentless placoid chorioretinitis)
  - a. Hybrid between APMPPE and serpiginous
  - b. Multifocal, grey white areas of RPE, choriocapillaris, choroidal, and outer retinal inflammation
  - c. Anterior chamber and vitreous cells more prominent
  - d. Can be relentless and progressive involving the posterior pole and periphery, often

randomly

- e. Usually responds to corticosteroids and immunomodulatory therapy (IMT)
- f. Visual prognosis better that classic or macular serpiginous choroidopathy

## E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Clinical diagnosis based on characteristic peripapillary choroiditis with pseudopodal extensions
- 2. Laboratory testing
  - a. PPD or Gamma interferon release assay for TB
    - i. Tuberculous choroiditis (serpiginoid) can appear identical to classic serpiginous choroidopathy
    - ii. Should be ruled out especially before IMT
  - b. Chest radiograph or CT
  - c. Serologic
    - i. RPR/FTA-ABS
- 3. Fluorescein angiography
  - a. Older lesions are hypofluorescent with edges that stain
  - b. Active lesions are hypofluorescent early and stain late
- 4. Indocyanine green angiography
  - a. Active lesions are hypocyanescent in early phases and remain unchanged with minimal hypercyanescence even in the late phases of the angiogram
    - i. Even if minimal activity with a lesion
    - ii. Extremely useful in advanced disease or equivocal cases, especially those close to fovea
- 5. Fundus Autofluorescence
  - a. Hypoautofluorescence of areas of chorioretinal atrophy in quiet disease
  - b. Hyperautofluorescent signal of active areas during flare

# II. List the differential diagnosis

- A. Acute posterior multifocal placoid pigment epitheliopathy
- B. Multifocal choroiditis
- C. Sarcoid choroiditis
- D. Presumed ocular histoplasmosis syndrome
- E. Peripapillary choroidal neovascularization
- F. Acute zonal occult outer retinopathy
- G. Choroidal ischemia/infarct from systemic vasculitides and hypercoagulable states

- H. Tuberculosis (Tuberculous serpiginous-like choroiditis)
- I. Syphilis
- J. Non-Hodgkin lymphoma rare

# III. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Corticosteroids mainstay for acute inflammatory choroiditis
  - a. High dose oral for active choroiditis, short term control
  - b. Periocular corticosteroids may also be used
  - c. Intravitreal corticosteroid can be considered for rapid control of vision threatening lesion
- 2. Immunomodulatory therapy
  - a. Cyclosporine monotherapy moderately beneficial
  - b. Antimetabolite methotrexate and azathioprine moderately beneficial
  - c. Alkylating agents most successful for long term remission (>5years)
  - d. Combination triple therapy with cyclosporine, Azathioprine, and corticosteroids

#### B. Describe surgical therapy options

- 1. Intravitreal fluocinolone implant
  - a. Provides up to 3 years of inflammatory control
  - b. Ocular complications
    - i. Cataract inevitable
    - ii. Glaucoma >50%
- 2. CNV
  - a. Focal laser photocoagulation if extrafoveal
  - b. Intravitreal VEGF inhibitor
    - i. If juxtafoveal or subfoveal

# IV. List the complications of treatment, their prevention and management

- A. Corticosteroids (See Corticosteroids)
- B. Immunomodulatory therapy
  - 1. See specific immunomodulatory agent

# V. Describe disease-related complications

#### A. CNV - up to 35%

- 1. Peripapillary
- 2. Adjacent to areas of choriocapillaris and RPE atrophy
- 3. Important cause of visual loss even if inflammation is quiescent
- 4. Visual prognosis related to proximity to fovea

#### B. Chorioretinal atrophy

- 1. Natural progression of disease
- 2. Inactive lesions
- 3. Absolute scotoma

#### C. Subretinal fibrosis

- 1. Due to severe choroidal inflammation
- 2. Due to CNV
- 3. Poor prognosis if extends into fovea
- 4. Best treatment is prevention and aggressive treatment of acute choroidal inflammation
- D. Retinal vasculitis and retinal neovascularization rare

#### VI. Describe appropriate patient instructions

- A. Course of disease is highly variable with long periods of remission possible
- B. Severe loss of vision may occur if scarring involves both the macula and the peripheral retina
- C. Report changes in vision promptly
- D. Use Amsler grid to monitor central vision area
- E. Treatment with immunosuppressive drugs may slow or arrest disease

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
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# Systemic vasculitis - intraocular manifestations

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Retinal vasculitis associated with
  - a. Systemic Lupus Erythematosus (SLE)
    - i. Retinal or choroidal vasculitis or small vessel occlusive disease related to the vasculopathy of systemic lupus erythematosus (SLE)
    - ii. Contributory factors
      - i) Antiphospholipid antibodies
      - ii) Lupus anticoagulant
      - iii) Immune complex deposition
      - iv) Complement activation
  - b. Giant cell arteritis (GCA)
    - i. Large vessel vasculitis
  - c. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
    - i. Small and medium vessel vasculitis
  - d. Polyarteritis nodosa
    - i. Medium vessel vasculitis
  - e. Rheumatoid arthritis associated vasculitis

#### B. Define the relevant aspects of epidemiology of the disease

- 1. SLE
  - a. More common in young African American women
  - b. Severe retinal vaso-occlusive retinal disease more common in SLE patients with cerebral vasculitis
- 2. GCA
  - a. Adults > 50 years
  - b. Female > male
  - c. Northern European > Southern European > African or Hispanic
- 3. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
  - a. No age or racial restriction

#### 4. Polyarteritis nodosa

- a. Middle age
- b. Men > women
- 5. Rheumatoid arthritis associated vasculitis (rheumatoid vasculitis)
  - a. Epidemiology
    - i. Late stages of disease
    - ii. Men (1/9) >women (1/38)

#### C. List the pertinent elements of the history

- 1. Change in vision
- 2. Visual field defect, especially altitudinal
- 3. Vitreous floaters
- 4. SLE
  - a. Asymptomatic, or visual disturbance, or sudden, severe vision loss
  - b. Prior diagnosis of SLE or meets diagnostic criteria for SLE or antiphospholipid syndrome
  - c. History of vaso-occlusive events
  - d. History of miscarriage
- 5. GCA
  - a. Jaw claudication
  - b. Temporal head pain
  - c. Weight loss
  - d. Malaise
  - e. Polymyalgia rheumatica
- 6. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
  - a. Upper airway disease
  - b. Pulmonary symptoms
  - c. Renal disease
  - d. Sinusitis
- 7. Polyarteritis nodosa
  - a. Malaise
  - b. Skin lesions
  - c. Neuropathy
  - d. Hypertension

- e. Abdominal pain
- 8. Rheumatoid arthritis associated vasculitis
  - a. Leg Ulcers
  - b. Cerebral vasculitis
  - c. Mesenteric vasculitis
  - d. Nephropathy, renal failure
  - e. Pericarditis, ischemic heart disease
  - f. Ominous signs, high mortality

#### D. Describe pertinent clinical features

- 1. SLE
  - a. Spectrum of retinal vasculopathy
    - i. Background retinopathy, especially cotton wool patches. (25% of hospitalized patients with active lupus)
    - ii. Small vessel occlusions, especially arteriolar capillaries
    - iii. Areas of capillary closure can be extensive.
    - iv. Large vessel occlusions, especially arterioles including central retinal artery, but also thrombotic venular occlusion
    - v. Rarely, mild to moderate vitreous cellular reaction
  - b. Spectrum of choroidal vasculopathy
    - i. Thickening of choroidal layers with leakage of fluid in the subretinal space
    - ii. Fibrinoid subretinal deposits
    - iii. Exudative retinal detachments
  - c. Scleritis
  - d. Lupus optic neuropathy in 1%
- 2. GCA
  - a. Central or branch artery occlusion
  - b. Anterior ischemic optic neuropathy (AION)
  - c. Ocular ischemic syndrome
  - d. Background retinopathy consisting of peripapillary cotton wool patches
- 3. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
  - a. Ocular disease may be a presenting sign
  - b. Scleritis (necrotizing)
  - c. Peripheral ulcerative keratitis

- d. Orbital inflammatory disease
- e. Retinal branch arteriolar or venular occlusions
- f. Choroidal vascular occlusions
- 4. Polyarteritis nodosa
  - a. Small and large retinal and choroidal vascular occlusions
  - b. Scleritis (necrotizing)
  - c. Peripheral ulcerative keratitis
- 5. Rheumatoid arthritis associated vasculitis
  - a. AION rare
  - b. Retinal and choroidal vasculitis rare
  - c. Scleritis / scleromalacia perforans

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. SLE
  - a. Clinical diagnosis based of 4 of 11 criteria being present:
  - b. Antinuclear antibodies screen and lupus antibody panel including antibodies to doublestranded DNA
  - c. Antiphospholipid antibodies
  - d. Lupus anticoagulant
  - e. C3, C4, CH50
  - f. Fluorescein angiography
    - i. Delay in choroidal filling
    - ii. Capillary nonperfusion -
    - iii. Capillary leakage or large vessel staining
    - iv. Isolated or grouped pinpoint leaks resembling central serous retinopathy with variable degrees of pooling in the subretinal space
  - g. Indocyanine green angiography
    - i. Choroidal hypoperfusion if choroidal vasculopathy present
- 2. GCA
  - a. Erythrocyte sedimentation rate (ESR)
  - b. C-reactive protein (CRP)
  - c. Temporal artery biopsy
    - i. Should be performed within a few days of beginning oral corticosteroids
    - ii. Biopsy segment should be at least 1 cm in length to avoid biopsying a "skip" lesion

- iii. Pathologic diagnosis is based on the presence of arterial inflammation with mononuclear cells, giant cells, and fragmentation of the elastic lamina
- d. Fluorescein angiography
  - i. Delay in both retinal and choroidal circulation
  - ii. Small and large vessel occlusions
- e. Visual field
  - i. Altitudinal defects in arteritic anterior ischemic optic neuropathy
- 3. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
  - a. Anti-neutrophil cytoplasmic antibody (c-ANCA, an antibody to Proteinase-3) and anti-myeloperoxidase antibody
  - b. Imaging studies upper airways (i.e., chest X-ray and sinus computed tomography (CT) scan)
  - c. Urinalysis with microscopic, renal function studies
  - d. Biopsy of non-ocular or orbital sites showing necrotizing granulomas
- 4. Polyarteritis nodosa
  - a. Biopsy of tissue such as nerve or muscle biopsy for diagnosis of microscopic disease of small and medium sized arteries
    - i. Inflammation may be acute or chronic
    - ii. Lesions in all stages of evolution in the same specimen
    - iii. Thrombosis and fibrosis may be present
  - b. Anti-neutrophil cytoplasmic antibody (p-ANCA)
  - c. Hepatitis B surface antigen
  - d. Abdominal angiogram
- 5. Rheumatoid arthritis associated vasculitis
  - a. High Rheumatoid factor titers
  - b. Anti-cyclic citrullinated peptide antibodies
  - c. Low C3, C4

#### II. Define the risk factors

- A. GCA (older age, Caucasian and female)
- B. Lupus retinal and choroidal vasculitis SLE and antiphospholipid antibody syndrome
- C. Rheumatoid vasculitis advanced rheumatoid arthritis with high titers of rheumatoid factor and presence of anti-cyclic citrullinated peptide antibodies

# III. List the differential diagnosis

- A. Other systemic vasculitides have been associated with ocular inflammation of various types
  - 1. Churg-Strauss vasculitis
    - a. Eosinophilia
    - b. Pulmonary symptoms, including asthma
  - 2. Leukocytoclastic angiitis
    - a. Common
    - b. Involves mainly the skin with palpable lesions as well as other organs
    - c. May be self-limited
- B. Behçet retinal vasculitis
- C. Diabetic retinopathy
- D. Hypertensive retinopathy
- E. Embolic vascular occlusions
- F. Non-arteritic anterior ischemic optic neuropathy
- G. Necrotizing herpetic retinitis occlusive retinal vasculitis

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. SLE (In conjunction with rheumatologist)
  - a. Oral corticosteroids
  - b. Corticosteroid-sparing agents
    - i. Methotrexate
    - ii. Imuran
    - iii. Mycophenolate Mofetil
    - iv. Hydroxychloroquine (not as beneficial in treatment of ocular disease)
    - v. Alkylating agents may be necessary in cases of lupus nephritis
  - c. Anti-platelet
  - d. Anti-thrombotic agents
- 2. GCA
  - a. Oral corticosteroids
  - b. Follow-up with ESR and CRP monitoring
- 3. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
  - a. Cyclophosphamide and oral corticosteroids

- b. Rituximab is becoming a more common therapeutic option
- c. Methotrexate, azathioprine, cyclosporine as an alternative for chronic maintenance
- 4. Polyarteritis nodosa
  - a. Cyclophosphamide and oral corticosteroids
- 5. Maintenance regimen may consist of other corticosteroid-sparing agents such as mycophenolate mofetil or cyclosporine

#### B. Describe surgical therapy options

- 1. Panretinal photocoagulation for neovascular complications of vaso-occlusive disease
- 2. Otherwise none

#### V. Describe disease-related complications

- A. Scotomata, visual impairment or blindness
- B. Secondary neovascularization of retina, optic nerve, or anterior segment
- C. Ocular ischemic syndrome (GCA)

# VI. Describe appropriate patient instructions

- A. Follow physician instructions regarding medication
- B. Report changes in vision
- C. Examine eyes when systemic vasculitis flares up
- D. Regular eye examinations necessary

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# Sarcoidosis panuveitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Unknown
- 2. Environmental agents (infections or other exposures) thought to play a role, but definitive evidence is lacking for specific agents

#### B. Define the relevant aspects of epidemiology of this disease

- 1. More common between ages 20 50, but seen at other ages as well
- 2. Familial clustering
- 3. More prevalent among African-Americans and Scandinavians but has been reported in all racial groups
- 4. 15%-50% of patients with systemic sarcoid have ocular manifestations
- 5. 3%-10% of all cases of uveitis
- 6. Uncommon in children
  - a. Early onset (≤ 5 years of age less likely to manifest pulmonary disease, more likely to have cutaneous and articular involvement than adults)
  - b. Suspect Blau syndrome if onset in early childhood or family history of granulomatous disease (familial juvenile systemic granulomatosis)

#### C. Pathology

- 1. Multisystem disease characterized by granulomatous inflammation
- 2. Hallmark is a noncaseating granuloma containing epithelioid cells, multinucleated giant cells (Langhans giant cell with nuclei at the periphery of the cell) and a thin rim of lymphocytes

#### D. List the pertinent elements of the ocular history

- 1. Symptoms are variable from mild to severe
- 2. Pain, redness and photophobia
- 3. Blurred vision and floaters

#### E. Describe pertinent clinical features

- 1. Systemic
  - a. Pulmonary symptoms
  - b. Lymphadenopathy
  - c. Cutaneous (lupus pernio, perioral granulomatous plaques, erythema nodosum) Lupus pernio and perioral plaques are more suggestive clinically of sarcoidosis. Erythema nodosum, while classically associated with the disease is uncommon, and non-specific

- d. Central nervous system granulomatous disease
- e. Arthritis
- f. Cardiac involvement (rare)
- 2. Ocular
  - a. Acute or chronic anterior uveitis
  - b. Orbital and lacrimal gland involvement
  - c. Conjunctival granulomas
  - d. Nummular corneal infiltrates
  - e. Band keratopathy
  - f. Mutton fat keratic precipitates especially involving the anterior chamber angle
  - g. Koeppe and Busacca iris nodules
  - h. Large iris granulomata
  - i. Posterior synechiae, peripheral anterior synechiae
  - j. Snowballs, " string of pearls"
  - k. Vitritis
  - I. Perivenous sheathing (classic candle-wax dripping, or "taches de bougie")
  - m. Retinal and choroidal granulomas
  - n. Occlusive retinal vascular disease
    - i. Branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO)
    - ii. Retinal neovascularization
    - iii. Vitreous hemorrhage
  - o. Cystoid macular edema
  - p. Optic nerve edema may be secondary to uveitis or central nervous system disease
  - q. Optic nerve granulomatous invasion is direct involvement of the optic nerve by sarcoidosis
- 3. Syndromes
  - a. Lofgren syndrome
    - i. Erythema nodosum, febrile adenopathy, hilar adenopathy, acute iridocyclitis
  - b. Heerfordt syndrome (uveoparotid fever)
    - i. Parotitis, fever, facial nerve palsy, uveitis

#### F. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. More valuable
  - a. Chest X-ray (relatively low sensitivity and specificity)

- b. Chest computed tomography (CT) of thorax with contrast
- 2. Less valuable
  - a. Nonspecific tests
    - i. Serum angiotensin converting enzyme, lysozyme
    - ii. Gallium scan
- 3. Biopsy
  - a. Conjunctiva (directed)
  - b. Lacrimal gland
  - c. Lymph node
  - d. Pulmonary
    - i. Bronchoalveolar lavage
    - ii. Transbronchial lung biopsy
  - e. Skin rash
    - i. Biopsy of erythema nodosum is non specific

## II. List the complications of treatment, their prevention and management

- A. Cataract
- B. Glaucoma
- C. Macular edema
- D. Occlusive retinal vascular disease
  - 1. BRVO, CRVO
  - 2. Retinal neovascularization
  - 3. Vitreous hemorrhage

#### III. List the differential diagnosis

- A. Syphilis
- B. Lyme disease
- C. Tuberculosis
- D. Familial juvenile systemic granulomatosis (Blau syndrome) (children)
- E. Vogt-Koyanagi-Harada syndrome
- F. Behçet's disease
- G. Sympathetic ophthalmia
- H. Multifocal choroiditis with panuveitis
- I. Juvenile idiopathic arthritis (children)
- J. Idiopathic pars planitis
- K. Masquerade syndromes (intraocular lymphoma) (older patients)
- L. Coccidioidomycosis (endemic in certain areas of California). May present with an intraocular granuloma or granulomas that can mimic sarcoidosis. This is a rare and usually rapidly progressive endogenous endophthalmitis

#### IV. Describe patient management in terms of treatment and follow-up

- A. Topical, periocular and systemic corticosteroids are tailored to the location and severity of inflammation
  - 1. Intravitreal corticosteroids, including long lasting fluocinolone implants, may be useful, but keep in mind the patient may need systemic treatment for systemic disease
- B. Cycloplegia
- C. Immunomodulatory agents
- D. Work with internist regarding systemic disease and potentially fatal systemic complications (in particular, CNS and cardiac involvement)

### V. List the complications of treatment, their prevention and management (See Corticosteroids) (See Cycloplegics) (See Cyclosporine)

#### VI. Describe disease-related complications

- A. Dry eyes
- B. Cataract
- C. Band keratopathy
- D. Glaucoma
- E. Iris bombé
- F. Macular edema and epiretinal membrane formation
- G. Neovascularization of the retina, optic nerve
- H. Vascular occlusions
- I. Vitreous hemorrhage
- J. Optic atrophy

#### VII. Describe appropriate patient instructions

- A. Report redness, pain, photophobia, blurred vision or decreased vision (report systemic symptoms)
- B. Follow the doctor's instructions regarding medication

- C. Course of disease is variable
- D. Side effects of medications must be understood

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Dana MR, Merayo-Lloves J, Schaumberg DA, et al. Prognosticators for visual outcome in sarcoid uveitis. Ophthalmology. 1996;103:1846-1853.
- 3. Bonfioli AA, Orefice F. Sarcoidosis. Semin Ophthalmol. 2005; 20: 177-82.
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# Sympathetic ophthalmia

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

1. Autoimmune response to previously sequestered intraocular antigens

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Uncommon, bilateral, non-necrotizing, diffuse, granulomatous panuveitis
- 2. Occurs after injury to one eye (the exciting eye)
- 3. Latent period followed by development of uveitis in the uninjured globe (sympathizing eye)
- 4. Incidence has decreased with improved wound closure and early removal of severely damaged eyes
- 5. Shift in prevalence from penetrating ocular injury to surgical trauma is due to continually increasing numbers of intraocular surgeries being performed

#### C. Define the relevant pathological features

- 1. Diffuse granulomatous uveal involvement with lymphocytes, epithelioid cells, giant cells, and occasional eosinophils
- 2. Relative lack of retinal inflammation
- 3. Absence of inflammatory reaction in choriocapillaris
  - a. This is the classic historical teaching, which currently is theorized to be secondary to early enucleation in eyes that demonstrate this sparing of the choriocapillaris
- 4. Eosinophils are present in the choroid early in the course of disease
- 5. Phagocytosis of pigment by epithelioid cells
- 6. Dalen Fuchs nodules
- 7. Granulomatous process may extend to scleral canals and optic disc

#### D. List the pertinent elements of the history

- 1. Insidious onset with mild photophobia, redness and blurring of vision
  - a. These findings in the early post injury period must be differentiated from expected post-injury inflammation
- 2. Traditionally, in those eyes in which sympathetic ophthalmia develops, 80% do so within 3 months of injury and 90% within one year
  - a. Interval may be longer than previously appreciated
    - i. One-third developed SO within 3 months and less than half within a year in a recent series

#### E. Describe pertinent clinical features

#### 1. Ocular

- a. Severe panuveitis in the injured or operated eye
- b. Sympathizing eye
  - i. Thickening of the uveal tract
  - ii. Mutton fat keratic precipitates
  - iii. Infiltration of the iris, iris nodules
  - iv. Extensive peripheral anterior synechiae
  - v. Loss of accommodation
  - vi. Vitritis
  - vii. Multifocal, yellow-white, mid-equatorial choroidal lesions
  - viii. Peripapillary choroidal lesions
  - ix. Exudative retinal detachment
  - x. Papillitis
  - xi. Fluorescein angiogram shows multiple hyperfluorescent spots with pooling in subretinal fluid. Chorioretinal scars may show blockage due to hyperpigmentation with hyperfluorescence due to window defects
  - xii. B-scan ultrasonography shows choroidal thickening
- 2. Extraocular findings may overlap with those seen in Vogt-Koyanagi-Harada (VKH) syndrome
  - a. Cerebral spinal fluid pleocytosis
  - b. Sensory neural hearing disturbance
  - c. Alopecia, poliosis, vitiligo

#### II. Define the risk factors

#### A. Should suspect SO in patients with following risk factors

- 1. Perforation or penetration of the globe with or without uveal prolapse
  - a. Perforating ulcers
  - b. Scleral rupture
  - c. Following ocular surgery
    - i. Cataract surgery, especially with iris prolapse
    - ii. Trabeculectomy
    - iii. Iridencleisis
    - iv. Vitrectomy, especially when performed in the context of other penetrating ocular injuries or with multiple surgeries

- 2. Has been reported in non-penetrating situations as well
  - a. Severe contusion
  - b. Contact and noncontact YAG laser cyclodestruction
  - c. Cyclocryotherapy
  - d. Proton beam or helium ion irradiation for melanoma

#### III. List the differential diagnosis

- A. Bilateral uveitis following any ocular trauma or surgery should suggest SO
- B. Vogt-Koyanagi-Harada disease. Prior penetrating trauma or surgery excludes VKH
- C. Phacoanaphylactic endophthalmitis
- D. Ocular sarcoidosis
- E. Tuberculosis
- F. Syphilis
- G. Traumatic, postoperative, fungal endophthalmitis

#### IV. Describe patient management in terms of treatment and follow-up

- A. The course is characterized by chronic inflammation with frequent exacerbations
- B. Treatment
  - 1. Topical corticosteroids and cycloplegic agents as adjuncts for anterior chamber inflammation (insufficient for posterior involvement)
  - 2. Systemic corticosteroids
  - 3. Immunomodulatory therapy as extended therapy is anticipated in most patients
- C. Early enucleation within first week of trauma may prevent SO
- D. Once SO is established, enucleation has no effect on inflammation, but may be useful in establishing the diagnosis in a blind eye
- E. With advances in treatment, an exciting eye may turn out to be the eye with the better visual acuity
- V. Complications of treatment (See Corticosteroids) (See Cycloplegics) (See individual immunosuppressive agents: Methotrexate, Azathioprine, Mycophenolate mofetil, Cyclosporine, tacrolimus) (See Biologic response modifiers)

#### VI. Disease related complications

A. Peripheral anterior and posterior synechiae

- B. Glaucoma
- C. Cataracts
- D. Rubeosis iridis
- E. Pupillary membrane
- F. Cystoid macular edema
- G. Exudative retinal detachment
- H. Choroidal neovascularization
- I. Optic atrophy
- J. Vision loss

#### VII. Prognosis

A. Visual prognosis is good if the condition is recognized early and prompt aggressive treatment initiated, with 75% achieving 20/40 or better at 1 year

#### VIII. Describe appropriate patient instructions

- A. Report changes in vision promptly
- B. Medication instructions
- C. Follow-up instructions

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Sympathetic Ophthalmia, Module #5, 2004.
- 3. Gass JD. sympathetic ophthalmia following vitrectomy. Am J Ophthalmol 1982; 93:552-558.
- 4. Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. Br J Ophthalmol 2000; 84:259-263.
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- 6. Kilmartin DJ, Wilson D, Liversidge J, et al. Immunogenetics and clinical phenotype of sympathetic ophthalmia in British and Irish patients. Br J Ophthalmol 2001; 85:281-286.
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# Vogt-Koyanagi-Harada disease

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Unknown
- 2. Presumptive, cell-mediated autoimmune process against self-antigens associated with melanocytes
- 3. Immunogenetics of VKH disease and sympathetic ophthalmia (SO) similar in association with human leukocyte antigen (HLA)-DR4

#### B. Define the relevant aspects of epidemiology of the disease

- 1. More common among darkly pigmented ethnic groups
  - a. Asian, Native American Indian, Middle Eastern, Hispanic
  - b. 30 and 50 years of age
  - c. 1%-4% of uveitis cases in US, 8% in Japan

#### C. List the pertinent elements of the history

- 1. Headache
- 2. Stiff neck
- 3. Rarely, loss of consciousness, paralysis and seizures
- 4. Skin and hair signs
  - a. Alopecia, vitiligo, poliosis in 30% usually weeks to months later (or years) but may be simultaneous
- 5. Temporary hearing loss or tinnitus
- 6. Ocular history
  - a. Decreased vision
  - b. Pain
  - c. Redness
  - d. Photophobia

#### D. Describe pertinent clinical features

- 1. Prodromal stage
  - a. Headache
  - b. Meningismus
  - c. Cerebrospinal fluid (CSF) pleocytosis (80%)
  - d. Focal neurologic signs (rare)

- i. Hemiparesis, cranial neuropathies, aphasia, transverse myelitis
- e. Nausea
- f. Vertigo
- g. Dysacusia, tinnitus
- h. Fever
- i. Hypersensitivity of skin or hair to touch
- j. Photophobia
- k. Orbital pain
- 2. Acute uveitic stage
  - a. Acute onset bilateral, sequential decreased vision (1-2 days following central nervous system (CNS) signs
  - b. Mild to extremely severe bilateral anterior uveitis
    - i. Iris nodules, mutton-fat KPs
  - c. Variable degrees of vitritis
  - d. Choroidal thickening and elevation of peripapillary retinal-choroidal layer
  - e. Optic disc hyperemia and edema
  - f. Multiple serous neurosensory detachments
- 3. Convalescent stage
  - a. Weeks following acute uveitic stage
  - b. Resolution of neurosensory detachments
  - c. Depigmentation of the choroid resulting in orange-red discoloration known as the "Sunset glow fundus" with retinal pigment epithelial hypo and hyperpigmentation
  - d. Small, discrete, round depigmented lesions in the inferior peripheral fundus representing focal chorioretinal atrophy from old granulomas. These do not represent old Dalen Fuchs nodules
  - e. Perilimbal vitiligo (Sugiura sign) 85% Japanese patients
  - f. Integumentary changes 30%, may correspond to fundus depigmentation
    - i. Alopecia
    - ii. Vitiligo
    - iii. Poliosis
- 4. Chronic recurrent stage
  - a. Usually recurrent bouts of granulomatous anterior uveitis only
  - b. Recurrent posterior uveitis with exudative retinal detachments are uncommon
  - c. Granulomatous keratic precipitates ranging from small to large

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Diagnosis is clinical based on characteristic clinical findings
- Revised comprehensive diagnostic criteria include complete, incomplete and probable forms of VKH
- 3. Essential diagnostic features, irrespective of disease form include:
  - a. Bilateral involvement
  - b. Absence of a history of penetrating ocular trauma
  - c. No evidence of other ocular or systemic disease
- 4. Fluorescein angiography
  - a. Multiple focal areas of subretinal leakage in the early phase with late pooling of dye in the subretinal space in areas of neurosensory detachment
- 5. ICG angiography
  - a. Shows choroidal involvement
  - b. Delay in choroidal perfusion
  - c. Multiple hypofluorescent spots
- 6. Ultrasound
  - a. Diffuse choroidal thickening
- 7. OCT
  - a. Subretinal fluid
  - b. Enhanced depth imaging shows choroidal thickening
- 8. If a cerebrospinal fluid (CSF) tap is obtained
  - a. Lymphocytosis
  - b. Melanin laden macrophages

#### II. List the differential diagnosis

- A. Sympathetic ophthalmia
- B. Primary intraocular lymphoma
- C. Posterior scleritis
- D. Sarcoidosis
- E. Acute posterior multifocal placoid pigment epitheliopathy
- F. Uveal effusion syndrome
- G. Syphilis

#### III. Describe patient management in terms of treatment and follow-up

#### A. Systemic, periocular and local corticosteroids for at least 6 months

- Early and aggressive use of high dose oral or IV corticosteroids followed by slow tapering over 3 to 6 months may shorten duration of disease and progression into chronic stage and prevent extraocular manifestations
- 2. Patients who are corticosteroid intolerant, resistant or experience recurrent episodes of inflammation require treatment with immunomodulatory therapy including cyclosporine, azathioprine, mycophenolate mofetil, chlorambucil, or cyclophosphamide
- 3. Visual prognosis of patients managed in this fashion is fair
  - a. 60%-70% retaining vision of 20/40 or better

#### IV. Describe disease related complications

- A. Peripheral anterior synechiae
- B. Posterior synechiae
- C. Cataract
- D. Hypotony
- E. Secondary glaucoma
- F. Choroidal neovascularization (CNV)
- G. Subretinal fibrosis
- H. Phthisis bulbi

#### V. Describe appropriate patient instructions

- A. Report changes in vision promptly
- B. Medication instructions
- C. Follow-up instructions

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Laboratory Evaluation of Patients with Uveitis, Module #12, 2001, p.2-3.
- 3. Davis JL, Mittal KK, Friedlin V, et al. HLA associations and ancestry in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. Ophthalmology. 1990;97:1137-1142.
- 4. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol. 1995;39:265-292.
- 5. Bykhovskaya I, Thorne JE, Kempen JH, et al. Vogt-Koyanagi-Harada disease: clinical outcomes.

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- Read RW, Holland GN, Rao NA et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001; 131:647-652.
- 7. Read RW, Rechodouni A, Butani N et al. Complications and prognostic factors in Vogt-Koyanagi-Harada disease. Am J. Ophthalmol 2001; 131:599-606.
- 8. Shindo Y, Ohno S, Yamamoto T et al. Complete association of the HLA-DRB1\*04 and DZ1\*04 alleles with Vogt-Koyanagi-Harada disease. Hum Immunol 1994; 39:169-176.
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- 12. Rajendram R, Evans M, Rao NA. Vogt-Koyanagi-Harada disease. Int Ophthalmol Clin 2005; 45:115-34.
- 13. Rao NA. Pathology of Vogt-Koyanagi-Harada disease. Int Ophthalmol 2007;27:81-5.

# Behçet disease

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

1. Behçet disease is a multisystem disorder, classified as a chronic relapsing vasculitis. The etiology is unknown. There is a genetic aspect of the disease, and the HLA B51 marker is commonly positive

#### B. Define the relevant aspects of the epidemiology of this disease

- 1. Countries that line the ancient Silk Road, particularly East Asia and the Mediterranean
- 2. Usually age of onset is third to fourth decades of life
- 3. Men more commonly affected than women

#### C. List the pertinent elements of the history

- 1. Recurrent painful oral ulcers
- 2. Visual symptoms including pain, photophobia, floaters, or visual loss
- 3. Genital ulcers
- 4. Skin lesions
- 5. Other systemic manifestations such as arthritis, vasculitis

#### D. Describe pertinent clinical features

- 1. The most widely used diagnostic criteria are those of the International Study Group (1990). The five major features are
  - a. Recurrent oral aphthous ulcers (recurring at least 3 times in a 12 month period)
  - b. Recurrent genital ulcers (or scarring)
  - c. Eye lesions anterior, posterior or pan uveitis with or without hypopyon, retinal vasculitis and retinitis
  - d. Skin lesions: specifically erythema nodosum, pseudofolliculitis, or papulopustular lesions or acneiform papules in post adolescent patients without steroid treatment
  - e. Positive pathergy (skin hyper reactivity) testing: an intracutaneous needle stick with a 21G on the inside forearm results in a pustular reaction, read by a physician after 24-48 hours
- 2. Several other diagnostic schemes include other clinical features, known as "minor criteria"
  - a. Arthritis
  - b. Gastrointestinal symptoms
  - c. Epididymitis
  - d. Thrombophlebitis, arterial occlusions and aneurysms
  - e. Central nervous system or neuropsychiatric symptoms

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Definitive diagnosis of Behçet disease, based on the International study Group criteria, requires oral ulceration plus any two of the other five major criteria
- 2. Fluorescein angiography is highly useful to detect subtle retinal vasculitis, retinal vascular leakage, ischemia, retinal neovascularization, and extent of vasculitis
- 3. Presence of the HLA B-51 genetic marker is not a requirement for diagnosis

#### II. Define the risk factors

- A. Asian, Mediterranean or middle Eastern ancestry
- B. HLA-B51
- C. Male sex

#### III. List the differential diagnosis

- A. Sarcoidosis
- B. HLA-B27 related uveitis
- C. Syphilis
- D. Necrotizing viral retinitis (HSV, VZV, CMV)
- E. Tuberculosis
- F. Vasculitis related to collagen vascular diseases (i.e., lupus)
- G. Idiopathic retinal vasculitis or uveitis
- H. Vein occlusion

#### IV. Describe patient management in terms of treatment and follow-up

- A. Patient management includes consultation with a rheumatologist
  - 1. Life-threatening involvement of the gastrointestinal system, vascular system, and central nervous system may occur
- B. Systemic medical therapy with high dose corticosteroids is most useful in patients with acute disease (refer to specific outline)
- C. Immunomodulatory agents are required in patients with vision-threatening posterior segment disease. The long term goal is to prevent (or decrease) relapses
  - 1. Azathioprine is commonly the first-line approach to chronic disease control (See Azathioprine)
  - 2. Tumor necrosis factor (TNF) alpha antagonist agents show very promising results (refer to specific outline)
  - 3. Other medications of value in the management of non-ocular manifestations include cyclosporine, tacrolimus, methotrexate, cyclophosphamide, chlorambucil, mycophenolate, colchicine, thalidomide, and dapsone

- D. Interferon alpha (more commonly used outside the U.S.)
- E. Topical ocular therapy as adjunct may be considered for management of eye manifestations in patients with no evidence of vision threatening ocular disease
- F. Describe surgical therapy options
  - 1. Scatter laser photocoagulation to treat retinal nonperfusion after the development of optic nerve or retinal neovascularization
  - 2. Selected patients may require cataract extraction and vitrectomy
- V. List the complications of treatment, their prevention and management (See Corticosteroids) (See Azathioprine) (See Cyclosporine) (See Methotrexate) (See Cyclophosphamide and chlorambucil) (See Biologic response modifiers)
  - A. Colchicine: decreased fertility and azoospermia
  - B. Thalidomide: birth defects

#### VI. Describe disease-related ocular complications

- A. Retinal ischemia and degeneration
- B. Retinal neovascularization
- C. Retinal detachment
- D. Moderate to profound vision loss
- E. Optic atrophy
- F. Cataract
- G. Glaucoma
- H. Prognosis: guarded with approximately 25% of patients worldwide with legal blindness

#### VII. Describe appropriate patient instructions

- A. Take medication as instructed
- B. Discussion of the chronic, relapsing nature of the disease and the long-term risk of blindness
- C. Discussion of possible life-threatening systemic complications and other systemic manifestations of Behçet disease, and the importance of consultation and life-time follow-up by a rheumatologist

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.8.
- 3. Yazici H, Pazarli H, Barnes CG, et al. A controlled trial of azathioprine in Behçet's syndrome. N

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# Scleritis associated with systemic autoimmune diseases

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. 50% ocular and not associated with systemic disease
  - a. About 5% of individuals per year will develop a systemic rheumatic disease
- 2. 40% associated with a systemic disease
  - a. Majority will have a systemic diagnosis at presentation in a tertiary center
  - b. Rheumatoid arthritis- most common
    - i. 1.3 million individuals in US, 75% females
    - ii. Age of onset usually between 4th and 6th decades of life
    - iii. Symptoms
      - i) Morning stiffness
      - ii) Pain, swelling, limitation of movement in joints
        - (i) Any joint possible, but small joints in hands and feet most common
  - c. Inflammatory bowel disease
  - d. Systemic vasculitis syndromes
    - i. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
    - ii. Polyarteritis nodosa
    - iii. Behçet disease
    - iv. Giant cell arteritis
    - v. Takayasu arteritis
  - e. Connective tissue diseases
    - i. Systemic lupus erythematosus
    - ii. Relapsing polychondritis
  - f. Granulomatous disease
    - i. Sarcoidosis
  - g. Congenital erythropoietic porphyria
- 3. 10% Infectious

- a. Treatment requires corticosteroids because of significant sterile immunologic component to inflammation along with antibiotics
  - i. Varicella zoster virus
  - ii. Herpes simplex virus
  - iii. Syphilis
  - iv. Lyme disease
  - v. Tuberculosis
  - vi. Leprosy
- 4. Surgery related
  - a. SINS- Surgically Induced Necrotizing Scleritis
  - b. Infectious

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Most commonly present in fourth to sixth decade
- 2. Women more commonly affected than men
- 3. Occurs bilaterally in 50% of cases
- 4. Necrotizing scleritis has a 50% mortality rate without systemic treatment

#### C. List the pertinent elements of the history

- 1. Pain that can radiate to jaw or forehead
  - a. Typically severe, "boring" pain
  - b. Awakens from sleep
  - c. Worsened with eye movement
- 2. Redness: focal or diffuse
- 3. Photophobia

#### D. Describe pertinent clinical features

- 1. Eye pain and tenderness to palpation
  - a. Pain is absent in cases of scleromalacia perforans in advanced rheumatoid arthritis; pain is variable with posterior scleritis
- 2. Scleral edema
- 3. Violaceous appearance to sclera (bluish -red color)
  - a. Blanches incompletely with topical phenylephrine (Neo-Synephrine®)
- 4. Uvea visible in cases of necrotizing scleritis
- 5. Classification
  - a. Diffuse anterior scleritis

- i. Most common clinical presentation affecting 25-50% of scleritis patients
- ii. Least severe
- iii. Recurrent attacks
- iv. Distortion of deep as well as superficial vascular network
- v. Violet, blue, salmon color
- vi. After resolution involved areas have bluish gray appearance
- b. Nodular anterior scleritis
  - i. Second most common presentation of scleritis
  - ii. Recurrent attacks
  - iii. Firm, tender, immobile nodule
  - iv. Color of nodule is yellow to deep red
  - v. Systemic disease association in almost 50%
  - vi. Permanent visual loss and progression to necrotizing scleritis uncommon
- c. Necrotizing anterior scleritis with inflammation
  - i. Most severe
  - ii. Associated with greatest potential for visual loss
  - iii. Extreme discomfort and severe distress
  - iv. White avascular areas of sclera with surrounding scleral edema and congestion
    - i) Areas of capillary closure in episcleral vasculature
    - ii) Uveal tissues apparent as sclera thins
    - iii) Ciliary body and choroid may only be covered by conjunctiva
    - iv) Spontaneous perforation rare
    - v) Healing is remarkably good if inflammation controlled
- d. Necrotizing scleritis without clinically apparent inflammation scleromalacia perforans
  - i. Severe, bilateral
  - ii. No redness, pain, or edema
  - iii. Patients typically have long standing rheumatoid arthritis
  - iv. Thinning and atrophy of episcleral and loss of episcleral vasculature
  - v. Concomitant uveitis in active disease
- e. Posterior scleritis
  - i. 33% bilateral
  - ii. Symptoms

- i) Pain on eye movement
- ii) Decreased vision often profound
- iii. Clinical presentation
  - i) Exudative retinal detachment (often in posterior pole) most common
  - ii) Annular choroidal detachment
  - iii) Optic nerve edema
  - iv) Choroidal folds
  - v) Subretinal mass lesion
  - vi) Uveitis
  - vii) Retinal vasculitis

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Anti-neutrophil cytoplasmic antibodies (ANCA)
  - a. cANCA- Granulomatosis with polyangiitis (GPA) (previously known as Wegener's granulomatosis)
  - b. pANCA- Microscopic polyangiitis
  - c. All positive ANCA tests should be confirmed by testing for antibodies to proteinase-3 and/or myeloperoxidase confirmatory- increased specificity
- 2. Rheumatoid factor- if polyarthritis
- 3. Cyclic citrullinated peptide antibody (for rheumatoid arthritis)
- 4. Urinalysis
- 5. Fluorescent treponema antibody (FTA) absorption / microhemagglutination assay-Treponema pallidum (MHA-TP)
- 6. Chest X-ray
- 7. B-Scan/high frequency ultrasound in posterior scleritis
- 8. Other test to obtain in selected cases, based on history and clinical suspicion
  - a. Antinuclear antibodies
  - b. Lyme serology
  - c. Complete blood count (CBC) (If immunosuppressives are being considered)
  - d. HLA-B27
  - e. Purified protein derivative (PPD) skin test
  - f. Erythrocyte sedimentation rate (ESR) (If giant cell arteritis suspected, would want to obtain temporal artery biopsy)
  - g. Complete metabolic panel (If immunosuppressives are being considered)

#### II. Define the risk factors

- A. Exacerbation after recent unrelated intraocular surgery (such as cataract extraction)
- B. Poor control of associated systemic rheumatic disease

#### III. List the differential diagnosis

- A. Episcleritis
- B. Conjunctival lymphoma
- C. Conjunctival intraepithelial neoplasia /squamous cell carcinoma
- D. Orbital myositis
- E. Orbital inflammatory syndrome (pseudotumor)
- F. Infectious causes of scleritis- pseudomonas, nocardia, etc. (See Post-surgical and traumatic infectious scleritis)
- G. For posterior scleritis: Vogt-Koyanagi-Harada disease

#### IV. Management of non-infectious scleritis

#### A. Nonsteroidal anti-inflammatory drugs (NSAIDs)

- 1. Non-necrotizing scleritis
- 2. Relieve pain and reduce inflammation
- 3. No one drug is proven to be better than another
  - a. Indomethacin, flurbiprofen, naproxen preferred
  - b. In the case of failure to one of the above, a second one can be tried before switching to corticosteroids

#### B. Corticosteroids

- 1. Topical
  - a. Potentially useful only in very mild cases or as adjunctive therapy
- 2. Regional
  - a. Anterior non-necrotizing scleritis
  - b. Controversial, as regards potential complication of localized necrotizing disease following injection, though several case series suggest efficacy without significant risk
    - i. Extensive counselling of risk required
- 3. Systemic
  - a. Non-necrotizing scleritis not responsive to NSAIDs and necrotizing scleritis (initial agent)
  - b. Oral or high dose intravenous pulsed

#### C. Immunomodulatory therapy

- 1. Refer to treatment paradigm monograph
- 2. Cyclophosphamide or rituximab are the drugs of choice for granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis), polyarteritis nodosa

#### D. Pain management

- 1. Oral NSAIDs
- 2. Judicious use of oral narcotics
- 3. Topical atropine once or twice daily for ciliary spasm

#### E. Surgery

- 1. Scleral surgery may be needed to stop or repair scleral perforation and/or to harvest tissue for diagnostic studies, especially if infection has not been excluded as a possible cause
  - a. Materials used for grafting include sclera, but the scleral graft may melt and some have recommended autogenous periosteum
- V. List the complications of treatment, their prevention and management (See Nonsteroidal anti-inflammatory drugs) (See Corticosteroids) (See Cyclophosphamide and chlorambucil) (See Methotrexate) (See Azathioprine) (See Cyclosporine) (See Mycophenolate)

#### VI. Describe disease-related complications

- A. Occur late in the course of the disease
- B. Mainly in necrotizing scleritis cases
- C. Visual loss of necrotizing scleritis, due to
  - 1. Uveitis
    - a. Poor prognostic sign
  - 2. Keratitis
    - a. Peripheral ulcerative keratitis is particularly difficult to treat and poor visual prognosis
    - b. Interstitial keratitis in rheumatoid arthritis
  - 3. Glaucoma
    - a. Scleral edema
    - b. Increased episcleral venous pressure
  - 4. Cataract
    - a. Remove using a clear corneal incision
  - 5. Fundus abnormalities
    - a. Serous retinal detachments

b. Cystoid macular edema

#### VII. Describe appropriate patient instructions

A. Contact ophthalmologist for worsening pain or vision loss

#### B. Life threatening disease association especially with

- 1. Granulomatosis with polyangiitis (GPA) (previously known as Wegener's granulomatosis)
- 2. Polyarteritis nodosa
- 3. Relapsing polychondritis (laryngeal inflammation)

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Scleritis and Episcleritis: Diagnosis and Management, Module #9, 1995.
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# Herpetic anterior uveitis

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Herpes simplex
  - a. In most cases herpes simplex virus (HSV)-1, with or without herpetic corneal infection
  - b. Rarely HSV-2 may be associated with anterior segment Herpetic infection
- 2. Varicella-zoster virus (VZV)
- 3. CMV anterior uveitis in immunocompetent patients
  - a. Confirmed by PCR of aqueous

#### B. List the pertinent elements of the history that HSV or VZV as a cause of uveitis

- 1. HSV
  - a. Recurrent acute anterior uveitis with all recurrences being in the same eye (may rarely be bilateral)
  - b. Chronic unilateral anterior uveitis (rarely it is bilateral)
  - c. Foreign body sensation, pain and redness
    - i. Pain may be out of proportion to the amount of cellular inflammation
  - d. History of herpetic corneal disease (not necessary for diagnosis)
  - e. History of oral or genital cold sores (not necessary for diagnosis)
- 2. VZV
  - a. Usually have a history of ipsilateral herpes zoster skin lesions
    - i. Note rarely skin lesions are not present (zoster sine herpeticum)
  - b. Pain, redness, photophobia are common
- 3. CMV
  - a. May present with redness, pain, and photophobia similar to Posner-Schlossman syndrome
  - b. Asymptomatic presentation similar to Fuchs heterochromic uveitis may also occur

#### C. Describe pertinent clinical features

- 1. HSV
  - a. May be associated with herpes simplex corneal epithelial disease
    - i. Usually mild and transient
  - b. May be associated with herpes simplex corneal stromal disease
    - i. May be severe

- ii. Severity of uveitis not correlated with severity of corneal disease
- iii. May be associated with corneal edema ("endotheliitis")
- c. Associated with disciform keratitis
  - i. May see line of keratic precipitates resembling rejection line, or clustered under area of corneal stromal thickening
- d. Isolated anterior chamber inflammation with no corneal signs, or only corneal edema ("endotheliitis")
- e. Keratic precipitates (KP) highly variable, may be absent
  - i. Small and stellate, distributed throughout the entire corneal endothelial surface
    - i) The KP may also be large and mutton fat underlying an area of corneal haze, often in the central cornea
  - ii. Brown color may be present
- f. Corneal scarring or haze
  - i. May be subtle
  - ii. May be best seen with sclerotic scatter
  - iii. Herpetic iritis can occur in the absence of corneal disease
- g. Elevated intraocular pressure (IOP) with signs of acute iritis whereas most acute iritis is associated with low IOP
- h. Variable corneal anesthesia
- i. Pupillary dilation and irregular pupil (even in absence of synechiae)
- j. Intra-iris hemorrhage rarely occurs
- k. Iris atrophy; transillumination defects
  - i. Diffuse or sectoral with loss of iris pigment epithelium and iris stroma
- I. Hypopyon can occur but it is not common
- m. The presence of blood admixed with the white blood cells should suggest the diagnosis of herpes
- 2. VZV
  - a. May occur in absence of corneal disease
  - b. Intraocular pressure is often high
  - c. Keratic precipitates are small or large
  - d. May be severe anterior chamber reaction with fibrin
  - e. Iris atrophy with transillumination defects
  - f. May be associated with scleritis
- 3. CMV

- a. Intraocular pressure may be very high (>40mm Hg)
- b. Mild intraocular inflammation (<2+ cells)
- c. Small, diffuse keratic precipitates
- d. Iris atrophy without heterochromia
- e. No iris nodules
- f. No posterior synechiae

#### D. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Primarily a clinical diagnosis
- 2. May (rarely) do aqueous paracentesis for polymerase chain reaction (PCR)
- 3. Serology rarely helpful
  - a. Absence of antibody probably excludes disease

#### II. Define the risk factors

#### A. HSV anterior uveitis

- 1. Herpetic corneal disease
- 2. Prior HSV infection

#### B. VZV anterior uveitis

- 1. Increased risk with immunosuppression
  - a. Advanced age
  - b. Secondary to immunosuppressive agents
  - c. Leukemia, lymphoma and human immunodeficiency virus (HIV) infection

#### III. List the differential diagnosis

- A. Glaucomatocyclitic crisis
- B. Fuchs heterochromic iridocyclitis
- C. Idiopathic acute or chronic anterior uveitis
- D. Uveitis associated with sarcoidosis
- E. Anterior uveitis associated with toxoplasmosis and high intraocular pressure
- F. Anterior uveitis associated with CMV retinitis in an immunocompetent patient

#### IV. Describe patient management in terms of treatment and follow-up

A. HSV anterior uveitis

- 1. Associated with epithelial keratitis
  - a. Treat epithelial keratitis with topical antivirals
  - b. May add cycloplegic agent
  - c. Avoid topical corticosteroids unless given with oral antiviral
  - d. May benefit from oral antivirals in standard doses for herpes simplex infection
    - i. Acyclovir
    - ii. Famciclovir
    - iii. Valacyclovir
  - e. Topical corticosteroids
  - f. Topical antivirals (primarily if there is also epithelial disease)
  - g. Long term, low dose systemic maintenance anti-viral therapy may be necessary in severe, recalcitrant cases
- 2. Unassociated with active corneal disease
  - a. May benefit from oral antivirals
    - i. Acyclovir
    - ii. Famciclovir
    - iii. Valacyclovir
  - b. Topical corticosteroids
  - c. Topical cycloplegia

#### B. VZV anterior uveitis

- 1. Systemic antiviral therapy
  - a. Ideally started within 72 hours of skin lesions
  - b. Agents include
    - i. Acyclovir
    - ii. Valacyclovir
    - iii. Famciclovir
  - c. Such treatment may reduce incidence of anterior uveitis
- 2. Topical corticosteroids and cycloplegics
- 3. Pain control
  - a. Consider referral to pain clinic for post-herpetic neuralgia
- 4. Disease may persist for years and requires regular follow up
  - a. Long term, low-dose systemic anti-viral therapy may be necessary for severe, recalcitrant cases

#### C. CMV anterior uveitis

- 1. Oral valganciclovir in conjunction with topical corticosteroids
  - a. Used for several months or years
  - b. Recurrence may occur if therapy stopped
- 2. Topical corticosteroids and cycloplegics
- 3. Glaucoma control may be difficult
- 4. Disease may persist for years

#### V. List the complications of treatment, their prevention and management

#### A. Elevated IOP from topical corticosteroids

- 1. Use judiciously
- B. Epithelial keratitis from toxicity from prolonged topical antivirals
- C. Acyclovir is well tolerated in patients with normal renal function
  - 1. Monitor renal function yearly; more often where other renal risk factors

#### VI. Describe disease-related complications

- A. Glaucoma
- B. Hypotony
- C. Cataract
- D. Iris atrophy
- E. Dilated pupil
- F. Post-herpetic neuralgia

#### VII. Describe appropriate patient instructions

- A. May require long term use of antiviral agents
- B. Sometimes may also require chronic low dose topical corticosteroids
- C. Necessity of follow-up, medication compliance

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.2-3.
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# Necrotizing herpetic retinitis: acute retinal necrosis and progressive outer retinal necrosis

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Varicella zoster virus (VZV)
  - a. Most common agent
- 2. Herpes simplex virus (HSV), usually HSV II
  - a. Most common etiologic virus in patients < 25 years old
  - b. Has occurred years after prior herpetic encephalitis
- 3. Cytomegalovirus least common in the immunocompetent patient

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Acute retinal necrosis
  - a. Relatively immunocompetent patient
  - b. Diagnosis of ARN syndrome implies prominent intraocular inflammation
- 2. Progressive outer retinal necrosis
  - a. Immunosuppressed patients. e.g., acquired immune deficiency syndrome (AIDS) with low CD4 count
  - b. Absence of prominent intraocular inflammation

#### C. List the pertinent elements of the history

- 1. Decreased vision
- 2. Floaters
- 3. May have pain in patients with acute retinal necrosis, rare in progressive outer retinal necrosis

#### D. Describe pertinent clinical features

- 1. Acute retinal necrosis
  - a. Peripheral retinal necrosis with discrete borders
  - b. Rapid progression in the absence of anti-viral therapy
  - c. Circumferential spread
  - d. Occlusive vasculopathy involving retinal arterioles
  - e. Prominent inflammation in anterior chamber and vitreous, with or without optic nerve

inflammation

- f. May have associated scleritis
- 2. Progressive outer retinal necrosis
  - a. Relatively clear vitreous
  - b. Clinical features suggestive of outer retinal or full thickness retinal necrosis involving peripheral retina with or without macular involvement and relative sparing of retinal arterioles
  - c. Lesions rapidly coalesce
  - d. Extremely rapid progression to total retinal detachment and optic atrophy

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Polymerase chain reaction (PCR) of aqueous or vitreous fluids
- 2. Intraocular antibody determinations

#### II. Define the risk factors

- A. Prior herpetic infection, especially, herpetic encephalitis
- B. Immunosuppression in cases of progressive outer retinal necrosis
- C. Herpes zoster ophthalmicus in patients with immunocompromise

#### III. List the differential diagnosis

- A. Other infections
  - 1. Toxoplasmosis
  - 2. Fungal
- B. Behçet's disease with retinal vasculitis
- C. Primary CNS lymphoma with ocular involvement
- D. Systemic leukemias and primary intraocular lymphomas

#### IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options for acute retinal necrosis

- 1. Initial IV acyclovir followed by oral acyclovir
- 2. Initial oral valacyclovir (1 gram three times daily), usually combined with intravitreal antiviral injections, followed by oral valacyclovir or acyclovir
- 3. Initial oral famciclovir, usually combined with intravitreal antiviral injections, followed by oral famciclovir or acyclovir
- 4. Duration of maintenance therapy with oral anti-viral agents to prevent involvement of second eye:

6 weeks to 3 months if normal immunity

- a. Most involvement of second eye occurs within first 3 months
- b. Late disease after 3 months can occur in contralateral eye
- c. Recurrences in same eye are rare
- d. Prolonged oral therapy often given even if both eyes involved initially
- e. The duration of treatment with oral anti-viral agents to protect the second eye is not well established. Some have suggested indefinite prophylaxis especially if the agent is herpes simplex, if tolerated as second eye involvement (or retinitis after herpes encephalitis) can be delayed by many years
- 5. Oral prednisone usually prescribed in early stages of ARN, usually within 24 hours of systemic and/or intravitreal therapy to treat the significant inflammatory component of this disease and tapered over weeks. Supplementary periocular corticosteroid injections may be useful to reduce inflammation after the infection is controlled

#### B. Describe medical therapy options for progressive outer retinal necrosis

- 1. IV acyclovir high risk of bilateral blindness
- 2. Combination IV therapy with 2 agents (e.g., acyclovir or ganciclovir plus foscarnet) improved efficacy compared to monotherapy with acyclovir
- 3. Combination systemic antiviral therapy plus intravitreal therapy with ganciclovir and/or foscarnet at induction, then maintenance doses

#### C. Describe surgical therapy options

- 1. Consider laser photocoagulation surgery for prophylaxis of retinal detachment
- 2. Consider vitrectomy with demarcated laser photocoagulation in eyes with dense vitritis or media opacity preventing laser photocoagulation
- 3. Vitrectomy with silicone oil for retinal detachment

#### V. List the complications of treatment, their prevention and management

- A. Risk of renal failure with high dose IV acyclovir
- B. Crystalluria with high doses
- C. Patients with baseline impairment in creatinine clearance require reduction in dose frequency or amount
- D. Monitor creatinine, encourage high oral intake, measure input and output

#### VI. Describe disease related complications

#### A. Retinal detachment

- 1. Often occurs at time of vitreous detachment 8 to 12 weeks after onset
- 2. Laser prophylaxis to demarcate necrotic retina may reduce risk of detachment

#### B. Optic atrophy

- 1. May be secondary to overall loss of retinal substance
- 2. May be primary and related to direct optic nerve involvement, especially in post-encephalitic cases

#### C. Capillary non-perfusion

- 1. Related to retinal vascular inflammation
- 2. Can involve macular region
- D. Epiretinal membranes
- E. Vitreous membranes
- F. Cataract
- G. Hypotony

#### VII. Describe appropriate patient instructions

- A. Risk of developing the retinitis in the contralateral eye (if disease unilateral)
- B. Risk of retinal detachment
- C. Potentially blinding disease
- D. Need for adequate hydration with high dose acyclovir
- E. Follow-up is every one to four weeks during the first 3 months after infection and periodically thereafter

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, HIV/AIDS and the Eye: A Global Perspective, 2002.
- 3. AAO Focal Points: Clinical Modules for Ophthalmologists, Infectious posterior uveitis, Module #3, 2005.
- 4. Bonfioli AA, Eller AW. Acute retinal necrosis. Semin Ophthalmol 205;20:155-60.
- 5. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005.
- 6. Huynh TH, Johnson MW, Comer GM, Fish DN. Vitreous penetration of orally administered valacyclovir. Am J Ophthalmol 2008;145(4):682-6.

# Cytomegalovirus retinitis

#### I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Cytomegalovirus (CMV) is in the herpesvirus family
- 2. Transmission
  - a. Congenital infection with vertical transmission from a mother infected during pregnancy
  - b. Acquired infection from sexual contact, contact with other body fluids, including urine
  - c. Transfusion of infected blood
  - d. Transplantation of an organ from a CMV+ donor to a CMV- recipient
- 3. Latency
  - a. CMV is a deoxyribonucleic acid virus that can establish latency in a variety of human cell types
  - b. Recurrence from latency can occur when the immune system becomes impaired
- 4. Clinical manifestations of CMV infection
  - a. Congenital infection can have devastating neurologic and ocular effects, including blindness
  - b. Acquired infection in children or adults may cause signs and symptoms similar to the infectious mononucleosis syndrome
  - c. Recurrent infection depends on body tissue affected
    - i. In HIV/AIDS, retinitis is the most common, clinically important disease associated with CMV
    - ii. Retinal involvement occasionally occurs with other forms of immunosuppression such as patients undergoing solid organ transplantation
    - iii. CMV retinitis patients with HIV/AIDS may have symptomatic CMV infection in other organs, particularly the GI tract (esophagitis, colitis), and the central nervous system

#### B. Define the relevant aspects of epidemiology of this disease

- 1. Certain populations are more likely to have serologic evidence of prior infection with CMV
  - a. Men who have sex with men
  - b. Childcare workers or women with more pregnancies
  - c. Hemophiliacs have a low rate of prior exposure
  - d. Persons from developing countries
- 2. CMV retinitis from recurrent disease occurs in patients who are immunocompromised
  - a. Patients with HIV/AIDS

- b. Organ-transplant patients and other patients with iatrogenic systemic immunosuppression
- c. Rarely, after local immunosuppression with intravitreal injection of triamcinolone or placement of fluocinolone acetonide implant
- 3. CMV retinitis is still one of the major opportunistic infections (OIs) in patients with AIDS
  - a. Approximately 30% of AIDS patients developed CMV retinitis in the pre-highly actively anti-retroviral therapy (HAART) era in western countries
  - b. Number of new cases in developed countries was reduced by 80% with the advent of HAART and has stabilized at this level in the post-HAART era
  - c. In developing countries, particularly in resource-poor settings, CMV retinitis remains an unmet clinical challenge and a substantial cause of blindness
- 4. In AIDS, CMV retinitis usually occurs in patients with CD4+ T-lymphocyte counts < 50 cells/mm<sup>3,4</sup> (rate ~20%/person-year) and rarely occurs at CD4 counts > 200 (rate < 5%/person-year)

#### C. List the pertinent elements of the history

- 1. Ocular symptoms
  - a. The eye is virtually always pain-free, and the patient may be entirely asymptomatic
  - b. Blurred vision is the most common ocular symptom followed by vitreous floaters. Some patients have photopsia
  - c. Peripheral disease may not produce perceived scotomata and most patients with central disease will complain of blurred vision rather than field loss
  - d. Presentation with moderate to severe permanent vision loss in one eye is not uncommon
- 2. CMV retinitis, as the first manifestation of AIDS leading to diagnosis, is uncommon (less than 1%) in western countries
  - a. History of human immunodeficiency virus (HIV) infection with recent CD4 counts < 50 is helpful
  - b. History of other opportunistic infections
  - c. History of prior infection with CMV in another organ
- 3. Newly diagnosed CMV retinitis usually occurs in the setting of active viral shedding in blood and urine
  - a. Other body tissues commonly involved
  - b. Constitutional symptoms such as fever, malaise and weight loss are common and may be related to disseminated infection in the blood
  - c. Symptoms related to specific organ systems may occur
    - i. Diarrhea from gastrointestinal involvement
    - ii. Pain on swallowing from esophageal involvement
    - iii. CMV radiculopathy
- 4. Inquire about risk factors for HIV infection

- 5. If an organ transplant patient, inquire about CMV status of donor and recipient at time of transplantation, any CMV prophylaxis treatment, and immunosuppressive drugs
- 6. In patients with HIV/AIDS and at high risk of CMV retinitis (CD4 count below 50), routine screening with the pupil fully dilated and using an indirect ophthalmoscope can be carried out every 3 months, because examination based only on history and symptoms is unreliable

#### D. Describe pertinent clinical features

- 1. CMV causes a necrotizing retinitis with the following basic characteristics
  - a. Dense retinal whitening
  - b. An irregular active or advancing border with satellite lesions is highly characteristic
  - c. Intraretinal hemorrhage is common but not invariable, and not essential to diagnosis
  - d. Centrifugal spread with central clearing
  - e. Tendency to follow vessels
- 2. The patient with CMV retinitis may predominantly show one of several different typical clinical presentations
  - a. Thick or fluffy, edematous retinal necrosis with hemorrhage along one of the major vascular arcades ("cottage cheese and ketchup")
  - b. Dry granular appearing retinal whitening of the peripheral retina
  - c. Isolated involvement of the optic nerve, having the same appearance as necrotizing retinitis, occurs is a small percentage of cases. The optic nerve is more commonly involved from spread from adjacent retinitis
  - d. Frosted branch angiitis occurs in small percentage of patients
- 3. Unilateral disease is more common, but one-third to one-half of cases are bilateral. Most eyes contain only one focus of retinitis
- 4. Intraocular inflammation is generally "low-grade" with a clear media
  - a. A few anterior chamber cells, and some keratic precipitates (KP) and fibrin strands on the corneal endothelium are common
  - b. The eye is white and there are usually not posterior synechiae, except with immune recovery

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. An eye examination by an experienced ophthalmologist is the clinical standard for diagnosing CMV retinitis in patients with a high risk of disease
- 2. HIV antibody status and CD4 count are the essential tests to establish the level of risk for most patients suspected of having CMV retinitis
- Differentiating CMV retinitis from other types of necrotizing retinitis in equivocal cases is best done by polymerase chain reaction (PCR) for herpes class viruses and toxoplasmosis on aqueous humor collected by anterior chamber paracentesis
- 4. Differentiating CMV retinitis from HIV retinopathy is accomplished by serial examination after

#### II. Define the risk factors

- A. HIV infection with CD4+ T-lymphocyte count <200 cells/ml, with much higher risk if CD4+ count < 50
- B. Organ transplant recipient on immunosuppressive medication, especially those who were negative for CMV antibodies pre-transplant and received a transplant from a seropositive donor
- C. Other patients on high-dose immunosuppressive medication

#### III. List the differential diagnosis

- A. HIV retinopathy with hemorrhages and cotton wool spots
- B. Necrotizing herpetic retinitis due to varicella zoster or herpes simplex virus
- C. Toxoplasmic chorioretinitis
- D. Syphilitic chorioretinitis
- E. Intraocular lymphoma
- F. Other bacterial and fungal infection of the retina

#### IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Induction therapy with high doses of anti-viral medication for 2 to 3 weeks
  - a. Oral valganciclovir
  - b. Intravenous ganciclovir
  - c. Intravenous foscarnet
- 2. Maintenance therapy with lower doses of anti-viral medication until there is improvement in the immune system
  - a. Oral valganciclovir
  - b. Intravenous ganciclovir
  - c. Intravenous foscarnet
- 3. Withdrawal of specific anti-CMV therapy is generally possible under the following conditions
  - a. HAART therapy and reconstitution of the immune system with the CD4 count above 100 for at least 3 months if the retinitis is completely inactive

#### B. Describe surgical therapy options

1. Intravitreal injection of ganciclovir or foscarnet (off-label) for induction therapy for patients with immediately sight-threatening lesions, therapy for relapsed or resistant disease, or for patients intolerant to systemic medication
- 2. Laser barrier for retinal detachment prophylaxis may be considered for patients with inactive retinitis and large (>25% retinal surface) areas of chorioretinal atrophy.
- 3. With the development of HAART, availability of effective oral therapy for CMV (valganciclovir), and increased clinical experience with simple intraocular injection, the indications for surgical insertion of a ganciclovir-containing intraocular device into the vitreous cavity have largely vanished. The ganciclovir implant remains a consideration for patients who are non-compliant

# V. List the complications of treatment, their prevention and management

# A. Hematologic toxicity

- 1. Neutropenia, anemia, and thrombocytopenia common with ganciclovir
- 2. Anemia may occur with foscarnet
- 3. Treatment
  - a. Bone marrow stimulants
  - b. Withdrawal of other bone-marrow suppressive drugs

#### B. Renal toxicity

- 1. Common with foscarnet
  - a. Incidence reduced with careful dose calculation based on creatinine clearance
  - b. Adequate hydration may also help prevent toxicity
- C. Other: nausea, penile ulceration and pancreatitis from foscarnet

# VI. Describe disease-related complications

- A. Blindness from retinitis involving either the macula or optic nerve
- B. Retinal detachment
- C. Immune Recovery Uveitis (IRU) with reconstitution of the immune system in HIV-positive patients with CMV retinitis, with vision loss from
  - 1. Vitritis
  - 2. Cystoid macular edema
  - 3. Epiretinal membrane
  - 4. Cataract
- D. Death from coincident extra-ocular CMV disease

# VII. Describe appropriate patient instructions

- A. Take all prescribed CMV medications without skipping doses
- B. Report changes in vision promptly

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, HIV: HIV/AIDS and the Eye: A Global Perspective, 2002, p. 56-62.
- 3. Holbrook JT, Jabs DA, Weinberg DV, et al. Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before widespread availability of highly active antiretroviral therapy. Arch Ophthalmol 2003;121:99-107.
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# Other rare infections: Human T-cell lymphotrophic virus

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Infection with human T-cell lymphotrophic virus (HTLV-1), a single stranded RNA retrovirus
- 2. HTLV-1 is the cause of a number of diseases
  - a. Adult T-cell leukemia (ATL)
  - b. HTLV-1-associated myelopathy (HAM)/tropical spastic paresis (TSP)
  - c. HTLV-1 uveitis
  - d. Other inflammatory diseases

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Worldwide, 10-20 million people are infected but most are asymptomatic
- 2. Transmitted by sexual contact, sharing of contaminated needles and syringes, blood transfusion, as well as vertical transmission from mother to child including breast-feeding
- 3. Endemic areas include:
  - a. Japan: highest prevalence
  - b. Parts of Central Africa
  - c. Parts of South America
  - d. Caribbean islands
  - e. Southeastern United States
- 4. Rare in North America- except S.E. U.S.(see above)

#### C. List the pertinent elements of the history

- 1. Most infected patients remain asymptomatic
- 2. Patents with HTLV-1 uveitis frequently report blurred vision and floaters

#### D. Describe pertinent clinical features

- 1. Manifestations appear to differ by presence or absence of major systemic disease
  - a. Asymptomatic, infected patients
    - i. Keratoconjunctivitis sicca
    - ii. Scleritis
    - iii. Interstitial keratitis
    - iv. Uveitis (anterior and intermediate uveitis most common)

- i) Anterior uveitis (granulomatous/nongranulomatous)
- ii) Intermediate uveitis
- iii) Retinal vasculitis
- iv) Retinochoroidal lesions
- v) Papilledema
- vi) Cystoid macular edema (CME)
- vii) Optic atrophy

## E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Screening tests
  - a. Enzyme immunoassay (EIA)
  - b. Particle agglutination test
- 2. Confirmatory tests
  - a. Western blot: indeterminate results may occur
  - b. Polymerase chain reaction (PCR)

# II. Define the risk factors

- A. Unprotected sexual intercourse
- B. Children with an infected mother (intrauterine/ peripartum transmission, breast feeding)
- C. Sex workers
- D. Sharing needles or syringes
- E. Transfusion of infected blood products

# III. List the differential diagnosis

- A. HIV
- B. Syphilis
- C. Cytomegalovirus
- D. Epstein-Barr virus
- E. Multiple sclerosis
- F. Lyme disease
- G. Sarcoidosis

# IV. Describe patient management in terms of treatment and follow-up

A. Describe the natural history, outcome and prognosis

- 1. Most patients with anterior uveitis or intermediate uveitis respond to therapy with corticosteroids
  - a. 60% are unilateral
  - b. Recurrent disease in up to 50% of patients
- 2. Patients with retinal vasculitis typically respond to therapy with periocular or systemic corticosteroids
- 3. Chronic interstitial keratitis may occur
  - a. More common in patients with HAM/TSP
  - b. White anterior stromal opacities: do not respond to topical corticosteroid therapy

#### B. Describe medical therapy options

- 1. Corticosteroids
  - a. Topical
  - b. Periocular
  - c. Systemic

# V. List the complications of treatment, their prevention and management

- A. Cataract
- B. Glaucoma

# VI. Describe disease-related complications

- A. Cataract
- B. Glaucoma
- C. Epiretinal membrane
- D. Retinal vascular occlusion
- E. Retinal degeneration
- F. Optic atrophy
- G. CME

# VII. Describe appropriate patient instructions

A. None

# Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

- 2. Buggage RR. Ocular manifestations of human T-cell lymphotropic virus type 1 infection. Curr Opin Ophthalmol 2003;14:420-425.
- 3. Verdonck K, González E, Van Dooren S, et al. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis 2007;7:266-281.

# Ocular histoplasmosis syndrome

# I. Approach to establishing the diagnosis

# A. Describe the etiology of the disease

- 1. Ocular histoplasmosis syndrome is believed to be due to exposure to *Histoplasma capsulatum* via the respiratory tract
  - a. Respiratory flu-like illness as child or young adult
  - b. The organism may then spread through the bloodstream from the lungs to the choroid
- 2. Definitive histopathological evidence of *Histoplasma capsulatum* in chorioretinal scars and PCR evidence as well

# B. Define the relevant aspects of epidemiology of the disease

- 1. This condition occurs most frequently in patients who live near the Ohio River and Mississippi River valley areas and watershed areas
- 2. Mid-Atlantic region
- 3. Similar syndrome seen in Northern Europe, in areas not endemic for Histoplasma

# C. List the pertinent elements of the history

- 1. Asymptomatic if no choroidal neovascularization (CNV)
- 2. Central scotoma, visual loss and metamorphopsia if CNV develops

#### D. Describe pertinent clinical features

- 1. Atrophic "punched-out" round or streak-shaped scars often prominent in retinal periphery
- 2. Peripapillary atrophy
- 3. CNV (arising from macular scars or peripapillary scars)
- 4. Absence of vitreous cells required for diagnosis although choroidal inflammation without vitreous cells or choroidal neovascularization may occur and cause vision loss in immunocompetent patients
- 5. In rare cases immunocompromised patients exposed to the fungal pathogen may develop
  - a. Endophthalmitis from Histoplasma capsulatum
  - b. Solitary histoplasmic granuloma
  - c. Systemic antifungal therapy is required in these cases

# II. Define the risk factors

- A. Exposure to Histoplasma as a child or young adult
- B. Residing in endemic areas (Mississippi and Ohio River Valleys)

# III. List the differential diagnosis

- A. Multifocal choroiditis and panuveitis
- B. Age-related macular degeneration (AMD)
- C. Multifocal toxoplasmosis
- D. Idiopathic CNV
- E. Punctate inner choroidopathy (PIC)
- F. Myopic degeneration and CNV

# IV. Describe patient management in terms of treatment and follow-up

#### A. If no CNV is present

- 1. Observation
- 2. Amsler grid
- 3. If no CNV is present and vision loss occurs from parafoveal active choroiditis
- 4. Oral, periocular, or intravitreal corticosteroids
- 5. +/-Oral antifungals Itraconazole
- 6. Close follow-up for development of choroidal neovascularization

#### B. If CNV develops

- 1. Anti-vascular endothelial growth factor (VEGF) therapy
  - a. Bevacizumab (Avastin), pegaptanib sodium (Macugen), ranibizumab (Lucentis) intravitreal injection
  - b. Not currently FDA-approved for CNV in histoplasmosis
- 2. Periocular or Intravitreal triamcinolone
- 3. Laser therapy options
  - a. Photodynamic therapy (VOH study)
  - b. Thermal laser photocoagulation for extrafoveal and juxtafoveal CNV if classic CNV or well-defined CNV
- 4. Rarely large lesions with poor vision and extrafoveal vascular ingrowth sites may be amenable to subfoveal surgery

# V. List the complications of treatment

- A. Intravitreal anti VEGF therapy: rare cardiovascular complications (myocardial infarction (MI), stroke), endophthalmitis
- B. Intravitreal triamcinolone: glaucoma, cataract, endophthalmitis (infectious, sterile)

- C. Laser: extension of laser burn or scar into fovea
- D. Recurrence of CNV despite treatment

# VI. Describe disease-related complications

A. Loss of central vision due to subfoveal CNV

# VII. Describe appropriate patient instructions

- A. Amsler grid for both eyes
- B. Prognosis depends on location of atrophic scars, although CNV can develop in eye with previously normal macula

# Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 12: Retina and Vitreous, 2013-2014.
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- 3. Busquets MA, Shah GK, Wickens J, et al. Ocular photodynamic therapy with verteporfin for choroidal neovascularization secondary to ocular histoplasmosis syndrome. Retina 2003;23:299-306.
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- 7. Berger AS, Conway M, Del Priore LV, et al. Submacular surgery for subfoveal choroidal neovascular membranes in patients with presumed ocular histoplasmosis. Arch Ophthalmol 1997;115:991-6.
- 8. Melberg NS, Thomas MA, Dickinson JD, et al. Managing recurrent neovascularization after subfoveal surgery in presumed ocular histoplasmosis syndrome. Ophthalmology 1996;103:1064-7; discussion 1067-8.
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- 11. Callanan D, Fish GE, Anand R. Reactivation of inflammatory lesions in ocular histoplasmosis.

Arch Ophthalmol. 1998;116:470-474.

# Toxoplasmic retinochoroiditis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of the disease - Toxoplasmosis gondii

- 1. Protozoal infection of the retina
  - a. The choroid may also be infected in immunocompromised hosts
- 2. Exists as inactive scars, latent infection encysted in host cells at borders of scars, or active replicating infection
- 3. Active infection produces inflammatory reaction
- 4. Infection is tissue destructive

# B. Define the relevant aspects of epidemiology of the disease

- 1. Regional differences in prevalence of toxoplasmosis infection
- 2. Definitive host is the cat
- 3. Infective forms are oocysts (soil forms which are ingested) and tachyzoites (metabolically active and antigenic organism)
  - a. Usually ingested in contaminated food or water or in undercooked meat
- 4. Vertical transmission (intrauterine infection) possible
  - a. Formerly thought to be the most common type of transmission
  - b. Acquired disease in postnatal period is more common than previously appreciated
  - c. Thought to occur only if mother acquires infection for the first time while pregnant
- 5. Most toxoplasma retinochoroiditis is acquired after birth (>50%)

#### C. List the pertinent elements in the history

- 1. Exposure to materials fecally contaminated by cats
  - a. Litter boxes
  - b. Garden soil
  - c. Improperly stored water (unsecured reservoirs)
  - d. Food
- 2. Exposure to undercooked meats from infected animals, which in turn were exposed to material fecally contaminated by cats
- 3. Exposure to uncooked vegetables grown in fecally contaminated soil
- 4. Maternal prenatal infection
- 5. Recent febrile illness or lymphadenopathy (acquired toxoplasmosis)

# D. Describe pertinent clinical features

- 1. Unilateral focal chorioretinitis adjacent to healed chorioretinal scar
  - a. Healed scars may be multiple, but usually only one reactivates at a time
  - b. Atypical forms of extensive chorioretinitis can occur in immunocompromised individuals e.g., patients with acquired immunodeficiency syndrome (AIDS) or those over age 70
    - i. Up to 25% of AIDS patients with ocular toxoplasmosis may have concomitant CNS toxoplasmosis
  - c. In acquired disease, the typical chorioretinal scar may not be present
  - d. Active chorioretinitis is yellow-white, slightly elevated, with a relatively well-defined border
- 2. Intraocular inflammation
  - a. Anterior uveitis
    - i. Often granulomatous
  - b. Intermediate uveitis
    - i. Often intensified over the lesion
  - c. Vasculitis
    - i. Variably present
      - i) Often arteritis, but also periphlebitis
      - ii) May be remote from the chorioretinitis
  - d. Optic neuropathy
    - i. Secondary inflammation in nerve or infective neuroretinitis
  - e. Ocular hypertension
    - i. Resolves with treatment of the anterior uveitis
- 3. Pathologic findings
  - a. Intracellular cysts containing bradyzoites are found at the border of healed lesions
  - b. Active lesions are characterized by the presence of tachyzoites
  - c. Both cysts and tachyzoites are found in retina and not in choroid
  - d. Retinal necrosis ensues from active disease with granulomatous inflammation in the choroid
  - e. Healed lesions show destruction of retina, retinal pigment epithelium, and choroid with variable hyperpigmentation

# E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Confirmation of exposure to toxoplasmosis by serum antibody titers
  - a. High sensitivity and low specificity because of high prevalence of positive antibody titers in general population (a positive serology does not make the diagnosis but only confirms exposure)
  - b. Immunoglobulin (Ig) M antibody determinations helpful in the diagnosis of acquired

toxoplasmosis

- c. Cases of confirmed toxoplasmosis have been reported in which serum toxoplasmosis titers were negative
- 2. Determination of toxoplasmosis IgG or IgA antibody titers in aqueous humor useful in cases with atypical features
- 3. Polymerase chain reaction (PCR) of aqueous humor for toxoplasmosis DNA useful in older patients with large lesions or in patients who are immunocompromised
- 4. CT or MRI of the brain in patients with AIDS and toxoplasmosis since up to 25% may have CNS toxoplasmosis

# II. Define the risk factors

#### A. Risk of congenital infection

- 1. Acquired toxoplasmosis infection in a pregnant woman
  - a. Most severe effects on fetus if acquired during first trimester
  - b. Risk of transmission greatest if acquired during third trimester
- 2. Screening programs for non-immune mothers are in place in Europe
  - a. Seroconversion treated with antibiotic therapy
  - b. Prenatal treatment reduces fetal effects

#### B. Risk of acquired infection

- 1. Residence in endemic area
- 2. Contact with cat litter or soil contaminated by cats
- 3. Consumption of undercooked meat
- 4. Consumption of uncooked vegetables from soil contaminated by cats
- 5. Consumption of contaminated water

#### C. Risk of recurrent infection

- 1. Intraocular surgery such as cataract surgery or instrumentation of glaucoma filtering blebs
- 2. Impairment of immune system (esp. AIDS) or advanced age

# III. List the differential diagnosis

#### A. Infections

- 1. Toxocariasis
- 2. Cytomegalovirus retinitis
- 3. Necrotizing herpetic retinitis

- 4. Syphilis
- 5. Focal fungal or bacterial infections
- B. Posterior uveitis
- C. Masquerade syndromes
  - 1. Intraocular tumors
  - 2. Intraocular lymphoma

# IV. Describe patient management in terms of treatment and follow-up

- A. Decision to treat based on proximity to macula and optic nerve, amount of inflammation, and vision
  - 1. Sight-threatening infections always treated
  - 2. Small, peripheral lesions often observed
  - 3. Infection is self-limited in most cases in healthy patients

# B. Antibiotic treatment - there are no studies to suggest that one therapy is more effective than another

- 1. Combined therapy
  - a. Pyrimethamine has been classically employed
    - i. Can be combined with sulfadiazine or triple-sulfa, azithromycin, or clindamycin
    - ii. Usually given with leucovorin to mitigate hematologic toxicity
  - b. Trimethoprim-sulfamethoxazole increasing in use
    - i. Can be combined with clindamycin for increased efficacy
    - ii. Economical
- 2. Monotherapy generally reserved for non-sight-threatening disease
  - a. Doxycycline or minocycline
  - b. Azithromycin
  - c. Atovaquone
  - d. Clindamycin. Pregnancy Category B
- 3. Other agents
  - a. Clarithromycin
  - b. Intravitreal clindamycin
- 4. Maintenance therapy
  - a. Usually used and may be required in
    - i. Patients with AIDS who do not demonstrate immune reconstitution

- ii. Patients with multiple sight threatening recurrences
- b. Reduced drug dosage and frequency compared to induction levels
- c. A common regimen is Bactrim DS® three times weekly
- 5. Congenital toxoplasmosis
  - a. Antibiotic therapy may be required for up to 1 year in newborns
- 6. Duration of Therapy There are no specific guidelines on duration of antibiotic therapy but duration is tailored to response and requires a minimum of 4-6 weeks of systemic antibiotics

#### C. Anti-inflammatory treatment

- 1. Topical corticosteroids in patients with significant anterior chamber reaction
- 2. Oral corticosteroids
  - a. Indicated for vision threatening inflammation
  - b. Low to moderate doses for 2 to 3 weeks
  - c. Not given alone because of risk of worsened infection without antibiotic coverage
  - d. Periocular corticosteroids felt to be contraindicated by many experts because of reports of uncontrolled infection after injection
  - e. Generally not used in immunocompromised patients with toxoplasmosis

# V. List the complications of treatment, their prevention and management

#### A. Pyrimethamine

- 1. Hematologic toxicity
  - a. Prevention
    - i. Leucovorin use
  - b. Periodic blood counts if high doses given

#### B. Clindamycin

- 1. Pseudomembranous colitis
  - a. Management
    - i. Culture of diarrhea stool
    - ii. Oral vancomycin

#### C. Sulfa drugs

- 1. Rash
- 2. Nausea
- 3. Stevens-Johnson syndrome
- 4. Aplastic anemia

#### a. Management

- i. Discontinuation of medication
- ii. Supportive care

## D. Tetracyclines

- 1. Photosensitivity
- 2. Discoloration of tooth enamel in children < 11 years or in babies of treated mothers

# E. Corticosteroids

- 1. Possible increase in risk of recurrence
- 2. Risk of impairment of immune responses with spread of infection
  - a. Prevention
    - i. Limit quantity and duration of use
    - ii. Always give with antibiotic coverage

# VI. Describe disease-related complications

- A. Loss of vision related to chorioretinal scars
- B. Chronic vitreous opacification
- C. Epiretinal membrane formation
- D. Choroidal neovascularization
- E. Retinal hole formation and retinal detachment, including giant retinal tears
- F. Secondary cataract

# VII. Describe appropriate patient instructions

- A. Report redness, pain, blurred vision, or sensitivity to light immediately
- B. If infection was acquired, try to prevent infection in family and neighbors by finding the source
- C. If pregnant and the infection is newly acquired, take antibiotic treatment to reduce risk of severe fetal effects
- D. If pregnant and chorioretinitis is recurrent from prior disease, treatment is for maternal indications only
- E. Take all medications as instructed for the length of time indicated

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, HIV: HIV/AIDS and the Eye: A Global Perspective, 2002.

- 3. AAO, Focal Points: Ocular Toxoplasmosis: Clinical Presentations, Diagnosis, and Therapy. Module #10, 1999.
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- 15. AAO, Focal Points: Intraocular Lymphoma, Module #12, 2005.
- 16. AAO, Focal Points: Steroid Therapy for Ocular Inflammatory Disease, Module #7, 2006.

# Toxocariasis posterior uveitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Infestation of the retina/choroid with a second stage larva of Toxocara canis or Toxocara catis
- 2. Infestation is presumed to occur after ingestion or cutaneous infection with hematogenous spread to the eye

#### B. Define the relevant aspects of the epidemiology of this disease

- 1. Most cases occur in children because of their more frequent contact with soil
- 2. Age range of 3 to 4 years is typical
- 3. More common in lower socioeconomic settings
- 4. More common in subtropical or tropical climates where the ground does not freeze
- 5. More common where domestic animals are not routinely "wormed"

#### C. List the pertinent elements of the history

- 1. Severe loss of vision in one eye in a child
- 2. Loss of red reflex in one eye of a child
- 3. Strabismus with vision loss in one eye in a child
- 4. History of a red eye
- 5. Play in soil contaminated by pets
- 6. Pica
- 7. Unilateral floaters and blurred vision

#### D. Describe pertinent clinical features

- 1. Peripheral granuloma
  - a. Focal, elevated, white, peripheral nodule with variable degrees of surrounding peripheral membranes and pigmentary scarring
  - b. Falciform fold in retina from lesion to optic nerve
  - c. Possible retinal detachment
  - d. Vitreous opacities
  - e. Usually diagnosed in cicatricial phase when the inflammation is quiescent
- 2. Posterior granuloma
  - a. Focal, elevated, white nodule, usually < 1 disc diameter, with variable pigmentation
  - b. Vitreous opacities and membranes

- c. Secondary inflammatory changes more mild that with peripheral granuloma
- d. Prognosis depends on location
- 3. Endophthalmitis
  - a. Panuveitis with red, painful eye
  - b. Often no view of fundus
  - c. Ascribed to death of the parasite with a secondary exuberant inflammatory reaction

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Toxocaral serology (enzyme-linked immunosorbent assay (ELISA)) with compatible clinical picture is usually considered diagnostic although the level of antibody positivity in the community should be taken into account as toxocariasis is endemic in some populations
- 2. Antibody to toxocara may not be lifelong
- 3. Intraocular fluid can be assayed for specific anti-Toxocaral antibodies, cytology for eosinophilic leukocytes

# II. Define the risk factors

- A. Contact with soil or food contaminated with feces from infected animals (dogs and cats)
- B. Cutaneous larva migrans
- C. Visceral larva migrans

# III. List the differential diagnosis

- A. Toxoplasmosis
- B. Retinoblastoma
- C. Pars planitis (peripheral Toxocaral granuloma)
- D. Coats disease
- E. Other forms of uveitis
- F. Congenital falciform fold of the retina (peripheral granuloma)
- G. Cysticercosis

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe medical therapy options

- 1. Parasite is assumed to be dead when the patient presents with either cicatricial or acute inflammatory changes
- 2. Treatment with albendazole or thiabendazole of little value in cicatricial disease
  - a. Probably achieves intraocular levels

- b. Should provide no benefit in cicatricial disease
- c. Treatment not ordinarily given
- 3. Corticosteroid therapy
  - a. Mainstay of inflammatory control
  - b. Can reduce secondary damage from intraocular inflammation
  - c. Systemic, periocular, and topical corticosteroids may be used

## B. Describe surgical therapy options

- 1. Diagnostic biopsy of vitreous (cytology for eosinophils, anti-toxocaral antibodies)
- 2. Repair of retinal detachment is possible with vitreoretinal techniques
- 3. Excision of granuloma may be necessary (if small and posteriorly located)
- 4. Possibility of severe amblyopia limiting response to treatment especially in children less than 11 years of age

# V. Describe disease-related complications

#### A. Phthisis or atrophia bulbi

- 1. Diffuse endophthalmitic form uncontrolled inflammation
- 2. Irreparable retinal detachment

#### B. Retinal folds and retinal detachment

- 1. Anti-inflammatory treatment
- 2. Pars plana vitrectomy, possible scleral buckle
- C. Macular scar from macular granuloma
- D. Amblyopia
  - 1. May occur ex anopsia from vitreous opacification during acute inflammation
  - 2. Treat by moderating inflammation and following patching schedule appropriate for age
- E. Cataract

# VI. Describe appropriate patient instructions

- A. Assess home environment for risks to other children
- B. Report changes in vision that may indicate retinal detachment

# Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

- 2. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005.
- 3. Woodhall D, Starr MC, Montgomery SP, Jones JL, Lum F, Read RW, Moorthy RS. Ocular toxocariasis: Epidemiologic, anatomic, and therapeutic variations based on a survey of ophthalmic subspecialists. Ophthalmology 2012 Feb 14 [Epub ahead of print].

# Other infectious uveitis: cysticercosis

# I. Establishing the diagnosis

# A. Describe the etiology of this disease

- 1. The pork tapeworm is *Taenia Solium* 
  - a. Ocular disease is caused by the tapeworm's larva Cysticercus cellulosae

# B. Define the relevant aspects of epidemiology of the disease

- 1. Endemic to Mexico, Africa, Southeast Asia, eastern Europe, Central and South America and India
- 2. Especially in areas of poor hygiene
- 3. Often occurs between ages 10 and 30 years
- C. List the pertinent elements of the history
  - 1. Ingestion of potentially contaminated food (pork), vegetables, fruit or water in endemic areas

# D. Describe pertinent clinical features

- 1. Hematogenous spread to eye
- 2. Larvae can be found in any ocular or adnexal tissue
  - a. Most often sub-retinal, causing exudative detachment
  - b. May then break through retina to vitreous
    - i. Cyst is 1.5-6 disc diameters
      - i) Round, translucent or white
- 3. May present with other organ involvement, for example,
  - a. Seizures with CNS involvement

# E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Cyst may be seen in intraocular tissue including vitreous
- 2. Enzyme-linked immunoabsorbent assay (ELISA)
  - a. Not sensitive (only in 50% of patients with ocular involvement)
- 3. Anterior chamber paracentesis
  - a. May show eosinophils
- 4. B-scan
  - a. May reveal cysts
- 5. Computed tomography (CT) for CNS involvement
  - a. Calcification or hydrocephalus
- 6. Stool may be positive for eggs of *T. solium*

# II. Define the risk factors

A. Ingestion of contaminated food or water in endemic area

# III. List the differential diagnosis

A. Causes of leukocoria

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe the natural history, outcome and prognosis

1. Blindness with posterior segment involvement over 3-5 years

#### B. Describe medical therapy options

- 1. Anti-helminthic therapy not effective for ocular disease
- 2. Useful for systemic and CNS disease with corticosteroids

# C. Describe surgical therapy options

- 1. Laser
  - a. May result in poor outcome as dead larvae remains in the eye
- 2. Surgical removal of larvae offers best chance of visual recovery

#### Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.

# Diffuse unilateral subacute neuroretinitis (DUSN)

# I. Describe the approach to establishing the diagnosis

## A. Describe the etiology of this disease

- 1. Solitary nematode; two different sizes
  - a. Smaller worm probably Ancylostoma caninum (dog roundworm) or Toxocara canis or Toxocara catis
  - b. Larger worm probably Baylisascaris procyonis (raccoon roundworm)

# B. Define the relevant aspects of epidemiology of the disease

- 1. Rare disorder affecting healthy young patients (mean age 14 years; range 11-65 years)
  - a. *T. canis* endemic to the southeastern U.S., Caribbean islands, and Brazil
  - b. *B. procyonis* found in the northern midwestern U.S. and Canada. Associated with raccoon infestations

#### C. List the pertinent elements of the history

1. Gradual, unilateral visual loss; rarely bilateral

#### D. Describe pertinent clinical features

- 1. Recurrent, focal, multifocal, and diffuse inflammation of the retina, retinal pigment epithelium (RPE), and optic nerve. Most cases are unilateral
- 2. Early stage
  - a. Mild to moderate visual acuity loss
  - b. Mild to moderate vitritis
  - c. Optic disc edema
  - d. Crops of multiple, gray-white or yellow-white evanescent lesions; 300-500 µm in diameter located in the post equatorial retina. Overlying serous retinal detachment may be present
  - e. Subretinal nematode or subretinal tracks may be visible
  - f. Abnormal electroretinogram (ERG)
- 3. Late stage
  - a. Retinal arteriolar narrowing
  - b. Optic atrophy
  - c. Diffuse RPE degeneration
  - d. Abnormal ERG
  - e. Choroidal neovascularization rare

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Systemic and laboratory testing usually negative
- 2. ERG may be abnormal; even during early stages of the disease
- 3. Fundus examination is most important to determine the presence of a motile worm in the subretinal space

# II. Define the risk factors

- A. Exposure to raccoons or canines
- B. *B. procyonis* can be found in many other animals in addition to raccoons, but exposure to raccoon activity is most common zoologic historical feature

# III. List the differential diagnosis

#### A. Early stage

- 1. Multifocal choroiditis with panuveitis (See Multifocal choroiditis with panuveitis)
- 2. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) (See Acute posterior multifocal placoid pigment epitheliopathy)
- 3. Multiple evanescent white dot syndrome (MEWDS) (See Multiple evanescent white dot syndrome)
- 4. Sarcoidosis-associated Uveitis (See Sarcoidosis panuveitis)
- 5. Serpiginous choroidopathy (See Serpiginous choroidopathy)
- 6. Behçet disease (See Behçet disease)
- 7. Toxoplasmosis (See Toxoplasmic retinochoroiditis)
- 8. Ocular histoplasmosis syndrome (See Ocular histoplasmosis syndrome)
- 9. Optic neuritis
- 10. Papillitis
- 11. Cysticercosis

# B. Late stage

- 1. Post-traumatic chorioretinopathy
- 2. Occlusive vascular disease
- 3. Toxic retinopathy
- 4. Retinitis pigmentosa

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe the natural history, outcome and prognosis

- 1. Without treatment, the nematode may migrate within the subretinal space for several years
- 2. Progressive ocular damage and visual loss occurs due to optic atrophy and widespread RPE degeneration
- 3. The prognosis in untreated patients is poor although spontaneous death of the nematode and stabilization undoubtedly occurs in some cases
- 4. Frequent examinations are indicated both before and after effective treatment has been applied
  - a. Resolution of vitritis is presumptive evidence that the nematode has died
  - b. Formation of a dominant white lesion after treatment with anti-helminthic drugs may indicate death of the nematode
- 5. Fundus photography useful to detect changes in spots that may indicate movement of the nematode and need for focused examination

#### B. Describe medical therapy options

- 1. Antihelminthic therapy should be considered in two situations
  - a. If the nematode cannot be initially located; may immobilize the worm
  - b. In patients who continue to have signs of inflammation following laser photocoagulation
- 2. Two agents are used
  - a. Albendazole for up to 30 days. Well tolerated
  - b. Thiabendazole for 2 to 4 days. Poorly tolerated
- 3. Corticosteroids alone may produce transient improvement, but recurrence of symptoms occurs followed by progression

#### C. Describe surgical therapy options

1. Direct laser photocoagulation of the subretinal nematode during the early stage. Typically results in stabilization of visual acuity. Does not cause a severe inflammatory reaction

# V. List the complications of treatment, their prevention and management

#### A. Medical therapy

- 1. Albendazole
  - a. Hepatoxicity may occur; liver function tests should be obtained prior to initiating therapy and every 2 weeks thereafter
  - b. Pancytopenia rarely occurs; a complete blood count should be obtained prior to initiating treatment and every 2 weeks while on therapy
  - c. Should not be used in women who are pregnant except in those situations where no alternative exists
- 2. Thiabendazole
  - a. Most side effects are transient and mild including nausea, vomiting, anorexia, and dizziness

- b. Transient increases in liver function tests have been reported
- 3. Corticosteroids (See Corticosteroids)

# VI. Describe disease-related complications

- A. Optic atrophy
- B. Diffuse retinal pigment epithelium (RPE) degeneration
- C. Severe to profound vision loss

# VII. Describe appropriate patient instructions

- A. Use medications as prescribed
- B. Report any changes in vision

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Basic and Clinical Science Course. Section 12: Retina and Vitreous, 2013-2014.
- Gass JD. Stereoscopic Atlas of Macular Diseases. Diagnosis and Treatment. 4th ed. St. Louis: Mosby; 1997:622-628.
- 4. McEvoy GK, ed. AHFS: Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2007.
- de Amorim Garcia Filho CA, Gomes AH, de A Garcia Soares AC, de Amorim Garcia CA. Clinical features of 121 patients with diffuse unilateral subacute neuroretinitis. Am J Ophthalmol 2012;153(4):743-9.

# Delayed-onset pseudophakic uveitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of the disease

- 1. Propionibacterium acnes -most common (40% of cases)
- 2. Other slow-growing bacteria and fungi (Candida, aspergillus species)

# B. List the pertinent elements of the history

- 1. Late onset (6 weeks to years) after cataract surgery
- 2. Blurred vision
- 3. Recent neodymium yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy

# C. Describe pertinent clinical features

- 1. Indolent late postoperative anterior chamber inflammation that may initially respond to topical corticosteroid treatment but later recur
- 2. Anterior chamber cells and flare
- 3. Hypopyon is less common than acute bacterial endophthalmitis
- 4. Granulomatous or fine keratic precipitates
- 5. Deposits on the intraocular lens,
- 6. Capsular plaque is characteristic
- D. Describe appropriate testing and evaluation for establishing the diagnosis
  - 1. Careful gonioscopy
    - a. With the pupil maximally dilated
    - b. Look for capsular plaque behind the iris
  - 2. Look carefully for retained lens fragments
    - a. In the chamber angle gonioscopy
    - b. On the pars plana indirect ophthalmoscopy with scleral depression
  - 3. Vitreous and anterior chamber "taps" (aspirations)
    - a. Culture and cytology
    - b. PCR for P. acnes, consider pan bacterial or pan fungal PCR if available
  - 4. Incisional posterior capsulectomy for culture

# II. Define the risk factors

# A. Posterior YAG laser capsulotomy

1. May release organisms into vitreous

# III. List the differential diagnosis

- A. Inflammation due to retained lens fragments
- B. Rule out other infectious or non-infectious causes of uveitis Masquerade syndrome (lymphoma)

# IV. Describe patient management in terms of treatment and follow-up

# A. Definitive treatment involves a step-wise approach

- 1. Combine medical (intraocular antibiotics) and surgical (pars plana vitrectomy) therapy
- 2. Partial or total capsulectomy,
- 3. intraocular lens explantation (with or without vitrectomy)
- 4. intraocular lens exchange (delayed or simultaneous)

# B. Describe management - medical and surgical therapeutic options

- 1. Pars Plana Vitrectomy (PPV), posterior capsulectomy, intravitreal and endocapsular antibiotics
  - a. Intraocular antibiotics may occasionally be given alone without PPV
  - b. Consider combination therapy
    - i. Vancomycin
    - ii. Clindamycin
    - iii. Voriconazole or Amphotericin
  - c. Should be given both in the vitreous and within capsule
- 2. If recurrent inflammation off corticosteroids, then repeat (1) or proceed to (3)
- 3. If recurrent inflammation again, then complete capsulectomy and removal of intraocular lens (IOL)
  - a. Primary IOL lens exchange sutured in sulcus
  - b. Delayed IOL placement sutured in sulcus

# V. List the complications of treatment, their prevention and management

- A. Complications of intraocular antibiotics
- B. Complications of vitreous tap/vitrectomy surgery
- C. Complications of capsulectomy and/or IOL removal

# VI. Describe disease-related complications

A. Posterior synechiae and peripheral anterior synechiae

# B. Glaucoma

C. Cystoid macular edema

# VII. Describe appropriate patient instructions

- A. Medication instructions
- B. Follow-up instructions (importance of follow-up and risk of vision loss)

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- Meisler DM, Palestine AG, Vastine DW, DeMartini DR. Chronic Propionibacterium endophthalmitis after extracapsular catarract extraction and intraocular lens implantataion. Am J Ophthalmol 1986;102:733-739.
- Winward KE, Pflugfelder SC, Flynn HW Jr., Foussel TJ, David JL. Postoperative Propionibacterium endophthalmitis. Treatment strategies and long-term results. Ophthalmology. 1993 Apr;100(4):447-51.
- 4. Shirodkar AR, Pathengay A, Flynn HW Jr, Albini TA, Berrocal AM, Davis JL, Lalwani GA, Murray TG, Smiddy WE, Miller D. Delayed-versus acute-onset endophthalmitis after cataract surgery. Am J Ophthalmol. 2012 Mar;153(3):391-398.e2. Epub 2011 Oct 25.

# Syphilitic panuveitis

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Sexually transmitted multi-systemic disease caused by the spirochete Treponema pallidum
- 2. Acquired and congenital forms

# B. Define the relevant aspects of epidemiology of the disease

- 1. Incidence
  - a. Marked reduction primary and secondary syphilis in the United States and other industrialized nations with introduction of penicillin and effective screening programs
- 2. Can affect individuals of any socioeconomic group
  - a. Recent increased incidence among men and African Americans (5.2 times greater than among non-Hispanic whites)
- 3. Increased risk among homosexual and heterosexual patients engaging in high risk sexual behavior and those with acquired immune deficiency syndrome (AIDS)
- 4. 1%-2% of all uveitis cases

# C. Describe pertinent stages and features of systemic disease

- 1. Acquired disease
  - a. Primary syphilis
    - i. Incubation 3 weeks
    - ii. Painless chancre
  - b. Secondary syphilis
    - i. 6-8 weeks later
    - ii. Lymphadenopathy
    - iii. Contagious macular-papular rash prominent on palms and soles
    - iv. Uveitis in less than 10% of secondary syphilis cases
  - c. Latency : one year (early latency) to decades (late latency)
  - d. Tertiary syphilis
    - i. Benign (gumma: skin, mucus membranes)
    - ii. Cardiovascular syphilis
    - iii. Neuro-syphilis
    - iv. Uveitis in 2.5-5% tertiary cases
  - e. Disease course may be atypical or more fulminant in patients with AIDS

#### 2. Congenital disease

- a. Early ( $\leq 2$  years of age)
  - i. Hepatosplenomegaly
  - ii. Characteristic long-bone changes
  - iii. Abdominal distension
  - iv. Pneumonia
  - v. Desquamative skin rash, low birth weight, anemia
- b. Late congenital disease (≥ 3 years of age)
  - i. Hutchinson teeth, Mulberry molars
  - ii. Abnormal facies
  - iii. Cranial Nerve (CN) VIII deafness
  - iv. Saber shins
  - v. Perforations of hard palate
  - vi. Rhagades (cutaneous lesions)
  - vii. Neurosyphilis

#### D. Ocular manifestations

- 1. Protean: may affect all ocular structures
- 2. Conjunctiva, sclera, cornea, lens, uveal tract, retina, retinal vasculature, optic nerve, cranial nerves and pupillomotor pathways
- 3. Uveitis most common, and may occur at any stage of infection although most often is secondary stage

#### E. List the pertinent elements of the ocular history

- 1. Onset 6 weeks to years after primary systemic disease
- 2. Sudden or insidious
- 3. Variable severity
- 4. Variable pain, redness and photophobia
- 5. Blurred vision or floaters
- 6. May be bilateral in one-half of the patients

# F. Describe pertinent ocular features

- 1. Secondary syphilis
  - a. Interstitial keratitis
    - i. Unilateral
    - ii. Deep stromal vascularization

- iii. Necrotizing stromal keratitis- rare
- b. Nodular or diffuse anterior scleritis
- c. Iridocyclitis
  - i. Acute or chronic
  - ii. Granulomatous or non-granulomatous
  - iii. Unilateral or bilateral
  - iv. Granulomatous iris nodules, Iris roseola (dilated iris vessels), vascularized papules (iris papulosa)
- d. Cystoid macular edema
- e. Vitritis
- f. Diffuse or localized choroiditis or chorioretinitis
- g. Focal posterior plaque of chorioretinitis or multiple yellow-gray subretinal lesions with overlying subretinal fluid, arteritis and perivasculitis thought to be highly suggestive of secondary syphilis
  - i. Later stages, extensive gliosis, atrophy and pigment proliferation
- h. Retinitis (focal or necrotizing)
- i. Retinal vasculitis
- j. Exudative retinal detachment
- k. Isolated papillitis
- I. Neuroretinitis
- 2. Tertiary syphilis
  - a. Interstitial keratitis (unilateral)- deep stromal ghost vessels
  - b. Anterior or posterior uveitis
  - c. Mild to severe iridocyclitis
  - d. 1/4 have central nervous system involvement
  - e. Gummas of the uveal tract or miliary granulomas
  - f. Chorioretinitis may be focal or multifocal
  - g. Lens dislocation
- 3. Congenital syphilis
  - a. Early congenital syphilis
    - i. Acute iritis at 6 months of age in untreated infants
    - ii. Necrotizing stromal keratitis (rare), bilateral
    - iii. Posterior uveitis with multifocal inflammation of the choriocapillaris

- iv. Postinflammatory changes
  - i) Diffusely scattered foci of chorioretinal atrophy
  - ii) Proliferation of retinal pigment epithelium
  - iii) Narrowed retinal vessels
  - iv) Salt and pepper spots can be diffuse or in the periphery
- b. Late congenital syphilis (5-20 years of age)
  - i. Interstitial keratitis (bilateral)accompanied by anterior uveitis
  - ii. Nodular or diffuse anterior scleritis
  - iii. Recurrent iridocyclitis in adults is uncommon
  - iv. Residual signs: multifocal, hypopigmented chorioretinal scars
- c. Other
  - i. Optic neuritis, glaucoma, cataract

#### G. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. It is important to obtain both a treponemal and non-treponemal test for diagnosis
- 2. Serodiagnosis: treponemal tests Most important tests to obtain to confirm etiology
  - a. Anti-treponemal IgG
  - b. Fluorescent treponemal antibody absorption (FTA-Abs)
  - c. Microhemagglutination assay Treponema pallidum (MHA-TP)
  - d. False positive results may occur due to antigenic cross-reactivity in individuals who may be positive for other spirochetal infections (Lyme disease, leptospirosis) and autoimmune disease (systemic lupus erythematosus)
- 3. Serodiagnosis: nontreponemal tests
  - a. Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR)
    - i. Positive VDRL or RPR indicates active disease and exposure to the bacteria
      - i) Titers return to normal with effective therapy
      - ii) Titers may also return to normal without treatment in patients with late latent and tertiary syphilis
    - ii. Biological false positive results may result from cross reactive lipoidal antibodies and it occurs more commonly in human immunodeficiency virus-infected patients and in the geriatric population
      - i) Other causes for false positive tests include
        - (i) Recent viral infection
        - (ii) Immunization
        - (iii) Pregnancy

- (iv) Lupus anticoagulant
- (v) Antiphospholipid antibodies
- iii. False negatives can occur due to the prozone effect (Antibody excess), if the undiluted RPR is extremely high. If syphilis is strongly suspected, request repeat testing with at least a 1:2 dilution of serum
- 4. Cerebrospinal fluid (CSF) analysis
  - a. In patients with uveitis and positive serology, asymptomatic neurosyphilis must be ruled out
  - b. In latent syphilis, serum VDRL may be positive or negative but the fluorescent treponemal antibody absorption (FTA-Abs) is positive, and CSF is negative
  - c. In tertiary syphilis or in neurosyphilis, serum and CSF FTA-Abs are both positive but the VDRL may be negative
    - i. CSF VDRL may be insensitive but its presence is highly specific for neurosyphilis
  - d. CSF VDRL may be negative in CNS syphilis. Elevated protein and leukocytes in CSF are presumptive evidence of syphilis even if the VDRL is negative
- 5. Darkfield microscopy
  - a. Direct visualization of spirochetes
- 6. Direct fluorescent antibody test of lesion exudates or tissue
- 7. PCR (not commonly used)
- 8. Human immunodeficiency virus (HIV) testing on all patients with syphilis given high rate co-infection
- 9. Congenital syphilis
  - a. Darkfield microscopy or fluorescent antibody test of cutaneous lesions, placenta, umbilical cord
  - b. Immunoglobulin M (IgM) FTA-Abs in infant
    - i. IgG crosses placenta

# II. List the differential diagnosis

#### A. Syphilis is the "great masquerader"

- 1. Retinitis pigmentosa
- 2. Necrotizing herpetic retinopathies (acute retinal necrosis, progressive outer retinal necrosis)
- 3. Cytomegalovirus retinitis
- 4. Tuberculosis
- 5. Lyme disease
- 6. Sarcoidosis

- a. Consider the possibility of syphilis in any case of diffuse uveitis unresponsive to conventional anti-inflammatory therapy
- 7. Toxoplasmosis (especially in AIDS patients)
- 8. Neuroretinitis

# III. Describe patient management in terms of treatment and follow-up

# A. Ocular inflammation secondary to syphilis should be treated as neurosyphilis

- 1. Aqueous, crystalline penicillin G, 18-24 million units (MU), administered as 3-4 MU every 4 hours or as a continuous infusion for 10 14 days
- 2. May be supplemented with intramuscular benzathine penicilliln G at at dose of 2.4 MU weekly for 3 weeks
- 3. Alternative regimen for neurosyphilis is Procaine Penicillin G delivered as 1.2 million unit intramuscular injections twice daily for 10 to 14 days combined with probenecid 500 mg four times daily for 10 to 14 days and followed by the 3 benzathine penicillin G injections as above for 3 weeks

# B. In patients allergic to penicillin

- 1. Strongly consider desensitization therapy to penicillin by allergist
- 2. Doxycycline 100 mg by mouth twice a day or tetracycline 500 mg by mouth 4 times a day for 28 days
- 3. Topical, regional or oral corticosteroids may be used to quiet anterior or posterior segment inflammation
- 4. Intravenous ceftriaxone has not been fully validated as a treatment for neurosyphilis

# C. For patients with positive CSF serology, repeat CSF exam every 6 months until cell count, protein and VDRL return to normal

# D. Congenital syphilis

1. Aqueous penicillin G 100,000/150,000 units/kg per day administered as 50,000units/kd per day IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

# IV. Describe appropriate patient instructions

- A. Importance of long term serologic monitoring
- B. Monitor patient for development of Jarisch-Herxheimer reaction during first 24 hours of treatment

# Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Aldave AJ, King JA, Cunningham ET, Jr. Ocular syphilis. Curr Opin Ophthalmol 2001;12:433-441.

Uveitis
- 3. Browning DJ. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regiment of penicillin therapy, and the influence of human immunodeficiency virus status on response. Ophthalmology 2000;107:2015-2023.
- 4. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR 2002;51 (No. RR-6).
- 5. Gass JD, Braunstein RA, Chenoweth RG. Acute syphilitic posterior placoid chorioretinits. Ophthalmology 1990;97:1288-97.
- 6. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005.

# Lyme disease

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

1. Tick-borne spirochetal disease caused by *Borrelia burgdorferi* 

#### B. Define the relevant aspects of epidemiology of this disease

- 1. Most prevalent vector-borne illness in the United States (US)
  - a. Northeastern U.S.
  - b. Western Wisconsin/Upper Midwest
- 2. Men and women nearly equally affected
- 3. Bimodal distribution Children (5-14) and Adults (50-59)
- 4. Seasonal outbreaks
  - a. Early summer and mid autumn
- 5. Animal reservoirs
  - a. Rodents
    - i. White footed mouse may be obligate carrier
    - ii. Found in nearly all states west of the Rocky Mountains
    - iii. Ticks bite the infected mice and then bite any other animal or human and transmit disease
  - b. Deer
  - c. Birds
  - d. Cats
  - e. Dogs
- 6. Transmitted to humans through the bite of a tick
  - a. Ixodes dammini (eastern US)
  - b. *Ixodes pacificus* (western US)

#### C. List the pertinent elements of the history

- 1. Stage 1
  - a. Erythema chronicum migrans
    - i. Elevated annular erythematous skin lesion with central clearing at the site of the tick bite
    - ii. Most characteristic feature of Stage 1 60-80%

- iii. Develops within 4 weeks after tick bite
- b. Headache
- c. Stiff neck
- d. Malaise
- e. Myalgias
- f. Arthralgias
- g. Fever
- 2. Stage 2
  - a. 1-4 months after infection
  - b. Neurologic (cranial nerve palsies), musculoskeletal, cardiac involvement characterized by Bells palsy
  - c. Encephalitis or meningitis
  - d. Arthritis
  - e. Tendonitis
  - f. Joint effusions
  - g. Myocarditis
  - h. Heart block
  - i. Erythema chronicum remote sites from bite
- 3. Stage 3
  - a. 5 months or more after infection
  - b. Chronic arthritis most common manifestations
  - c. Chronic atrophic skin changes
  - d. Chronic meningitis
  - e. Adult respiratory distress syndrome

#### D. Describe pertinent clinical features (ophthalmic)

- 1. Stage 1
  - a. Follicular conjunctivitis
  - b. Interstitial Keratitis
  - c. Episcleritis
- 2. Stage 2 (Uveitis most common in Stage 2)
  - a. Anterior uveitis granulomatous
  - b. Intermediate uveitis (one of the most common presentation)
  - c. Panophthalmitis

- d. Multifocal choroiditis
- e. Optic neuritis, papillitis, neuroretinitis
- f. Neuro-ophthalmic manifestations(CN VII palsy most common)
- g. Interstitial keratitis
- 3. Stage 3
  - a. Keratitis
    - i. Most common manifestations
    - ii. Bilateral, patchy, focal, and stromal infiltrates
  - b. Chronic iridocyclitis and vitreitis less common than in stage 2

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Diagnosis is based on history, clinical presentation, and serology
- 2. High rate of false positive and poor predictive value for serology
- 3. *Borrelia burgdorferi* expresses common bacterial antigens that are cross reactive with antigens on other bacteria
- 4. 2- Step serological diagnosis is commonly used:
  - a. Indirect immunofluorescence assay or enzyme-linked immunosorbent assay for immunoglobulin M and immunoglobulin G use whole *Borrelia burgdorferi* as antigen source
  - b. If enzyme immunoassay is positive, Western blot testing indicated to confirm serologic screening CDC Guidelines
    - i. IgG a positive Western blot at least 5 of the 10 possible designated bands should be present
    - ii. IgM at least 2 of 3 designated bands should be present
  - c. No standardization of assays
  - d. Wide differences between laboratories
- 5. PCR testing of ocular fluids, skin, and synovial fluids may be useful

# II. Define the risk factors

- A. Tick bites
- B. Endemic areas (e.g. Northeastern U.S.)

# III. List the differential diagnosis

- A. Syphilis
- B. Pars planitis or intermediate uveitis
- C. Sarcoidosis

#### Uveitis

- D. Multiple sclerosis
- E. JIA in children
- F. Large cell lymphoma

#### IV. Describe patient management in terms of treatment and follow-up

- A. Antibiotic treatment of suspected Lyme eye involvement should be treated as central nervous system (CNS) involvement
- B. Easier to eradicate in earlier stages
- C. Regimens
  - 1. Tetracycline
  - 2. Doxycycline
  - 3. Penicillin
  - 4. Azithromycin
  - 5. Duration of treatment determined by clinical response (2-4 weeks)
  - 6. Newer ketolide antibiotics may be of value (telithromycin or cethromycin)
- D. CNS (Intraocular-uveitic) involvement requires intravenous antibiotic
  - 1. IV ceftriaxone or penicillin x 10-14 days is advised for neurologic or neuroophthalmologic disease
  - 2. Topical corticosteroids along with antibiotic treatment
  - 3. Systemic corticosteroids controversial
    - a. Increased incidence of antibiotic treatment failures
    - b. But Jarisch-Herxheimer reaction with antibiotics alone may require some systemic corticosteroids

# V. List the complication of treatment, their prevention and management

- A. Penicillin allergy, anaphylactic shock
- B. Tetracyclines
  - 1. Photosensitivity
  - 2. Discoloration of tooth enamel in children <11 years
- C. Corticosteroids
  - 1. Cataract
  - 2. Glaucoma
- D. Describe disease-related complications
- E. Exposure keratopathy or corneal ulceration from facial paralysis
- F. Macular edema

- G. Exudative retinal detachment
- H. Optic atrophy
- I. Pupillary abnormalities
- J. Cranial nerve palsies

# VI. Describe appropriate patient instructions

- A. Report recurrent symptoms of redness, pain or blurred vision
- B. Try to prevent infection in family members by avoiding tick bites, cover extremities when in endemic areas

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005.
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- 4. Hilton E, Smith C, Sood F. Ocular Lyme borreliosis diagnosed by polymerase chain reaction in vitreous fluid. Ann Intern Med 1996; 125:424-425.
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# Leptospiral uveitis

# I. Describe the approach to establishing diagnosis

#### A. Describe the etiology of the disease

- 1. Leptospira interrogans
  - a. 200 strains
  - b. Pathogenic to humans species
  - c. Very thin spiral-shaped tightly coiled gram negative aerobic spirochete that is motile and flexible

#### B. Define the relevant aspects of the epidemiology of the disease

- 1. Zoonotic infection common in
  - a. Endemic areas tropical and subtropical regions
    - i. Any area where wild animals may contaminate water sources with infected urine
    - ii. In U.S. Hawaii accounts for 50% of cases
    - iii. South East Asia India
  - b. High risk occupations
    - i. Sewer workers, farmers, dairy farmers, fishery workers, water sportsman whitewater rafting
- 2. Infected rodents and other animals pass the bacteria in their urine into contaminating soil and water reservoirs
- 3. Humans acquire disease by bacteria invading intact mucosa or abraded skin and hematogenously disseminating the organism into various organ systems including kidneys, liver, lungs, heart and central nervous system
- 4. Age 3<sup>rd</sup> through 5<sup>th</sup> decades
- 5. Men more commonly affected than women
- 6. Bilateral 50% of the time

#### C. Describe pertinent clinical features

- 1. Biphasic disease
- 2. Acute leptospiremic phase 2-4 weeks after exposure
  - a. Patients usually have a febrile illness, headache, fatigue and myalgias with variable severity of fever
    - i. In four to seven days the Leptospira organisms are eliminated from the body except in immunologically privileged sites such as the eyes and brain
    - ii. 80-90% have self-limited anicteric disease

- iii. 10-15% Weil Disease hepatitis, nephritis
  - i) 3-6 days after infection
  - ii) Mortality 15-30%
- b. Yellow sclera and circumlimbal conjunctival injection and chemosis is regarded as pathognomonic sign for acute phase of Leptospirosis
- 3. Immune phase
  - a. May start weeks or years after initial exposure
  - b. Organisms that are not cleared by the immune system remain in immunologically privileged sites like the brain and eye
  - c. Meningitis and leptospiruria-most important features
  - d. Uveitis may start two days to four years after systemic infection but typically three to six months after initial illness
    - i. Anterior uveitis 10%
      - i) Conjunctival Injection
      - ii) Nongranulomatous keratic precipitates
      - iii) Fine and diffusely distributed
      - iv) Anterior chamber cells and flare
        - (i) 12% Hypopyon (in tropical countries one of the most common causes is leptospiral uveitis)
        - Young males develop leptospirosis as well and this must be differentiated from HLA-B27 associated disease and Behçet disease
    - ii. Interstitial keratitis 18%
    - iii. Panuveitis 44%
      - i) May be characteristic
      - ii) Significant vitritis
        - (i) May be difficult to differentiate from endogenous endophthalmitis
        - Significant vitreous debris and precipitates along with vitreous "snowball" like opacities and vitreous veils
      - iii) Retinal Vasculitis /periphlebitis
        - (i) mainly involving the retinal venules but occasionally the arteries
        - (ii) perivascular sheathing and inflammation
          - (a) Nonischemic
      - iv) Disc hyperemia and edema
    - iv. Neuro-ophthalmic manifestations

- i) Neuroretinitis
- ii) Optic neuritis (retrobulbar as well)
- iii) Other neuro-ophthalmic manifestations compatible with central nervous system disease and encephalitis include cranial nerve palsies, chronic headaches

#### D. Describe appropriate testing and evaluation for establishing diagnosis

- 1. Microscopic agglutination test (MAT) is gold Standard
  - a. Difficult to perform and not widely available
- 2. Anti-leptospiral IgG and IgM antibody testing-highly sensitive and specific
  - a. ELISA
  - b. Complement fixation
- 3. PCR under development
- 4. Leptospirosis causes false positive RPR or FTA-ABS

# II. List the differential diagnosis

- A. HLA-B27 associated anterior uveitis
- B. Behçet disease
- C. Syphilis
- D. Sarcoidosis
- E. Pars planitis
- F. Tuberculosis
- G. Eales Disease

# III. Describe medical treatment options

#### A. Acute phase illness

- 1. IV penicillin G 1.5MU Q6 hours for 1 week
- 2. Ideal if begun in the first 4 days of acute phase
- 3. Doxycycline 100mg po BID
- 4. Useful for mild cases
- 5. Whether systemic antibiotics given in acute phase prevent uveitis is unknown
- B. Immune phase uveitis
  - 1. Systemic antibiotic treatment should be given as part of uveitis treatment
  - 2. Corticosteroids
    - a. Mainstay of treatment of uveitis

- b. Systemic, periocular, and topical corticosteroids
- 3. Mydriatics/cycloplegics

# IV. List complications of treatment and prevention management

#### A. Antibiotic

- 1. Drug allergies to specific agents
- 2. Corticosteroids (See Corticosteroids)

#### V. List disease-related complications

- A. Cataracts
- B. Glaucoma

#### VI. Patient instructions

- A. The course of Leptospiral uveitis can be highly variable but the visual prognosis is quite good with treatment.
- B. Report exposure to contaminated water related to outdoor activities to your physician
- C. Report any severe fevers to your physician
- D. Report any severe increase in pain or loss of vision to your physician.
- E. Leptospirosis can become a chronic relapsing and recurrent illness if not treated aggressively with systemic antibiotics at the onset of acute phase illness

#### Additional Resources

- AAO, Basic and Clinical Science Course. Section 9. Intraocular Inflammation and Uveitis. Chapter 8: Infectious Uveitis: Leptospirosis. 2013-2014.
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# Tuberculous uveitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Intraocular inflammation resulting from Mycobacterium tuberculosis infection
- 2. Transmitted by aerosolized respiratory droplets with the primary site of infection being the lung
- 3. High affinity for highly oxygenated tissues
  - a. Apex of lung
  - b. Choroid
- 4. 90% of individuals infected with the organism remain asymptomatic
- 5. 5% of infected patients develop disease within 1-2 years
- 6. 5% of infected persons develop disease several to many years later
- 7. Ocular involvement indicates extra-pulmonary dissemination of the organisms
- 8. Hematogenous dissemination of tuberculosis (TB), in the form of miliary disease, is seen in immunosuppression

#### B. Describe the relevant aspects of the epidemiology of the disease

- 1. United States
  - a. 1-2% of uveitis is related to TB
  - b. Increased incidence with acquired immunodeficiency syndrome (AIDS) epidemic
  - c. Increased incidence among foreign-born patients
- 2. Worldwide distribution
  - a. Most important systemic disease worldwide
  - b. Accounts for up to 10% of uveitis cases
  - c. 8 million new systemic TB cases and 3 million deaths annually
  - d. 95% of new cases occur in developing countries

#### C. List the pertinent elements in the history

- 1. History of previous exposure to TB
- 2. Immigrant from the developing world with endemic TB
- 3. Immunosuppression especially with human immunodeficiency virus (HIV)
- 4. History of Bacille Calmette Guerin (BCG) vaccination
- 5. Previous treatment for TB
- D. Describe the pertinent clinical features

- 1. Systemic infection
  - a. Pulmonary TB is common (~80%)
  - b. Extra-pulmonary disease is seen in about 20%
  - c. 50% of patients with extra-pulmonary disease show a normal chest radiograph
  - d. Up to 20% of patients with extra-pulmonary disease can be negative for purified protein derivative (PPD) skin test
  - e. Extra-pulmonary disease is common in HIV infected and other immunocompromised hosts
- 2. Symptoms of systemic TB
  - a. Systemic disease manifests with
    - i. Fever
    - ii. Night sweats
    - iii. Weight loss
    - iv. Extra-pulmonary disease may be asymptomatic and may not have these constitutional symptoms
  - b. Tuberculous uveitis patients may or may not present with systemic disease and its symptoms
- 3. Ocular manifestations of TB are due to
  - a. Active infection involving ocular tissue
  - b. Paucibacillary disease: May represent immunologic reaction to the organism that may be present in small numbers in the eye or in systemic organs
- 4. External eye and adnexal TB
  - a. Primary inoculation of the eye or contiguous spread from the sinuses or face
    - i. Very rare
    - ii. May present as an eyelid tubercle, conjunctivitis, dacryoadenitis, dacryocystitis
- 5. Intraocular TB tuberculous uveitis
  - a. Ocular symptoms
    - i. Waxing and waning course
    - ii. Progressive increase in floaters
    - iii. Worsening of vision due to progressive intraocular inflammation, choroidal and retinal involvement or due to cystoid macular edema
  - b. Hematogenous dissemination of the organism, usually from lung
  - c. Chronic granulomatous anterior or posterior or intermediate or panuveitis or sclerouveitis
  - d. Scleritis
    - i. Nodular anterior scleritis

- ii. Posterior scleritis with acute angle closure glaucoma
  - i) Rare TB should be considered in such cases
- e. Anterior uveitis
  - i. Mutton-fat keratic precipitates (KP)
  - ii. Iris nodules
  - iii. Posterior synechiae
  - iv. Secondary glaucoma
  - v. Nongranulomatous uveitis may also occur
- f. Intermediate uveitis
  - i. Vitreous cells and opacity
  - ii. Cystoid macular edema
  - iii. Retinal periphlebitis
  - iv. Posterior uveitis or panuveitis
  - v. Waxing and waning course
  - vi. Accumulation of vitreous opacities
  - vii. Disseminated choroiditis-most common presentation
    - i) Choroidal tubercles
  - viii. Deep, multiple, discrete, yellowish lesions
  - ix. Single, large elevated choroidal mass (tuberculoma)
  - x. Serpiginous-like choroiditis
  - xi. Retinal periphlebitis-Eales disease
  - xii. Subretinal abscess in immunocompromised host
  - xiii. Optic neuritis
  - xiv. Acute panophthalmitis

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Definitive diagnosis requires demonstration of mycobacteria from bodily fluids or affected tissues
  - a. This is not accomplished in most cases of ocular TB, but:
    - i. Acid fast staining should be performed in all cases of chorioretinal biopsy performed for uveitis unresponsive to therapy
- Diagnosis is therefore presumptive in the majority of cases and is based on indirect evidence such as positive PPD or Gamma interferon release assay response tests and therapeutic response to anti-TB agents
- 3. A positive PPD is indicative of prior exposure to TB but not necessarily of active systemic infection

- a. In the United States, PPD is considered positive requiring intervention if
  - i. Induration of  $\geq 5$  mm in
    - i) Patients with HIV
    - ii) Patients with contact with active TB
    - iii) Radiographs consistent with healed TB lesions
  - ii. Induration of > 10 mm in
    - i) Patients with diabetes mellitus
    - ii) Patients with renal failure
    - iii) Patients using immunosuppressive agents
    - iv) Health care workers
    - v) Recent immigrants from high prevalence countries
  - iii. Inducation is  $\geq$  15 mm in patients with no known risk factors
- b. False-negative skin testing occurs at a rate of 25%
  - i. Profound acute illness
  - ii. Immunosuppression
  - iii. Corticosteroid use
  - iv. Advanced age
  - v. Poor nutrition
  - vi. Sarcoidosis
- c. False-positive skin testing
  - i. Individuals infected with atypical mycobacteria
  - ii. Immunized with BCG
  - iii. Treated with intra-luminal BCG injections for bladder carcinoma
- 4. Definitive diagnosis may require intraocular fluid analysis or tissue biopsy
  - a. Nucleic acid amplification techniques
    - i. Polymerase chain reaction (PCR)
  - b. Biopsy of affected ocular tissue
- 5. Interferon Gamma Release Assays (IGRAs) Quanti-Feron-TB<sup>™</sup> or Gold Assay, or T-spot TB<sup>™</sup> assay
  - a. Measure interferon gamma release from subjects' lymphocytes after exposure to selected tubercular antigens notably not the BCG antigen
  - b. Good sensitivity in detecting latent disease

# II. Define risk factors - CDC high risk groups

#### A. Groups at higher risk of exposure to or infection with *M. Tuberculosis*

- 1. Close contacts of persons known or suspected to have TB
- 2. Foreign-born persons, including children from areas that have a high TB incidence or prevalence (e.g., Asia, Africa, Latin America, Eastern Europe, Russia)
- 3. Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, mental institutions, other long-term residential facilities and shelters for the homeless)
- 4. Health care workers who serve high-risk clients
- 5. Some medically underserved, low-income populations as defined locally
- 6. High-risk racial or ethnic minority populations, defined locally as having an increased prevalence of TB (e.g., Asians and Pacific Islanders, Hispanics, African Americans, Native Americans, migrant farm workers or homeless persons)
- 7. Infants, children and adolescents exposed to adults in high-risk categories
- 8. Persons who inject illicit drugs, any other locally identified high-risk substance users (e.g., crack cocaine users)

# B. Persons who are at higher risk of developing TB disease once infected with *M. tuberculosis* include

- 1. Persons with HIV infection
- 2. Persons who were recently infected with *M. tuberculosis* (within the past 2 years), particularly infants and very young children
- 3. Persons who have medical conditions which result in immune suppression (e.g., diabetes mellitus, end-stage renal disease) or who are iatrogenically immunosuppressed
- 4. Persons who inject illicit drugs, other groups of high-risk substance users (e.g., crack cocaine users)
- 5. Persons with a history of inadequately treated TB

# III. List the differential diagnosis

- A. Sarcoidosis
- B. Toxoplasmosis
- C. Syphilis
- D. Masquerade syndrome
- E. Multifocal choroiditis
- F. Serpiginous choroiditis
- G. Pars planitis
- H. Retinal vasculitis
- I. Chronic fungal endophthalmitis

# IV. Describe patient management in terms of treatment and follow up

#### A. Systemic antibiotic therapy

- 1. Note that this is typically coordinated through an infectious disease specialist or state health department
- 2. Indications
  - a. Patients with uveitis with positive bacterial cultures or PCR results or presumed TB
  - b. Recently converted TB skin test
  - c. Positive QuantiFERON-TB Gold or similar Gamma interferon release assay test
  - d. Abnormal chest radiograph

#### B. Multiple-agent therapy, usually isoniazid (INH), rifampin and pyrazinamide for 6 to 9 months

- 1. Increasing incidence of resistance to isoniazid
- 2. Multi-drug-resistant TB (MDRTB)
  - a. Risk factors for MDRTB development
    - i. Noncompliant patients on single-agent therapy
    - ii. Migrant or indigent populations
    - iii. Immunocompromised patients, e.g., HIV patients
    - iv. Recent immigrants from countries where INH and rifampin are available over the counter
  - b. If drug-resistant
    - i. Add ethambutol or streptomycin
  - c. Direct observed therapy (DOT) ideal

#### C. Corticosteroids

- 1. Topical and systemic corticosteroids
  - a. Should only be used with appropriate anti-TB coverage
  - b. Intensive corticosteroid treatment administered without appropriate anti-TB coverage leads to progressive worsening of ocular disease

#### D. Prophylactic treatment: single agent

- 1. Positive PPD or abnormal chest film
  - a. If systemic treatment of corticosteroids is being considered
  - b. If patient received corticosteroids for longer than 2 weeks at doses greater than 15mg per day
    - i. Prophylactic treatment with INH for 6 months to a year
- 2. If anti-TNF therapy is being considered in patients with latent TB (positive PPD or IGRA)

a. INH prophylaxis beginning at least 3 weeks prior to the first infusion

# V. List complications of treatment, their prevention and management

#### A. Side effects of therapeutic agents

- 1. INH
  - a. Hepatotoxicity
  - b. Neurotoxicity due to pyridoxine deficiency
    - i. Peripheral neuropathies
    - ii. Seizures
    - iii. Agitation
    - iv. Insomnia
    - v. Treated with pyridoxine
- 2. Pyrazinamide
  - a. Hepatotoxicity
- 3. Rifampin
  - a. Thrombocytopenia
  - b. Nephritis
  - c. Hepatotoxicity
- 4. Ethambutol
  - a. Optic neuritis
    - i. Can improve with drug cessation

#### B. Non-compliance

- 1. Leads to MDRTB
- 2. Recurrence of disease
- 3. Reduced by DOT

# VI. Describe disease-related complications

- A. Cataract
- B. Glaucoma
- C. Cystoid macular edema
- D. Choroidal neovascularization
- E. Subretinal abscesses
- F. Spontaneous scleral rupture

- G. Retinal neovascularization
- H. Retinal detachment
- I. Neovascular, or angle closure ( with posterior scleritis) glaucoma
- J. Fulminant panophthalmitis

# VII. Describe appropriate patient instructions

- A. Importance of compliance with medical therapy
- B. Report any dramatic weight loss, new fevers and chills to physician
- C. Report any significant visual loss while on therapy to physician
- D. Importance of regular laboratory evaluation while on long-term anti-tuberculosis therapy
- E. Need for screening of patient's close contacts

#### Additional Resources

- 1. AAO, Basic Clinical and Science Course Section 9. Intraocular inflammation and uveitis, 2013-2014.
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# Ocular bartonellosis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Several species of Bartonella
  - a. In particular B. henselae and quintana
  - b. Identified in intraocular fluid of patients with intraocular inflammation
- 2. Bartonella
  - a. Small, rod-shaped, gram negative, bacteria
  - b. Hemotropic
- 3. Pathogenesis of ocular involvement is still unknown.
  - a. Direct infection
  - b. Secondary immune reaction
- 4. The bacteria chronically infect
  - a. Erythrocytes
  - b. Macrophages
  - c. Vascular endothelial cells

#### B. Describe the relevant aspects of the epidemiology of the disease

- 1. Ocular bartonellosis
  - a. Uncommon compared to non-ocular disease
  - b. Cat-scratch disease (CSD): annual occurrence of 9.3 per 100,000 population in the US
  - c. Highest incidence is among children younger than ten years
  - d. But has been reported in all ages
- 2. Cat-scratch disease is seasonal
  - a. Occurs predominantly in the fall and winter
  - b. Most prevalent in southern states, California and Hawaii
  - c. Ocular involvement in 5-10% of CSD

#### C. List the pertinent elements of the history

- 1. Exposure to pet cats
  - a. Asymptomatic cats serve as a major persistent reservoir for years
  - b. Harboring Bartonella in or on the surface of erythrocytes
- 2. Flea and tick bites

- a. Cat and dog fleas and, less often, deer and dog ticks carry the bacteria and serve as the main vector of transmission
  - i. From cat to cat and
  - ii. From cats to humans
- 3. Clinical History
  - a. Skin entry site
    - i. Papule, vesicle or pustule
    - ii. Forms 3-10 days later
  - b. One week later regional lymphadenopathy
  - c. Mild to moderate flu-like symptoms
  - d. Then ocular findings develop
- 4. Systemic dissemination of the bacteria can cause
  - a. Encephalopathy
  - b. Aseptic meningitis
  - c. Osteomyelitis
  - d. Hepatosplenic disease
  - e. Pneumonia, and pleural
  - f. Pericardial effusions

#### D. Describe pertinent clinical features

- 1. Usually unilateral
- 2. Focal Chorioretinitis is most common manifestation
  - a. Can look like Toxoplasma retinochoroiditis
- 3. Neuroretinitis (most well recognized finding-only in 1-2% of CSD)
- 4. Macular star formation
- 5. Papillitis
- 6. Multifocal chorioretinitis
- 7. Isolated anterior uveitis
- 8. Parinaud oculoglandular syndrome
- E. Describe the appropriate laboratory testing for establishing the diagnosis
  - 1. Serologic testing
    - a. Indirect fluorescent antibody testing (>1:64 considered positive)
    - b. Enzyme immunoassay
    - c. Western blot analysis

- 2. Standard bacterial culture (highly sensitive and specific, takes longer)
  - a. Low sensitivity
  - b. Requires one to four weeks of incubation
  - c. Special techniques to increase sensitivity of cultures
- 3. Polymerase chain reaction (PCR) analysis of DNA for 16S rRNA gene or B. henselae DNA

# II. List the differential diagnosis

- A. Syphilis
- B. Sarcoidosis
- C. Lyme disease
- D. Toxoplasmosis
- E. Herpes viral infection
- F. Mumps
- G. Acute chlamydia infection
- H. Toxocariasis
- I. Leptospirosis
- J. Tuberculosis
- K. Histoplasmosis
- L. Rocky Mountain Spotted Fever
- M. Ehrlichiosis
- N. Tularemia
  - 1. Ocular manifestations: conjunctivitis and glandular swelling like Parinaud syndrome rarely if ever causes uveitis
  - 2. Diagnostic studies: culture, immunofluorescent antibody analysis (IFA), serology or by a polymerase chain reaction (PCR) assay from affected tissues

# III. Describe patient management in terms of treatment and follow-up

- A. Effectiveness of antibiotics for this self-limited disease have not been established, nor have optimum durations of treatment
- B. Antibiotics administered orally or intravenously include
  - 1. Doxycycline
    - a. Typical therapy (>8 years old): 100mg twice daily for 2-4 weeks
  - 2. Azithromycin (alternative to doxycycline in children)
  - 3. Rifampin (should be used in combination with other therapy to avoid resistance)

- 4. Ciprofloxacin
- 5. Trimethoprim
- C. Systemic corticosteroid use has not been established but may be needed. Topical corticosteroid treatment is warranted to reduce inflammatory damage to ocular structure

# IV. List the complications of treatment, their prevention and management

A. Complications of systemic antibiotics

# V. Describe disease-related complications

- A. Permanent macular dysfunction and scarring may occur in severe cases
- B. Optic neuropathy or atrophy

# VI. Describe appropriate patient instructions

- A. Medication instructions
  - 1. Take oral antibiotics with six ounces of water
- B. Follow-up instructions
  - 1. Frequency of followup visit tailored to the severity of the disease
- C. Natural history of the disease
  - 1. Self-limited disease course with good visual outcomes
- D. Appropriate infectious disease consultation
  - 1. Referral to infectious disease specialist for evaluation of systemic manifestation of disease and selection of antibiotics

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005, p.3.

# Brucellar uveitis

# I. Describe approach in establishing diagnosis

#### A. Describe the etiology of disease

- 1. Caused by Brucella Melitensis, B. abortus, B. canis, and B. suis
- 2. Most cases of human disease are caused by B melitensis, the most virulent species
- 3. B. abortus most prevalent Brucella species in North America
- 4. Humans acquire disease by
  - a. Consuming unpasteurized milk or milk products from infected animals
  - b. Eating meat products from infected animals
  - c. Occupational contact of infected animals and products
  - d. Organisms enter body through abraded skin or mucous membranes or by aerosolization

#### B. Define relevant aspects of epidemiology of the disease

- 1. Worldwide distribution, more common in Latin America
- 2. Endemic areas such as Peru, Kuwait, Saudi Arabia
- 3. Important health problem in Middle East, Mediterranean, Mexico, Central and South America
- 4. Less common now with quality control of animal products, adequate livestock vaccination
- 5. Women (2/3) >men (1/3)
- 6. Age 16 to 35 years
- 7. High-risk groups
  - a. Dairy farmers
  - b. Meat inspectors
  - c. Animal handlers
  - d. Veterinarians
  - e. Travelers to endemic areas

#### C. Describe pertinent elements in the history

- 1. Ocular involvement variably seen with acute phase or chronic phase of systemic illness (up to 25%)
- 2. Acute phase of systemic Brucellosis
  - a. Fever, drenching sweats, chills, and weakness
    - i. Reticuloendothelial system preferentially involved
      - i) Bone, CNS, heart, lungs, liver, testes, and skin

- b. Patient may have unilateral or bilateral sudden onset of
  - i. Pain
  - ii. Decreased vision
  - iii. Floaters
  - iv. Scotoma
  - v. Metamorphopsia
- 3. Relapsing and chronic phases of the illness 10%
  - a. Blurred vision
  - b. Central scotoma
  - c. Metamorphopsia

#### D. Describe pertinent clinical features

- 1. Acute phase of illness
  - a. Nummular keratitis
  - b. Scleritis
    - i. Diffuse
    - ii. Nodular
  - c. Anterior Uveitis
    - i. Granulomatous or non-granulomatous
    - ii. May be more common in acute phase
  - d. Vitritis
  - e. Peripapillary, nodular or multifocal choroiditis
  - f. Panuveitis
  - g. Endophthalmitis
  - h. Retinitis
  - i. Retinal vasculitis
  - j. Cystoid macular edema
  - k. Neuro-ophthalmic manifestations can include
    - i. Papilledema
    - ii. Retrobulbar optic neuritis
    - iii. Optic atrophy
- 2. Chronic phase of illness
  - a. Anterior uveitis chronic smoldering

b. Posterior, panuveitis, optic nerve edema

#### E. Describe appropriate testing and evaluation in establishing the diagnosis

- 1. Clinical diagnosis based on febrile illness in endemic areas or after exposure to unpasteurized dairy products and presence of anterior uveitis, nodular choroiditis, retinal edema and hemorrhages
  - a. History of recent exposure to infected animals and animal products, presence of systemic features of disease is also helpful
  - b. Brucella agglutination test
  - c. Blood cultures, specifically using tryptic soy broth
    - i. Will be positive in the acute phase
    - ii. May take 6 weeks to grow
  - d. PCR of ocular fluids
  - e. ELISA based serologic testing for anti-Brucella IgM for acute disease and IgG for chronic and recurrent phases of disease

# II. List the differential diagnosis

- A. Tuberculosis
- B. Sarcoidosis
- C. Syphilis
- D. HLA-B27 positive anterior uveitis
- E. Outer retinal toxoplasmosis
- F. Multifocal choroiditis and panuveitis
- G. Lyme disease
- H. Behçet disease (in endemic areas)

# III. Describe medical therapy

#### A. Systemic antibiotics

- 1. Doxycycline must be used in combination with one of the following
  - a. Rifampin drug of choice and recommended by WHO
  - b. Streptomycin IV
  - c. Gentamicin IV
  - d. Trimethoprim/Sulfamethoxazole in children under 6 when tetracyclines contraindicated
- 2. Given for 6 weeks in the acute phase and up to 3 months for chronic disease

#### B. Corticosteroids

1. Systemic, periocular, and topical given concomitantly with systemic antibiotics

# IV. Describe disease-related complications

- A. Chronic smoldering uveitis may cause
  - 1. Cataracts
  - 2. Glaucoma
- B. Macular scars secondary to choroiditis

#### C. Visual prognosis

- 1. Most cases of acute Brucellosis curable with prompt antibiotic therapy
- 2. Uveitis prognosis is good if diagnosis is made and treatment instituted early
- 3. Worse in patients with
  - a. Posterior and panuveitis particularly if there is macular scar present
  - b. Optic neuritis

# V. Patient instructions

#### A. Prevention of infection best

- 1. Avoid exposure in endemic areas
  - a. Pasteurize all milk
  - b. Heating milk to 60°C for 10 minutes kills Brucella sp.

# B. Report high fevers with exposure to unpasteurized milk, infected meat products, or infected animals

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Ronaldo I. Olarte L. Vilchez G., et al. Ocular Manifestations Associated with Brucellosis: A 26 Year Experience in Peru. Clin Infect Dis. 2008; 46: 1338-45.
- 3. Rolando I. Vilchez G., Olarte L., et al. Brucellar Uveitis: Intraocular Fluids and Biopsy Studies. Int J Infect Dis. 2009; 13: e206-211.
- 4. Sungur G. K., Hazirolan D Gurbuz Y, et al. Ocular Involvement in Brucellosis, Can J Ophthalmol. 2009; 44: 598-601.
- 5. Vitale AT. Brucellosis. In Diagnosis and Treatment of Uveitis. Eds. Foster CS and Vitale AT. WB Saunders. Philadelphia. 2002. pp.278-285.

# Post-surgical and traumatic infectious scleritis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Pseudomonas species
  - a. Most common after pterygium excision
- 2. Actinomyces species and Nocardia
- 3. Mycobacteria
- 4. Fungal
  - a. Fusarium
  - b. Aspergillus
- 5. Gram positive cocci
  - a. Staphylococcus pneumococcus and Streptococcus species

#### B. Define the relevant aspects of epidemiology of this disease

- 1. Men and women equally affected
- 2. Previous ocular surgery
  - a. Pterygium surgery
    - i. Beta irradiation utilized
    - ii. Mitomycin C utilized
  - b. Scleral buckle
  - c. Cataract surgery
  - d. Pars plana vitrectomy
- 3. Trauma
  - a. Penetrating injury contaminated by soil or vegetable matter

#### C. List the pertinent elements of the history

- 1. Pain
- 2. Redness
- 3. Decreased vision
- 4. Recent anterior segment surgery
  - a. Can be delayed presentation (rarely many years)

#### D. Describe pertinent clinical features

- 1. Necrotic, thin, avascular sclera with inflammation at edges
- 2. Usually at site of a surgical or traumatic wound
- 3. May have mucopurulent discharge
- 4. Worsening with local corticosteroids or systemic immunosuppressive therapy

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Cultures superficial at base of scleral necrosis
  - a. Bacterial and fungal
  - b. Causative organisms can be difficult to grow
- 2. Gram stain
- 3. Consider scleral biopsy if history of trauma or surgery
  - a. 5-8 mm square block of sclera at the margins of necrotic base including some healthy sclera
  - b. Pathological evaluation for presence of bacteria and fungi
  - c. PCR studies after homogenization and extractions
  - d. Immunohistochemistry (e.g., labeled anti-herpes antibody probes
- 4. Work-up for non-infectious necrotizing scleritis should be performed
  - a. Anti-neutrophil cytoplasmic antibodies (ANCA)
    - i. cANCA- Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
    - ii. If positive, test for antibodies to myeloperoxidase and proteinase-3-confirmatory, increased specificity
    - iii. pANCA- Microscopic polyangiitis
  - b. Urinalysis
  - c. Fluorescent treponema antibody absorption/MHA-TP
  - d. Rheumatoid Factor, anti-cyclic citrullinated peptide antibodies
    - i. If polyarthritis
  - e. Lyme serology
  - f. Chest X-ray
  - g. SSA and SSB
  - h. Less useful tests
  - i. Antinuclear antibodies
    - i. Least useful tests

- i. Complete blood count (CBC)
  - i) If immunosuppressives are being considered
- ii. Human leukocyte antigen (HLA) B27
- iii. Purified protein derivative (PPD) skin test
- iv. Erythrocyte sedimentation rate (ESR)
  - i) If giant cell arteritis suspected, would want temporal artery biopsy
- v. Complete metabolic panel
  - i) If immunosuppressives are being considered

#### II. Define the risk factors

#### A. Previous ocular surgery - especially anterior segment

- 1. Pterygium with mitomycin C or beta irradiation
- 2. Cataract or glaucoma surgery (especially if mitomycin C used)
- 3. Scleral buckle

#### B. Trauma

- 1. Penetrating ocular injury
- 2. Contaminated with soil or vegetable matter

# III. List the differential diagnosis

#### A. Non-infectious necrotizing scleritis

- 1. Granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis)
- 2. Polyarteritis nodosa
- 3. Relapsing polychondritis
- 4. Rheumatoid arthritis
- 5. Sjögren Syndrome

# IV. Describe patient management in terms of treatment and follow-up

#### A. Best outcomes when medical and surgical treatment combined

- 1. Surgical debridement of infected tissues, often combined with cryotherapy
- 2. Multiple surgeries may be required
- 3. Systemic antibiotics
- 4. Topical antibiotics and subconjunctival antibiotics

- 5. Systemic analgesics
  - a. Nonsteroidal anti-inflammatory drugs
  - b. Judicious use of mild oral narcotics
- B. Avoid corticosteroids
- C. Systemic and Topical Antibiotic Treatment may be needed for six or more weeks
- D. Scleral patch grafting may be needed in cases with severe thinning

# V. List the complications of treatment, their prevention and management

- A. Globe perforation during surgery; be prepared with scleral graft tissue
- B. Inadequate excision of infected tissues can result in recurrence of disease
- C. Toxicity of topical and systemic antibiotics

# VI. Describe disease-related complications

- A. Corneal extension
- B. Globe perforation spontaneous
  - 1. Rare
- C. Endophthalmitis
  - 1. From intraocular extension
- D. Serous retinal detachments
- E. Blind and painful eye

# VII. Describe appropriate patient instructions

- A. Long term treatment may be needed
- B. Severe visual loss or loss of eye possible
- C. Contact ophthalmologist for severe pain or vision loss
  - 1. These two symptoms may indicate increased activity of the scleritis or persistence of the infectious process requiring changes to the therapeutic regimen

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Scleritis and Episcleritis: Diagnosis and Management, Module #9, 1995, p.6.

# Candida and Aspergillus endophthalmitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease - Candida albicans and Aspergillus spp

- 1. Hematogenous dissemination Multiple sources of infection:
  - a. Systemic infections
    - i. Endocarditis
    - ii. Gastrointestinal and hepatic infections
    - iii. Urinary tract infections
    - iv. Cutaneous infections
    - v. Pulmonary infections Aspergillus
  - b. Intravenous drug use
  - c. latrogenic
    - i. Indwelling intravenous catheters
    - ii. Contaminated intravenous fluids
    - iii. Contaminated injectable medications (Propofol Candida)
    - iv. Parenteral nutrition
    - v. Invasive surgical/diagnostic procedures
    - vi. Hemodialysis

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Uncommon
- 2. Can affect all ages; from neonates to the elderly
- 3. Bilateral in up to 25%
- 4. Patients typically present with systemic infection but others may appear healthy (rare)
  - a. Fungal: over 50% of all cases of endogenous endophthalmitis
    - i. Candida albicans
      - i) Candida endophthalmitis occurs in 37% of patients with candidemia
        - (i) *C. glabrata* becoming important pathogen in post-penetrating keratoplasty exogenous endophthalmitis. Voriconazole resistance
    - ii. Aspergillus spp.

#### C. List the pertinent elements of the history

1. Many patients have an underlying systemic infection or potential source of infection (Refer to

section 1A Describe the etiology of this disease - Candida albicans and Aspergillus spp.)

#### D. Describe pertinent clinical features

- 1. Symptoms
  - a. Ocular pain
  - b. Decreased vision
  - c. Floaters or scotoma
  - d. Constitutional symptoms (not always present)
- 2. Signs
  - a. Eyelid swelling possible
  - b. Conjunctival injection in some patients
  - c. Anterior chamber inflammation with or without hypopyon
  - d. Vitritis; may be severe; "string of pearls" or "fungus ball"
  - e. Vitreous abscess
  - f. Retinal hemorrhages
  - g. Vascular sheathing
  - h. Chorioretinitis multiple, white , bilateral, well circumscribed lesions <1mm in diameter in posterior pole Candida endophthalmitis
  - i. Diffuse Macular chorioretinitis characteristic of Aspergillus endophthalmitis

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Cultures
  - a. Blood
  - b. Other suspected sites of infection based upon clinical suspicion; urine, sputum, cerebrospinal fluid, etc.
  - c. Indwelling catheters and/or intravenous lines
- 2. Intraocular fluid analysis useful in absence of positive cultures from elsewhere
  - a. Vitreous biopsy
    - i. Giemsa stain, culture, sensitivities
    - ii. Polymerase chain reaction (PCR); may be useful with unusual organisms or culturenegative samples. Results may be available within 24 hours
- 3. Screening recommendations in patients with confirmed candidemia
  - a. All patients should have a baseline eye exam
  - b. Only patients with visual symptoms or those unable to verbalize symptoms should have dilated fundus exam within 72 *hours* and followed closely for 2 weeks for ocular involvement

# II. Define the risk factors

- A. Known/confirmed candidemia or systemic aspergillosis
- B. Recent major gastrointestinal surgery
- C. Bacterial sepsis
- D. Systemic antibiotic use
- E. Indwelling catheters
- F. Hyperalimentation
- G. Immunocompromised and chronically ill patients
- H. Immunomodulatory therapy
- I. Intravenous drug use
  - 1. Most common risk factor for Candida or Aspergillus endophthalmitis

# III. List the differential diagnosis

- A. Adults
  - 1. Exogenous endophthalmitis
  - 2. Infectious retinitis or retinochoroiditis
    - a. Toxoplasmosis or toxocariasis
    - b. Viral retinitis
      - i. Acute retinal necrosis
      - ii. Cytomegalovirus retinitis
    - c. Fungal chorioretinitis -other sp.
  - 3. Non-infectious uveitis
    - a. Anterior uveitis with spillover vitritis
    - b. Intermediate uveitis, pars planitis
    - c. Posterior uveitis
    - d. Panuveitis
  - 4. Masquerade syndromes
    - a. Ocular ischemic syndrome
    - b. Primary central nervous system lymphoma
    - c. Leukemia
    - d. Necrotic uveal melanoma
- B. Children
  - 1. Exogenous endophthalmitis

- 2. Infectious and non-infectious uveitis (Refer to section IIIA2 Infectious retinitis or retinochoroiditis and section IIIA3 Non-infectious uveitis)
- 3. Masquerade syndromes
  - a. Retinoblastoma
  - b. Leukemia
  - c. Occult intraocular foreign body

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe the natural history, outcome, and prognosis

- 1. Candida Variable prognosis
- 2. Aspergillus Poor prognosis
  - a. Secondary macular involvement
  - b. Vascular involvement

#### B. Describe medical therapy options

- 1. Consultation with an infectious disease specialist highly desirable
- 2. Topical therapy
  - a. Cycloplegics
  - b. Topical corticosteroid
- 3. Intravitreal therapy
  - a. Amphotericin B
  - b. Voriconazole
- 4. Systemic antifungals
  - a. Voriconazole (best ocular penetration of systemically administered drug)
  - b. Caspofungin
  - c. Fluconazole
  - d. Amphotericin in resistant cases
    - i. Liposomal lipid complex formulations to reduce renal toxicity

#### C. Describe surgical therapy options

- 1. Vitrectomy therapeutic and diagnostic
  - a. Vitreous culture and sensitivities
  - b. PCR analysis of Intraocular fluids
  - c. Debulk organisms, endotoxins and exotoxins, as well as vitreous opacities or membranes
  - d. Required in fungal endophthalmitis if vitreous involvement

- e. May not be necessary if only choroiditis (in candidiasis) is present without vitreous involvement
- f. Cases of pseudophakic Aspergillus endophthalmitis may require IOL removal

# V. List the complications of treatment, their prevention and management.

A. Side effects and risks of systemic medications, surgery, anesthesia

# VI. Describe disease-related complications

#### A. Ocular

- 1. Cataract
- 2. Glaucoma
- 3. Hypotony
- 4. Retinal detachment
- 5. Chorioretinal scar
- 6. Choroidal neovascularization
- 7. Phthisis
- 8. Enucleation

#### B. Systemic

1. Mortality : 5% or greater (especially with disseminated aspergillosis) associated with extraocular infection

# VII. Describe appropriate patient instructions

- A. Compliance with ocular and systemic therapy
- B. Report any changes in visual acuity, redness, or pain

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Basic and Clinical Science Course. Section 12: Retina and Vitreous, 2013-2014.
- 3. Smith SR, Kroll AJ, Lou PL, Ryan EA. Endogenous bacterial and fungal endophthalmitis. Int Ophthalmol Clin 2007;47(2):173-83.
- 4. Chee SP, Jap A. Endogenous endophthalmitis. Curr Opin Ophthalmol 2001;12:464-70.
- 5. Samiy N, D'Amico DJ. Endogenous fungal endophthalmitis. Int Ophthalmol Clin 1996;36:147-62.

- 6. Breit SM, Hariprasad SM, Mieler WF, et al. Management of endogenous fungal endophthalmitis with voriconazole and capsofungin. Am J Ophthalmol. 2005;139:135-140.
- 7. Essman TF, Flynn HW, Smiddy WE, et al. Treatment outcomes in a 10-year study of endogenous fungal endophthalmitis. Ophthalmic Surg Lasers. 1997;28:185-194.
- 8. Weishaar PD, Flynn HW Jr., Murray TG, et al. Endogenous Aspergillus endophthalmitis: clinical features and treatment outcomes. Ophthalmology. 1998;105: 57-65.
- 9. Dozier CC, Tarantola RM, Jiramongkolchai K, Donahue SP. Fungal Eye Disease at a tertiary care center : The utility of routine inpatient consultation. Ophthalmology. 2011; 118:1671-1676.
# Masquerade syndromes

Primary central nervous system intraocular lymphoma

# I. Describe the approach to establishing the diagnosis

#### A. Define the relevant aspects of epidemiology of the disease

- 1. Lymphoma arising in the eye or associated with the primary central nervous system lymphoma (PCNSL)
  - a. Also known as primary vitreoretinal lymphoma (PVRL)
  - b. 15% of patients with PVRL develop PCNSL and 65-90% of patients with PCNSL develop PVRL
  - c. Primary Intraocular lymphoma is usually a diffuse large B cell lymphoma
  - d. Previously it was known as reticulum cell sarcoma
  - e. T-cell lymphomas involving the eye are rare
- 2. Typical age of onset: > 50 years, mainly affects patients in the 6<sup>th</sup> and 7<sup>th</sup> decade
- 3. Incidence increased until last decade:
  - a. Approximately 1900 cases of PCNSL per year in USA, approximately 380 cases of PIOL/PVRL
  - b. >30 fold increase in cases in 3 decades
  - c. 0.3 % per 100,000 persons-years among immunocompetent patients
  - d. 4-5 per 1,000 person-years patients with Acquired Immunodeficiency Syndrome (AIDS)

#### B. List the pertinent elements of the history

- 1. Central nervous system (CNS) signs and symptoms
- 2. Confusion, weakness, deterioration in mental functions

#### C. Ocular history

- 1. Bilateral, but may start in an asymmetrical fashion
- 2. Decreased vision and floaters
- 3. Rarely, pain and redness
- 4. 25% PCNSL present in the eye at diagnosis

#### D. Describe pertinent clinical features

- 1. Mild or no anterior segment inflammation, synechiae are uncommon
- 2. Clumps and sheets of white cells in the vitreous
- 3. Multifocal subretinal and sub-pigment epithelial infiltrates

- 4. Atypical presentations: hemorrhagic retinitis resembling viral retinitis, exudative retinal detachment
- 5. Preservation of visual acuity disproportionate to amount of cells

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Must suspect the lymphoma in a patient who has chronic, medically unresponsive uveitis characterized by vitreous cells and subretinal or subretinal pigment epithelium (RPE) infiltrates
- 2. Vitreous biopsy, sub-RPE aspirate and/or retinal biopsy
  - a. Cytology
  - b. Immuno cytopathology
  - c. Flow cytometry
  - d. Cytokine analysis
  - e. Gene rearrangement
  - f. Handling of vitreous specimens (See Diagnostic vitreoretinal procedures in uveitis: vitreous biopsy)
    - i. Multiple vitreous specimens may be needed
- 3. Magnetic resonance imaging of the brain
- 4. Cerebrospinal fluid for cytology

#### F. Pathology

- 1. Cytology: gold standard
  - a. Lymphoma cells are large, pleomorphic with scanty cytoplasm, multiple nuclei and prominent nucleoli
  - b. Low sensitivity as samples are paucicellular, interpretation dependent on expertise of cytopathologist
- 2. Immunophenotyping
  - a. Immunohistochemistry or flow cytometry
    - i. Used to establish clonality of B lymphocytes
    - ii. Immunoglobulin kappa or lambda light chains restriction and the presence of monoclonal B-lymphocytes
    - iii. Predominant T-cell population with aberrant markers inverted CD4:CD8 ratio may indicate T-cell lymphoma
- 3. Cytokine analysis
  - a. High IL-10/IL-6 ratio suggestive of PCNSL
- 4. Gene rearrangement
  - a. Heavy chain gene rearrangements (IgH) for B-cell lymphoma or T-cell receptor gamma gene rearrangements for T-cell lymphoma

# II. Define the risk factors

- A. Age
- B. Immunosuppression
- C. AIDS

# III. List the differential diagnosis

- A. Sarcoidosis
- B. Syphilis
- C. Tuberculosis
- D. Acute retinal necrosis
- E. Behçet disease
- F. Cytomegalovirus retinitis
- G. Toxoplasmosis
- H. Birdshot chorioretinopathy
- I. Acute posterior multifocal placoid pigment epitheliopathy
- J. Multifocal choroiditis
- K. Vogt Koyanagi Harada disease
- L. Amyloid
- M. Metastatic Intraocular lymphoma

# IV. Describe patient management in terms of treatment and follow-up

- A. Corticosteroids are cytolytic to lymphoma cells leading to an apparent response to treatment initially. Corticosteroids also decrease the yield of biopsy
- B. Immediate referral to an oncologist for treatment and staging
- C. Chemotherapy alone
  - 1. Recommended for patients > 60 years to obviate radiation induced neurotoxicity
  - 2. High-dose methotrexate alone or in combination with other chemotherapeutic agents
  - 3. Blood brain barrier disruption in some centers (Ommaya reservoir)

#### D. Combination chemotherapy and coned-down radiation

- 1. Recommended for patients < 60 years of age
- 2. High-dose methotrexate alone or in combination with other chemotherapeutic agents
- 3. Intrathecal methotrexate via Ommaya reservoir
- 4. Intravitreal methotrexate/Rituximab in conjunction with systemic treatment
- E. Radiation alone is ineffective long-term treatment and associated with important adverse quality

#### of life issues

1. Not first line treatment anymore

#### F. Median survival rate is 2-3 months with supportive care alone

- 1. Intrathecal chemotherapy may increase survival rate
- 2. With treatment, longest median survival approaches 40 months

# V. List ocular complications of treatment

- A. Cataract
- B. Radiation retinopathy
- C. Retinal detachment

# VI. Describe disease-related complications

- A. Visual impairment or blindness
- B. Serous retinal detachments
- C. Optic atrophy

# VII. Describe appropriate patient instructions

- A. Importance of oncology referral
- B. Follow instructions regarding medications

Leukemia (as masquerade syndrome)

# I. Describe approach to establishing diagnosis

- A. Epidemiology
  - 1. Up to 75% of patients with acute leukemias may have intraocular findings

#### B. Ocular manifestations

- 1. Anterior uveal infiltration
  - a. Hypopyon (pseudohypopyon)
  - b. Hyphema
  - c. Both
- 2. Posterior segment
  - a. Intraretinal hemorrhages

- b. Cotton wool spots,
- c. White-centered retinal hemorrhages (Roth spots)
- d. Microaneurysms
- e. Occasionally peripheral retinal neovascularization.
- f. Vitritis rare leukemic cells can break through the internal limiting membrane
- g. Exudative retinal detachment choroidal involvement

#### C. Testing

- 1. Fluorescein angiography
  - a. Choroidal involvement
    - i. Similar to the pattern of Vogt-Koyanagi-Harada syndrome or posterior scleritis
    - ii. Multiple pinpoint areas of retinal pigment epithelial leakage in the early and mid phases
    - iii. Pooling of fluorescein in the subretinal space in the late phases
- 2. Cytologic evaluation of aqueous specimen if hyphema or hypopyon
  - a. Obtained through a clear corneal anterior chamber paracentesis
  - b. Can be diagnostic

# II. Therapy

- A. Oncology referral
- B. Systemic chemotherapy

# III. Disease-related complications

# A. Acute leukemic infiltration of the optic nerve

- 1. Sudden onset of no light perception vision
- 2. More common in children
- 3. Radiation-oncologic emergency

Uveal melanoma (as a masquerade syndrome)

# I. Describe approach to establishing diagnosis

# A. Epidemiology

1. Most common primary intraocular malignancy

#### B. Clinical manifestations

- 1. 5-20% percent of patients may present with intraocular inflammation
  - a. Episcleritis, scleritis
  - b. Anterior and posterior uveitis
  - c. Sectoral cataract
  - d. Endophthalmitis
- 2. Most that present with uveitis are epithelioid cell or mixed cell, necrotic tumors

#### C. Diagnostic testing

- 1. Ultrasonography
  - a. Characteristic low to medium reflectivity of lesions

# II. Therapy

- A. Enucleation
- B. Local therapy for smaller lesions
  - 1. Surgical excision smaller iris and ciliary body lesions
  - 2. Plaque radiotherapy for peripheral choroidal lesion

# III. Disease related complications

# A. Metastasis - especially with ciliary body tumors and large choroidal tumors

1. All patients require metastatic evaluation prior to therapy

Retinoblastoma (as masquerade syndrome)

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of this disease

- 1. Intraocular tumor arising from photoreceptor precursor cells
- B. Define the relevant aspects of epidemiology of the disease
  - 1. Most common malignant ocular tumor of childhood
  - 2. Diagnosed between 1 and 3 years of age
- C. List the pertinent elements of the history
  - 1. Most common initial sign is leukocoria, first noticed by the family
  - 2. Strabismus
  - 3. Suspected intraocular inflammation

#### D. Describe pertinent clinical features

- 1. Strabismus
- 2. Glaucoma
- 3. Proptosis
- 4. White retinal lesions
- 5. Retinal detachment
- 6. Calcification on B-scan or CT
- 7. Uveitis masquerade—aqueous or vitreous cellular infiltration mimicking uveitis
  - a. Vitreous seeding in endophytic retinoblastoma may be so extensive as to mimic endophthalmitis
  - b. Tumor cells may float in the anterior chamber (pseudo-iritis) and form a pseudohypopyon
  - c. No posterior synechiae

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Retinoblastoma must be excluded in any young child with leukocoria, strabismus or an undiagnosed uveitis
- 2. Pars plana vitrectomy or paracentesis for diagnosis is contraindicated in suspected retinoblastoma because it increases the possibility of metastasis
- 3. Computed tomography (CT) scan of the head and orbits
  - a. Intralesional calcification
- 4. B-scan
  - a. Intralesional calcification

# II. Describe patient management in terms of treatment and follow-up

- A. Urgent ocular oncology and pediatric oncology referral
- B. Enucleation still used in patients with large unilateral retinoblastoma
  - 1. Invasion of optic nerve and extraocular extension are associated with a relatively poor prognosis
- C. Neoadjuvant chemotherapy ("chemo reduction") is now used as primary treatment to reduce the size of the lesion
- D. Consolidation therapy is then performed with radiotherapy, cryotherapy or laser photocoagulation or transpupillary thermotherapy (TTT)
- E. External-beam radiotherapy for advanced retinoblastoma (tumor may recur and there is risk of secondary tumors)
- F. Local therapy for smaller tumors
  - 1. Plaque radiotherapy
  - 2. Cryotherapy and laser photoablation

# III. List the differential diagnosis of retinoblastoma/masquerade syndrome

- A. Coats disease
- B. Persistent hyperplastic primary vitreous
- C. Ocular toxocariasis
- D. Advanced retinopathy of prematurity
- E. Retinal dysplasia
- F. Retinal detachment
- G. If Pseudohypopyon consider leukemia, endogenous endophthalmitis, HLAB27 associated iridocyclitis, and Behçet disease (unlikely in the retinoblastoma age group)

# IV. List the complications of treatment, their prevention and management

#### A. Chemotherapy

- 1. Neutropenia
- 2. Opportunistic infection

#### B. Radiation therapy

- 1. Radiation retinopathy
- 2. Cataract
- 3. Increased rate of orbital sarcoma development

# V. Describe disease-related complications

- A. Secondary tumors in patients with heritable disease
- B. Midline brain tumors (trilateral retinoblastoma) in patients with heritable disease

# VI. Describe appropriate patient instructions

- A. Offspring are at risk for disease and should be examined shortly after birth
- B. Follow-up examination under anesthesia schedule is individualized based on patient's stage of disease

Bilateral diffuse uveal melanocytic proliferation

# I. Describe the approach to establishing the diagnosis

A. Describe the etiology of this disease

- 1. Unknown circulating anti-retinal antibodies reported in some cases
- 2. Associated with systemic malignancy paraneoplastic syndrome
  - a. Bronchogenic carcinoma
  - b. Ovarian Carcinoma
  - c. Squamous carcinoma of the lung
  - d. Uterine leiomyoma
  - e. Others

#### B. List the pertinent elements of the history

a. Rapid visual loss

#### C. Describe pertinent clinical features

- 1. Ocular manifestations
  - a. Cataracts
  - b. Multiple pigmented and non-pigmented iris nodules
  - c. Multiple pigmented and non-pigmented choroidal nodules
  - d. Serous retinal detachments

#### D. Histology

- 1. Diffuse uveal infiltration by benign nevoid and spindle shaped cells
- 2. Necrosis within tumors
- 3. Scleral involvement is common

#### II. Describe patient management in terms of treatment and follow-up

- A. Find primary malignancy
- B. Treat primary malignancy
- C. Plasmapheresis can be tried
- D. Corticosteroids and immunomodulatory therapy not very successful

Other masquerade syndromes

- I. Juvenile xanthogranuloma
- II. Metastatic cancer, melanoma or lymphoma
- III. paraneoplastic retinopathy

- I. Retinitis pigmentosa (RP)
- II. Chronic retinal detachment
- III. Retained intraocular foreign body
- **IV.** Pigment Dispersion Syndrome
- V. Ocular Ischemic Syndrome

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
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- 21. In: Ryan SJ. Retina. Complicated retinitis pigmentosa. Chapter 17, p.432.
- 22. AAO, Basic and Clinical Science Course. Section 12: Retina and Vitreous, 2013-2014.
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# Cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR)

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease

- 1. Rare paraneoplastic syndromes
- 2. Retinal degeneration presumably immunologically based
  - a. Autoantibodies directed against retinal antigens
    - i. 23kD protein recoverin-most common autoantibody isolated in CAR
    - ii. Bound to outer retinal segments (e.g., photoreceptors in CAR) or to inner retinal segments (e.g., bipolar cells in MAR) causing irreversible retinal dysfunction
  - b. Other protein targets have been identified
- 3. Associated with carcinomas
  - a. CAR most commonly associated with small-cell (oat cell) lung carcinoma
    - i. Diagnosis of CAR frequently precedes diagnosis of underlying malignancy
    - ii. Non-small cell lung, endometrial, breast, small cell cervical, and ovarian carcinoma also reported
  - b. MAR associated with malignant melanoma often with metastases
    - i. Diagnosis of melanoma typically predates visual symptoms in MAR

#### B. Define the relevant aspects of epidemiology of the disease

- 1. Most common among patients > 50 years of age
- 2. No sex predilection
- 3. Rare, prevalence not well-described

#### C. List the pertinent elements of the history

- 1. Bilateral progressive visual loss
- 2. Nyctalopia (night blindness) or photo aversion
- 3. Photopsias that may be pulsating, shimmering
- 4. Glare, photosensitivity
- 5. Ring scotomas in CAR; central visual field defects with peripheral field sparing in MAR

# D. Describe pertinent clinical features

- 1. Arteriolar narrowing
- 2. Mild vitreous inflammation

- 3. Rarely retinal periphlebitis
- 4. Often no pigmentary changes in retina especially early in disease course; end stage disease may resemble RP with optic nerve pallor and retinal atrophy/pigmentary changes
- 5. At the onset of the disease clinical signs are often minimal compared to the degree of visual loss

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. ERG: either severe reduction of both a-wave (photoreceptors) and b-wave (bipolar cells) responses OR negative pattern ERG (diminished scotopic b-wave but preserved a-wave responses). Delay in implicit times
  - a. MAR: negative pattern ERG is most typical
  - b. CAR: both rods and cones can be affected, cone ERG most often affected
- 2. Visual field testing may show rapid worsening in scotomas
- 3. Testing for antiretinal antibodies
  - a. Most often performed in research laboratories
  - b. CLIA certified testing available in some labs
  - c. Antiretinal antibodies are tested by
    - i. Western blot: serum electrophoresis displays antibodies present in high titers and defines the molecular weight of the antigenic target
    - ii. Immunohistochemical staining of human retinal tissue: Patient serum applied to retinal slices and bound immunoglobulin detected with secondary antibody tagged with fluorescent marker. Localizes the immunoglobulin binding to certain retinal cell layers
    - iii. ELISA: only for known antigens (i.e., recoverin)

# II. Define the risk factors

- A. Not well defined
- B. Positive prior history of or family history of cancer
- C. History of heavy smoking possibly a risk factor as well

# III. List the differential diagnosis

- A. Retinitis pigmentosa
- B. Cone-rod dystrophy
- C. Intermediate uveitis
- D. Syphilis
- E. Retinal drug toxicity
- F. Retinal degenerations associated with systemic disease

#### G. Acute zonal occult outer retinopathy (AZOOR)

# IV. Describe patient management in terms of treatment and follow-up

#### A. Describe the natural history, outcome and prognosis

- 1. Progressive, asymmetric visual acuity and visual field loss due to irreversible retinal degeneration
  - a. Rapid progression often seen with CAR is less common with MAR
- 2. Prognosis is generally poor even with treatment

#### B. Describe therapy options

- 1. Prednisone
  - a. May consider intravitreal steroids in refractory cases
- 2. Plasmapheresis
- 3. Intravenous immunoglobulin (IV Ig)
- 4. Immunosuppressive drugs
  - a. DMARDs including biologic agents such as alemtuzumab (pan-lymphocytic, anti-CD-52) and rituximab (B-cell, anti-CD 20)
- 5. Treatment for MAR similar to CAR with exception that typically diagnosis of the melanoma predates the ocular findings
- 6. Treatment needs to be coordinated with the oncologist to avoid adverse effect on the underlying malignancy

# V. List the complications of treatment, their prevention and management

- A. Related to prednisone: Side effects are related to dose of prednisone and may include weight gain, moon facies, elevated blood sugar or blood pressure, mood alterations, and bone loss. Rarely aseptic necrosis of bone may occur
- B. Related to immunosuppressive drug therapy: increased risk of infection, hepatotoxicity, cytopenias, and increased risk of cancers. Risks are dependent on drug selected and dose

# VI. Describe disease-related complications

- A. Systemic associations: Dependent upon the type of cancer associated with the retinopathy
- B. Ocular associations: loss of visual acuity and visual field related to the retinal degeneration, secondary optic atrophy/pallor

# VII. Describe appropriate patient instructions

A. Referral to primary care doctor for malignancy work up if not already diagnosed with a malignancy

#### B. Refer to services for visually impaired as needed

#### Additional Resources

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# Ocular manifestations of acquired immunodeficiency syndrome

Immune recovery uveitis

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of the disease

1. Presumed immunologic activity against CMV antigen

#### B. Describe the relevant aspects of the epidemiology of the disease

- 1. HIV infected patients on HAART
  - a. Definition of HAART
    - i. Multidrug therapy directed against HIV proliferation and infection of human cells through multiple mechanisms thereby preventing development of viral resistance
      - Nucleoside analogues that are incorporated into viral DNA of HIV by DNA polymerase of HIV (reverse transcriptase) preventing further viral DNA synthesis
      - ii) Protease inhibitors prevent cleavage of precursor proteins into viral elements needed for viral assembly
      - Non-nucleoside reverse transcriptase inhibitors direct inhibition of viral (HIV)
        DNA synthesis
      - iv) Fusion inhibitors prevent fusion of HIV to human cell membrane
    - ii. Three or more anti-retroviral agents from 2 or more of the above classes used simultaneously
    - iii. All initiated simultaneously to prevent early drug resistance
  - b. Treatment effects and treatment goals of HAART
    - i. Dramatic reduction in viral load
    - ii. Increase in CD4+ T-lymphocyte counts
    - iii. Delay in disease progression
    - iv. Reduction in opportunistic infections- by up to 82%
    - v. Fewer hospitalizations
    - vi. Improved survival
  - c. List the indications/contraindications for use of HAART
    - i. Indications

- i) HIV+
- ii) CD4 <350cells/mm<sup>3</sup> treat
- iii) HIV-1 RNA > 30,000 copies/ml treat
- iv) Symptomatic AIDS treat
- ii. Contraindications
  - i) Asymptomatic patients with CD4>500 cells/mm<sup>3</sup> and HIV -1 RNA <5000 copies /ml- defer treatment
- d. List the complications of HAART, their prevention and management
  - i. Emergence of drug resistant HIV strains
    - i) Alternative aggressive salvage therapy 5 agents
    - ii) HIV drug sensitivity testing for most anti-retroviral agents available
  - ii. Drug toxicity
    - i) Can cause interruption in HAART therapy
    - ii) Close follow-up and periodic laboratory investigations looking for drug-specific complications
    - iii) Switching to other agents in the three antiretroviral drug groups may result in reduction of side effects
- CD4+ T-lymphocyte counts (increase by at least 50 cells/mm3 after HAART) >100 cells/mm3, usually >250 cells/mm3
- 3. Pre-existing intraocular opportunistic infection (especially CMV retinitis)

#### C. List the pertinent elements of the history

- 1. Slow decline in vision with increasing CD4 counts
- 2. Blurred vision
- 3. Metamorphopsia
- 4. CMV retinitis (active or inactive)

#### D. Describe the pertinent clinical features

- 1. Cornea dendritic keratic precipitates
- 2. Anterior chamber with variable cells and flare can be severe
- 3. Iris
  - a. Rarely iris bombé and angle closure can occur
- 4. Lens
  - a. Intraocular lens may have cellular deposits
  - b. Posterior subcapsular (PSC) cataract
- 5. Vitreous

- a. Trace cells to 2+ cells vitreous haze
- 6. Macula
  - a. CME
  - b. Epiretinal membrane
  - c. Inactive CMV retinitis with retinal scarring and sclerotic vessels
- 7. Optic disc edema
- E. Describe appropriate testing and evaluation for establishing the diagnosis
  - 1. HIV serology- assumed to be positive
  - 2. CD4+ lymphocyte count
  - 3. Viral load usually undetectable-probably not predictive of uveitis

# II. Define the risk factors

- A. Rising CD4+ T-lymphocyte count with HAART
- B. CMV retinitis (risk proportional to surface area of retina involved)
- C. HAART therapy
- D. History of Cidofovir therapy

# III. List the differential diagnosis

- A. Active CMV retinitis
- B. Toxoplasmosis
- C. Drug-induced uveitis
  - 1. Rifabutin
  - 2. Cidofovir

# D. Disseminated mycobacterial infections - worsened immune response after HAART

#### E. Other causes of iridocyclitis

- 1. Human leukocyte antigen (HLA) B27 + (both HLA-B27 anterior uveitis and rifabutin-associated uveitis can present with a hypopyon, creating potential confusion in etiology)
- 2. Idiopathic

# IV. Describe patient management in terms of treatment and follow-up

#### A. Topical corticosteroids

- 1. Can control anterior chamber cells
- 2. May help CME especially in pseudophakic eyes

# B. Regional corticosteroids

# V. List the complications of treatment, their prevention and management (See Corticosteroids)

# VI. Describe disease-related complications

- A. CME
  - 1. Can be refractory to treatment
  - 2. Occasionally visual loss can be profound

#### B. Epiretinal membrane

- 1. Can be removed surgically
- 2. Vision may still be limited by underlying CME
- C. Posterior subcapsular cataract
- D. Iris posterior synechiae and iris bombé leading to angle closure rare

# VII. Describe appropriate patient instructions

- A. Decreasing vision and metamorphopsia should be reported
- B. Continued follow-up necessary even if CD4 counts are >300 and even if CMV retinitis is inactive off all anti-CMV medications

Human immunodeficiency virus (HIV) retinopathy

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of this disease- controversial

- 1. HIV retinal vascular endothelial infection
- 2. Hematologic abnormalities
  - a. Increased leukocyte activation
  - b. Increased leukocyte rigidity
  - c. Increased red cell aggregation
- 3. Immune complex deposition in retinal capillaries

#### B. Define the relevant aspects of epidemiology of this disease

 Occurs at CD4+ counts < 50 cells/µl (50-70% of patients at this level of immune suppression will develop HIV retinopathy)

#### C. List the pertinent elements of the history

- 1. Usually no symptoms
- 2. Rarely painless visual loss of sudden onset (3%)
  - a. Scotoma or blurred vision
  - b. Visual field defect in cases of vascular occlusion

#### D. Describe pertinent clinical features

- 1. Cotton wool spots
- 2. Retinal hemorrhages
- 3. Microaneurysms

#### E. Describe pertinent pathologic features

- 1. Resembles diabetic retinopathy
- 2. Pericyte necrosis
- 3. Endothelial cell swelling
- 4. Thickened basement membranes

#### F. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. HIV status positive
- 2. CD4+ counts often less than 50 cell/ µl
- 3. Rule out other common causes of retinal microvasculopathy
  - a. Check blood pressure
  - b. Fasting blood sugar

# II. Define the risk factors

- A. HIV positive
- B. CD4+ counts <50 cells/µl

# III. List the differential diagnosis

- A. Diabetic retinopathy
- B. Radiation retinopathy
- C. Hypertensive retinopathy

#### D. Cytomegalovirus (CMV) retinitis

- 1. Large cotton wool spots in HIV retinopathy may be confused for CMV retinitis
- 2. In HIV retinopathy
  - a. Cotton wool spots

- i. Do not enlarge and usually resolve in 4-6 weeks
- ii. Are smaller than 750 microns
- iii. Are not associated with contiguous areas of hemorrhage and intralesional hemorrhage
- iv. No iridocyclitis or vitritis (which, though mild, often occurs in CMV retinitis)
- E. Varicella zoster virus (VZV) retinitis

# IV. Describe patient management in terms of treatment and follow-up

A. None specific, focus on restoration of immune function with HAART therapy

# V. Describe appropriate patient instructions

- A. Have dilated examinations every 3 months performed if CD4+<50 cells/µl
- B. Should not typically have visual loss from these changes

HIV-related neuroretinal disorder (NRD)

# I. Describe the approach to establishing the diagnosis

#### A. Define the relevant aspects of epidemiology of this disease

1. Occurs in patients with AIDS with a history of low CD4+ count

#### B. List the pertinent elements of the history

- 1. Usually no symptoms
- 2. Rarely painless, insidious blurring of vision

#### C. Describe pertinent clinical features

- 1. Decreased contrast sensitivity, visual field and color vision
- 2. Often visual acuity is normal or near normal
- 3. Retinal vessels may be narrowed
- 4. Thinning of retinal nerve fiber layer on OCT testing.
- D. Describe appropriate testing and evaluation for establishing the diagnosis
  - 1. HIV status positive
  - 2. CD4+ count and viral load

# II. Define the risk factors

#### A. HIV positive

#### Uveitis

- B. CD4+ counts <50 cells/µl
- C. Unclear if this is a result of neuroretinal damage secondary to HIV retinopathy

Cytomegalovirus (CMV) retinitis (See Cytomegalovirus retinitis)

# I. Describe the approach to establishing the diagnosis

#### A. Describe the relevant aspects of epidemiology of this disease

- 1. Incidence of new CMV has fallen 60-80% since introduction of highly active anti-retroviral therapy (HAART)
- 2. It is still the most common opportunistic ocular infection in AIDS
- 3. Can resolve on HAART alone, provided patient responds to HAART
- 4. Has become self-limited disease that does not require lifetime maintenance therapy after immune reconstitution with HAART
- 5. CMV retinitis is still associated with a substantial risk of vision loss despite HAART
  - a. Those receiving HAART have reduced risk of vision loss
    - i. Some of that reduction of risk is lost if immune recovery uveitis is present
  - b. Causes of visual loss in the HAART era
    - i. Zone 1 involvement and retinal detachment most common overall
    - ii. Cataract, cystoid macular edema (CME), and epiretinal membrane in patients with HAART-induced immune recovery

Herpes zoster ophthalmicus (HZO) in patients with human immunodeficiency virus (HIV) infection

# I. Describe the approach to establishing the diagnosis

# A. Describe the etiology of the disease

- 1. Varicella zoster (VZV) virus
- B. Describe the relevant aspects of the epidemiology of the disease
  - 1. HIV+ individuals are six times more likely to develop HZO
  - 2. Not AIDS defining illness but suggests immune compromise
  - 3. Greater rates of recurrence than in non-AIDS patients
  - 4. Can occur at any CD4 count level
  - 5. Can be initial manifestation of AIDS
- C. List the pertinent elements of the history

- 1. Painful rash with paresthesias on face
- 2. Foreign body sensation
- 3. Redness
- 4. Decreased vision

#### D. Describe the pertinent clinical features

- 1. Cutaneous vesicular eruption along cranial nerve V1 (ophthalmic division)
  - a. Can be bilateral (multidermatomal) in HIV
- 2. Cornea-epithelial changes seen best with rose bengal
  - a. Small micro dendrites-multiple
  - b. Peripheral lesions
  - c. Geographic epithelial defect
- 3. Anterior chamber
  - a. Variable cells and flare
- 4. Iris
  - a. Chronic cases may show sectoral or diffuse stromal atrophy and transillumination defects
- 5. Vitreous
  - a. Presence of variable cells
- 6. Retinitis, progressive outer retinal necrosis (PORN)
- 7. Optic neuritis

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Clinical diagnosis- rarely are labs needed mainly to look for VZV (if obtained, negative results are helpful to rule out prior exposure while positive results only indicate prior exposure but are not proof that the current disease is secondary to the virus)
  - a. Cutaneous vesicles, cornea epithelial scraping and culture in Hank's medium
  - b. Aqueous paracentesis with polymerase chain reaction (PCR)

# II. Define the risk factors

- A. Exposure to another patient with active zoster infection
- B. Prior varicella infection (most common)
- C. CD4 counts <100 may be associated with more severe disease in HIV infected individual

# III. List the differential diagnosis

A. Herpes simplex virus keratitis/keratouveitis

#### B. Immune recovery uveitis

# IV. Describe patient management in terms of treatment and follow-up

#### A. Depends on location of involvement

- 1. If retinitis is present, then high levels of intravitreal antivirals are needed
  - a. IV acyclovir 10-14 days
    - i. Alternative: Foscarnet
  - b. Intravitreal foscarnet or ganciclovir
- 2. If anterior uveitis
  - a. Oral acyclovir 800mg 5 times daily for 14 days
  - b. Maintenance therapy with oral acyclovir may be needed if frequent recurrences of keratitis or iridocyclitis
  - c. Alternatives
    - i. Famciclovir, valacyclovir

#### B. Varicella vaccine - live attenuated viral vaccine

- 1. Should not be given in cases of AIDS
- 2. Consider in asymptomatic children with early HIV infection with near normal CD4 counts

#### C. Varicella zoster virus immunoglobulin

- 1. Consider for post-exposure prophylaxis in immunocompromised patients within 72 hours
- 2. May modify disease course for the exposed patient

# V. List the complications of treatment, their prevention and management

- A. Granulocytopenia acyclovir, famciclovir, valacyclovir
- B. Nephrotoxicity from Foscarnet

# VI. Describe disease-related complications

A. Post-herpetic neuralgia

#### B. Keratitis

- 1. Disciform keratitis
- 2. Chronic epithelial keratitis

#### C. Chronic iridocyclitis

- 1. Glaucoma
- 2. Cataract

- D. Optic atrophy (in cases of optic neuritis)
- E. Ipsilateral necrotizing scleritis
- F. Dilated pupil
- G. Increased risk of development of necrotizing herpetic retinitis (See Necrotizing herpetic retinitis: acute retinal necrosis and progressive outer retinal necrosis)

# VII. Describe appropriate patient instructions

- A. Report pain, redness, vision loss
- B. Recurrences are more common in HIV infection
- C. Importance of medication compliance

Rapidly progressive necrotizing herpetic retinitis in immunocompromised patients (See Necrotizing herpetic retinitis: acute retinal necrosis and progressive outer retinal necrosis)

# I. Describe patient management in terms of treatment and follow-up

A. Often requires more than one antiviral agent given via multiple routes (IV and intravitreal injections)

# II. Describe disease related complications

A. High rate of retinal detachment (>70%)

Toxoplasma retinochoroiditis in acquired immune deficiency syndrome (AIDS)

# I. Describe the approach to establishing the diagnosis

#### A. Describe the etiology of the disease

1. Toxoplasma gondii - obligate intracellular protozoan acquired infections or from pre-existing retinal focus

#### B. Describe the relevant aspects of the epidemiology of the disease

- 1. Human immunodeficiency virus (HIV)+ with or without previous toxoplasma scars
- 2. Patients with extraocular toxoplasma infections
- 3. Some population groups have higher prevalence e.g. Brazilians, Central Americans

# C. List the pertinent elements of the history

- 1. Floaters
- 2. Painless vision loss

3. Rarely - severe pain with extrascleral/orbital involvement

#### D. Describe the pertinent clinical features

- 1. Full thickness retinal necrosis with overlying vitreous inflammation, with or without adjacent chorioretinal scar (usually not seen)
- 2. Larger lesions (areas of retinitis) and multiple lesions more prevalent in AIDS than immunocompetent patients
- 3. Bilateral disease more likely, present in 1/3 of patients with ocular toxoplasmosis in AIDS patients
- 4. Inflammation less and variable in HIV+ patients (based on CD4 +lymphocyte count) compared to immunocompetent patients
- 5. Invariably progressive without treatment in HIV/AIDS
- 6. 25%-50% of HIV+/AIDS patients will have central nervous system toxoplasmosis

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. In cases of diagnostic difficulty consider pars plana vitrectomy or aqueous paracentesis and polymerase chain reaction on ocular fluid
- 2. Toxoplasma serology (anti-toxoplasma immunoglobulin G and immunoglobulin M) may not be reliable but should be obtained
- 3. Computed tomography or magnetic resonance imaging with contrast to rule out co-existing central nervous system (CNS) disease

# II. Define the risk factors

- A. HIV +
- B. Pre-existing toxoplasma retinochoroiditis scar
- C. Concomitant extraocular (especially CNS) toxoplasmosis

# III. List the differential diagnosis

- A. Acute retinal necrosis (more intraocular inflammation, early retinal vascular involvement)
- B. Cytomegalovirus retinitis (slower rate of progression, early retinal vascular involvement)
- C. Progressive outer retinal necrosis (PORN)
- D. Syphilitic chorioretinitis

# IV. Describe patient management in terms of treatment and follow-up

- A. Combination therapy with all 3 agents is effective in >75% of cases
  - 1. Pyrimethamine
  - 2. Sulfadiazine

3. Clindamycin

#### B. Alternative treatments

- 1. Atovaquone + clarithromycin
- 2. Trimethoprim-sulfamethoxazole (Bactrim DS) + clindamycin
- C. Avoid systemic and periocular corticosteroids in the immunocompromised patient
- D. Lifetime maintenance therapy is usually required even after the retinitis has become inactive
- E. If immune recovery occurs and CD4 increases to >500 cells/mm<sup>3</sup>, can consider stopping maintenance
- F. Bactrim double strength 1 daily or three times per week can aid in prophylaxis against toxoplasmosis

# V. List the complications of treatment, their prevention and management

- A. Pyrimethamine and sulfadiazine
  - 1. Sulfa drug allergies Stevens-Johnson syndrome
  - 2. Bone marrow suppression
  - 3. Zidovudine antagonizes anti-toxoplasma effects of pyrimethamine in vitro and in vivo

# VI. Describe disease-related complications

- A. Macular and retinal scarring
- B. Optic atrophy especially if optic nerve or peripapillary involvement
- C. Retinal arteriolar or venular occlusions
- D. Tractional and rhegmatogenous retinal detachments
- E. Progressive extrascleral and orbital involvement

# VII. Describe appropriate patient instructions

- A. Watch for severe loss of vision
- B. Watch for focal neurologic symptoms which suggest concomitant CNS disease
- C. Continue maintenance medication even if vision is stable

Syphilitic chorioretinitis in acquired immune deficiency syndrome (AIDS) (See Syphilitic panuveitis)

Infectious multifocal choroiditis in acquired immune deficiency syndrome (AIDS)

# I. Describe the approach to establishing the diagnosis

Uveitis

#### A. Describe the etiology of the disease

- 1. Pneumocystis carinii
- 2. Cryptococcus neoformans
- 3. Atypical mycobacteria (mycobacterium avium intercellular (MAI), others)
- 4. Histoplasma capsulatum
- 5. Candida albicans
- 6. Aspergillus fumigatus
- 7. Mycobacterium tuberculosis
- 8. Multiple organisms may be involved

#### B. Describe the relevant aspects of the epidemiology of the disease

1. Less than 5% of patients with AIDS

#### C. List the pertinent elements of the history

- 1. Often systemically very ill with sepsis and disseminated infection from one or more causative organisms
- 2. Usually no visual symptoms
- 3. Rarely visual loss may occur if lesions involve the macula and posterior pole

#### D. Describe the pertinent clinical features

- 1. Variable sized multifocal choroidal lesions
- 2. Slightly elevated, plaque-like, yellow-white lesions in choroid
  - a. <sup>1</sup>/<sub>4</sub> to 2 disc diameter sized lesions
  - b. Scattered throughout choroid
  - c. Minimal but variable vitritis
- 3. Cryptococcal meningitis can result in obstructive hydrocephalus and severe papilledema and subsequent optic atrophy
- 4. Fluorescein angiography
  - a. Choroidal lesions are hypofluorescent early and hyperfluorescent in late phases of angiogram

#### E. Describe appropriate testing and evaluation for establishing the diagnosis

- 1. Necessary if disseminated infection is suspected
  - a. Chest radiography
  - b. Arterial blood gas
  - c. Liver function tests
  - d. Abdominal computed tomography

# II. Define the risk factors

- A. Human immunodeficiency virus (HIV) +
- B. CD4+ <50 cells/µl
- C. Patients with disseminated infections or sepsis
  - 1. Disseminated extrapulmonary Mycobacterium tuberculosis
  - 2. Cryptococcal meningitis
  - 3. Pneumocystis sepsis or pneumonitis
  - 4. Disseminated MAI infection

# III. List the differential diagnosis

- A. Toxoplasma retinochoroiditis
- B. Primary central nervous system lymphoma with intraocular involvement
- C. Presumed ocular histoplasmosis syndrome (POHS) healed cases of multifocal choroiditis in AIDS may resemble POHS
- D. Idiopathic multifocal choroiditis

# IV. Describe patient management in terms of treatment and follow-up

A. Organism dependent

#### B. Pneumocystis choroiditis

- 1. 3 weeks IV trimethoprim and sulfamethoxazole or
- 2. 3 weeks IV pentamidine (4mg/kg/day)
- 3. Maintenance with systemic pentamidine, trimethoprim/sulfamethoxazole, or dapsone

#### C. Cryptococcus choroiditis

- 1. IV amphotericin B plus flucytosine for 2 weeks
- 2. Followed by oral fluconazole for 10 weeks and maintenance oral fluconazole
- 3. Maintenance probably indicated even with successful immune reconstitution with highly active anti-retroviral therapy

#### D. Atypical mycobacterial choroiditis may be more stubborn and take longer to respond

- 1. Clarithromycin+ Rifabutin+ Ethambutol induction and maintenance appears the most effective in the treatment of MAI and disseminated atypical mycobacterial infections in AIDS
  - a. Rifabutin induced uveitis can occur as a complication, especially when rifabutin given concurrently with macrolide antibiotic
    - i. Classically unilateral hypopyon iridocyclitis
      - i) Acute onset with redness, pain, photophobia, and decreased vision

- ii) Work-up is usually negative human leukocyte antigen B27 is not present
- ii. Treated with topical corticosteroids and cycloplegics
- iii. Drug dosage may be reduced but rifabutin does not need to be discontinued unless iritis recurs or does not respond completely
- E. With treatment, lesions disappear in 3-12 weeks and leave behind retinal pigment epithelium mottling

# V. Describe appropriate patient instructions

- A. If CD4+<100 cells/µl, importance of routine every 6 month follow-up even if no visual symptoms
- B. Sepsis or systemic dissemination of pneumocystis, cryptococcus, and MAI requires more frequent and detailed ophthalmologic evaluation

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, HIV/AIDS and the Eye: A Global Perspective, 2002.
- 3. Thorne JE, Jabs DA, Kempen JH, et al. Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 2006;113:1441-5.
- 4. Thorne JE, Jabs DA, Kempen JH, et al. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 2006;113:1432-1440.
- 5. Goldberg DE, Smithen LM, Angelilli A, Freeman WR. HIV-associated retinopathy in the HAART era. Retina 2005;25:633-49.
- 6. AAO, Focal Points: Infectious Posterior Uveitis, Module #3, 2005.
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- 8. Sugar EA, Jabs DA, Ahuja A, Thorne JE, Danis RP, Meinert CL for the Studies of the Ocular Complications of AIDS (SOCA) Research Group. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* 2012 Epub ahead of press.
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- 10. Freeman WR, Van Natta ML, Jabs D, et al; SOCA Research Group. Vision function in HIV-infected individuals without retinitis: report of the Studies of Ocular Complications of AIDS Research Group. Am J Ophthalmol. 2008 Mar;145(3):453-462.

# Treatment guidelines for non-infectious ocular inflammatory disease

# I. List the indications/contraindications

# A. Indications

- 1. Noninfectious ocular inflammatory disease
- 2. Other diseases in which an inflammatory component exists, if therapy directed against the primary etiology is also used (e.g., infectious disease)

# II. Paradigm

# A. Goal of therapy

1. Control of the inflammation so as to eliminate (or reduce as much as possible if other considerations limit therapeutic options) the risk to vision that may occur from the structural and functional complications resulting from unchecked inflammation

# B. Choice of agent

 The agent(s) and route(s) of administration chosen should be based on a careful consideration of all factors of pertinence, including the specific diagnosis; concurrent ocular or systemic disease (both those related to the ocular inflammatory disease and those that affect the choice of therapeutic agent); existing level of ocular function compromise already present; and patient desires

# C. Initial therapy

- 1. The initial goal of therapy should be to achieve control of inflammation as rapidly as possible
- 2. Corticosteroids are generally the most effective agent at achieving this goal and may be administered topically, regionally, and systemically (See Corticosteroids)
  - a. The Multicenter Uveitis Steroid Treatment Trial (MUST), a randomized, controlled, superiority trial, comparing systemic anti-inflammatory therapy, versus fluocinolone acetonide implant for intermediate, posterior and panuveitis was conducted and recently published the following results:
    - i. In each treatment group, mean visual acuity improved over 24 months, with neither approach superior, to a degree detectable with the study's power
    - ii. The specific advantages and disadvantages identified based on individual patients' particular circumstances, should dictate selection between these two alternatives
    - iii. Systemic therapy with aggressive use of corticosteroid-sparing immunosuppression, was well tolerated
  - b. For certain conditions such as mild scleritis, non-steroidal anti-inflammatory agents may be used instead of corticosteroids (See Nonsteroidal anti-inflammatory drugs)
- 3. Certain conditions may be considered indications for the early initiation of immunosuppression

#### therapy

- a. Strongly consider *early initiation* in
  - i. Behçet with posterior segment, vision threatening involvement (See Behçet disease)
  - ii. Sympathetic ophthalmia (See Sympathetic ophthalmia)
  - iii. Necrotizing scleritis with systemic association (See Scleritis associated with systemic autoimmune diseases)
  - iv. Serpiginous choroidopathy with vision threatening involvement (See Serpiginous choroidopathy)
- b. Some consider early initiation for other conditions such as:
  - i. Birdshot chorioretinopathy (See Birdshot retinochoroidopathy)
  - ii. Juvenile Idiopathic Arthritis Associated chronic uveitis, steroid-dependent
  - iii. Multifocal Choroiditis with Panuveitis
  - iv. Vogt Koyanagi Harada Disease
- 4. Tapering of initial therapy
  - a. If control of inflammation is achieved with initial therapy and disease is considered to be of acute or limited duration, then an appropriate taper of the initial agent(s) is warranted
  - b. If disease activity recurs with taper, then the dose of corticosteroid at which the flare occurred determines whether long-term corticosteroid therapy (baseline DEXA scan and bone preservation measures implemented) or second line therapy is used (See Corticosteroids).
- 5. If control is not achieved with initial therapy, then transition to second line therapy

# D. Second line therapy

- In chronic disease not controlled at a safe dose of corticosteroid (actually, there is no chronic dose of systemic corticosteroid considered by bone specialists to be safe for chronic use ) ); acute or limited duration disease in which initial corticosteroid therapy failed to achieve control; or in individuals unable to tolerate doses of initial therapy needed to achieve control, transition to second line therapy
- Multiple drug classes and agents within each drug class are available. Quality data from randomized controlled trials of specific agents in specific ocular inflammatory diseases is generally lacking to guide the choice of agent
  - a. Selection of agent is thus based on a consideration of an individual patient's comorbidities
- 3. Drug Classes (as new agents are continually being developed and released, this list may be incomplete)
  - a. Antimetabolites
    - i. Methotrexate (See Methotrexate)
    - ii. Azathioprine (See Azathioprine)
    - iii. Mycophenolate mofetil or mycophenolic acid (See Mycophenolate)

- b. Calcineurin inhibitors
  - i. Cyclosporine (See Cyclosporine)
  - ii. Tacrolimus
- c. Alkylating agents (See Cyclophosphamide and chlorambucil)
  - i. Cyclophosphamide
  - ii. Chlorambucil
- d. Biological response modifiers (See Biologic response modifiers)
  - i. Infliximab
  - ii. Adalimumab
  - iii. Etanercept
  - iv. Rituximab
  - v. Intravenous Immunoglobulin

#### E. Beyond second line therapy

- 1. If use of initial and second line therapy are ineffective in controlling inflammation, the literature becomes very sparse regarding efficacy data on combinations or newer agents. Considerations of the individual needs for each patient should guide choices
- 2. Options may include
  - a. Medical
    - i. Combination IMT multiple drugs from more than one class of drugs
  - b. Surgical therapy in specific uveitic entities (i.e. therapeutic PPV in pars planitis) (See Intermediate uveitis, including pars planitis)

# **III.** Special Considerations

A. Pregnancy testing: As part of the systemic work-up, prior to initiating systemic immunosuppressive therapy, a pregnancy test should be done

#### B. Vaccine recommendations

1. Patients receiving anti-TNF therapy should not have live vaccines, including, but not limited to varicella zoster, oral polio, or rabies vaccination, and the influenza vaccine made with a live virus

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.9-11.
- 3. AAO, Focal Points: Medical Therapy of Uveitis, Module #8, 1989, p.2-5.

4. Kempen, JH et al:Randomized Comparison of Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Implant for Intermediate, Posterior, and Panuveitis Steroid Treatment Trial. Ophthalmology 2011; 118:1916-1926.

# Cycloplegics

# I. List the indications/contraindications

# A. Indications

- 1. Anterior chamber involvement in uveitis
  - a. To prevent formation of new posterior synechiae with either continual or intermittent dilation
  - b. To decrease photophobia and pain due to ciliary and sphincter muscle spasm
  - c. To break recently formed posterior synechiae

#### B. Contraindications

1. Allergy or sensitivity to agent or to others in its class

# II. Describe the pre-procedure/therapy evaluation

- A. Comprehensive eye examination
- B. Question for history of allergy or adverse reaction
- C. Check angle depth because of possibility of inducing narrow-angle glaucoma

# III. List the alternatives to this procedure/therapy

A. To not use the therapy (mainly in cases of allergy or exceptionally mild anterior segment inflammation)

# IV. Describe the dosage (agents listed in decreasing order of duration of effect)

# A. The dosages are adjusted according to desired duration

- 1. Atropine 1% one to 4 times daily. The higher dose should be used with caution in young children
- 2. Scopolamine 0.25% one to four times daily
- 3. Homatropine 2% or 5% one to four times daily
- 4. Cyclopentolate 1% one to four times daily
- 5. Tropicamide 0.5% to 1% for prophylactic nightly dilation when the other agents produce prolonged daytime dilation
- B. Alpha-adrenergic agents provide greater dilation but are not ordinarily used
- C. Most effective use to prevent new synechiae requires monitoring of pupil size and shape by the patient

# V. List the complications of the procedure/therapy, their prevention and management
### A. Psychosis, acute psychotic reaction

- 1. Limit dosage to no more than recommended frequency
- 2. Most case reports in pediatric age group, but has been reported with adults
- 3. Treat with supportive care

# B. Tachycardia

- C. Fever
- D. Urinary retention
- E. Cycloplegia/blurred vision
  - 1. Can be minimized by use of a short acting cycloplegic with bedtime regimen (not indicated if patient is at highest risk for synechiae)
  - 2. Temporary use of reading eyeglasses (or temporary use of stronger reading eyeglasses)
- F. Posterior synechiae formation in the dilated position can be minimized by prescribing strong cycloplegics only with adequate anti-inflammatory treatment

# VI. Describe the follow-up care

- A. Routine monitoring of the extent of posterior synechiae and anterior inflammation
- B. Drawings or photos of pupil shape helpful

# VII. Describe appropriate patient instructions

- A. Inform the physician of any new symptoms while on the medication
- B. Use only as prescribed, not more frequently
- C. Explain to patient rationale for use, including need to keep pupil moving to prevent synechiae
- D. Recommend protection from bright light
- E. Counsel use of reading eyeglasses for near work (with bilateral use)

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002, p.11.

# Nonsteroidal anti-inflammatory drugs

# I. Pharmacology

# A. Mechanism of action

- 1. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), the enzyme which converts arachidonic acid to prostaglandin derivatives which mediate inflammation
- 2. There are two isoforms of cyclooxygenase, COX-1 and COX-2, both of which may be inhibited or selectively targeted (COX-2) by NSAIDs
  - a. COX-1 is responsible for maintenance of normal renal function, gastric mucosal integrity, and hemostasis. This isoform is constitutively expressed, and appears to be critical for housekeeping actions in the GI mucosa
  - b. COX-2 appears to be expressed in most tissues in response to growth factors and cytokines, under pathological conditions such as inflammation. Specific inhibitors should therefore have less risk of adverse events such as gastric ulceration and renal toxicity
  - c. However, all NSAIDS are now known to be associated with an increased risk of cardiovascular adverse events related to selective effects on the clotting system
    - i. Therefore, use of these agents for ophthalmic indications should be carefully considered in the context of a patient's comorbidities

# II. List the indications/contraindications

# A. Indications

- 1. Noninfectious ocular inflammatory disease, especially scleritis/episcleritis
  - a. Topical NSAIDs may be of benefit in episcleritis only
- 2. Maybe useful as a steroid -sparing adjunct during tapering of topical corticosteroids in selected cases of JIA/JRA and HLA-B27-associated iridocyclitis
- 3. Cystoid macular edema (CME)
  - a. Topical NSAIDs
- 4. Analgesia

# B. Contraindications

- 1. Renal insufficiency or other kidney disease
- 2. Allergy or sensitivity to agent or others in its class
- 3. Peptic ulcer disease
- 4. Bleeding diathesis
- 5. Use of COX- inhibitors with an established history or risk factors for cardiovascular or thrombotic disease

# III. Describe the pre-procedure/therapy evaluation

- A. Renal function panel
- B. Complete blood count
- C. Blood pressure
- D. Liver enzymes

# IV. List the alternative to this procedure/therapy

### A. For anti-inflammatory effect

- 1. Corticosteroids
- 2. Other immunosuppressives

# B. For analgesic effect

- 1. Opioid analgesics
- 2. Acetaminophen

# V. Describe the routes of administration

- A. Oral
- B. Topical

# VI. Agents available for use in USA

- A. Oral
  - 1. Non-selective COX inhibitors
    - a. Fenamate derivatives: Meclofenamate (Meclomen®), mefenamic acid (Ponstel®)
    - b. Indoleacetic acid derivative: Indomethacin (Indocin®)
    - c. Naphthylalkanone derivative: Nabumetone(Relafen®)
    - d. Oxicam derivative: Meloxicam (Mobic®), piroxicam (Feldene®), tenoxicam (Tilcotil®)
    - e. Phenylacetic acid derivative: Diclofenac (Voltaren®, Cataflam®)
    - f. Propionic acid derivatives: Fenoprofen (Nalfon®), flurbiprofen (Ocufen®), ibuprofen, ketoprofen, naproxen (Aleve®, Naprosyn®, Anaprox®), oxaprozin (Daypro®), tiaprofenic acid
    - g. Pyranoindoleacetic acid: Etodolac (Lodine®)
    - h. Pyrazole derivative: Phenylbutazone (Butazolidine®)
    - i. Pyrroleacetic acid derivatives: Sulindac, (Clinoril®) tolmetin (Tolectin®)

- j. Salicylic acid derivative: Diflunisal (Dolobid®)
- 2. COX-2 selective inhibitors
  - a. Celecoxib (Celebrex®)
- B. Topical (topical NSAIDs are of no value in uveitis or scleritis, but may be useful in episcleritis and CME)
  - 1. Ketorolac tromethamine (Acular®)
  - 2. Diclofenac sodium (Voltaren®)
  - 3. Flurbiprofen sodium (Ocufen®)
  - 4. Nepafenac (Nevanac®)
  - 5. Bromfenac (Xibrom®)

# VII. List the complications of the procedure/therapy, their prevention and management

- A. Oral
  - 1. Renal insufficiency
    - a. Management: dosage reduction or discontinuation
  - 2. Gastritis/peptic ulcer
    - a. Management: concurrent H2 blocker or proton pump inhibitor or misoprostol use
  - 3. Nausea
    - a. Management: take with food
  - 4. Decreased clotting ability (for non-specific COX inhibitors)
  - 5. Abnormal liver enzymes
- B. Topical
  - 1. Corneal epithelial breakdown, thinning, erosion, ulceration, perforation
    - a. Do not exceed recommended frequency of use
  - 2. Ocular wound healing delay
  - 3. Ocular bleeding
  - 4. Conjunctival hyperemia

# VIII. Describe the follow-up care

- A. Routine monitoring or blood work, response to therapy
  - 1. Hematocrit, creatinine, liver enzymes: periodic testing is recommended, based on the patient's clinical profile

# IX. Describe appropriate patient instructions

- A. Inform the physician of any new symptoms while on the medication
  - 1. Bleeding
  - 2. Increased bruising
  - 3. Changes in stool
  - 4. Changes in urination
- B. Take with food
- C. Do not use aspirin containing products or potentially nephrotoxic medications (Cyclosporine) concurrently
- D. Concomittant use of sytemic corticosteroids and NSAIDs significantly increases risk of peptic ulceration

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Scleritis and Episcleritis: Diagnosis and Management, Module 4, 2009.
- 3. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int. 2012 June; 32(6): 1491-1502.
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# Corticosteroids

# I. List the indications/contraindications

# A. Indications

- 1. Noninfectious ocular inflammatory disease
- 2. Acute endophthalmitis (as an adjunctive therapy)
- 3. Acute retinal necrosis (as an adjunctive therapy)
- 4. Other diseases in which an inflammatory component exists, if therapy directed against the primary etiology is also used (e.g., infectious disease)

# B. Contraindications

- 1. Infectious etiology, unless covered by appropriate antibiotics, e.g., toxoplasmosis, bacterial endophthalmitis
- 2. Poorly controlled or difficult to control diabetes
- 3. Peptic ulcer or erosive gastritis
- 4. A relative contraindication is a history of corticosteroid-induced intraocular pressure (IOP) elevation

# II. List the alternatives to this procedure/therapy for systemic use

A. The initial goal of therapy should be to achieve control of inflammation as rapidly as possible. Corticosteroids are generally the most effective agent at achieving this goal and may be administered topically, regionally, or systemically. (See Treatment guidelines for non-infectious ocular inflammatory disease)

# III. Describe the instrumentation and technique

# A. Describe the routes of administration

- 1. Oral
- 2. IV
- 3. Intramuscular
- 4. Regional (this usually refers to intravitreal and periocular)
- 5. Intravitreal
- 6. Topical/periocular

# B. Agents commonly used in the United States

- 1. Oral
  - a. Prednisone 1 mg/kg

- b. Prednisolone 1 mg/k/g
- c. Dexamethasone 0.2 mg/kg
- 2. Intravenous
  - a. Methylprednisolone 1 gm/day, typically for 3 days total
  - b. Dexamethasone 200 mg/day x 3 days
- 3. Regional (depot formulations, unless otherwise noted)
  - a. Sub-Tenons, retroseptal/orbital floor, subconjunctival
    - i. Triamcinolone acetonide 40 mg/ml, up to 1ml
    - ii. Triamcinolone diacetate 40 mg/ml, up to 1ml
    - iii. Methylprednisolone acetate 40 mg/ml or 80 mg/ml, up to 1 ml
    - iv. Betamethasone sodium phosphate/betamethasone acetate, 6 mg/ml, up to 1 ml (combination depot and immediate action formulation (must be given with lidocaine roughly 1:10)
    - v. Dexamethasone phosphate 4mg/ml (must be given with lidocaine roughly 1:10)
- 4. Intravitreal
  - a. Triamcinolone acetonide 40 mg/ml, 4 mg in 0.1 ml
  - b. (Preservative-free trimacinolone is approved formulation). This lasts at least 3 months, and less vitrectomized eyes.
  - c. Fluocinolone acetonide 0.59 mg intravitreal implant (elutes corticosteroid medication into the eye for up to 3 years). It requires a surgery for implantation, and is secured with partial thickness scleral sutures
  - d. Dexamethasone 0.7 mg injectable corticosteroid implant with extended drug release, it is a continuous release for 35 days, then it biodegrades
- 5. Topical (for all, dose varies by severity of disease) (no maximum except that limited by practical ability of patient to administer)
  - a. Prednisolone acetate 1%, 1/8%
  - b. Prednisolone sodium succinate 1%
  - c. Dexamethasone 0.1%
  - d. Rimexolone 1%
  - e. Loteprednol etabonate 0.5%
  - f. Fluorometholone acetate 0.1% or 0.25%
  - g. Difluprednate 0.05%

# IV. List the complications of the therapy, their prevention and management

#### A. For all forms

- 1. Posterior subcapsular cataracts (not reversible)
- 2. Increased intraocular pressure (IOP) (often reversible)

#### B. Systemic use

- 1. Note that there is some overlap between short and long term side effects
- 2. Short term
  - a. Weight gain
  - b. Mood effects, sleep disturbance and psychosis
  - c. Acute hyperglycemia
  - d. Manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in persons with diabetes
  - e. Exacerbation of hypertension, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, and hypertension
  - f. Aseptic necrosis of femoral and humeral heads (Dosages over 60mg/day associated with greater risk of aseptic necrosis of the femoral head)
  - g. Menstrual irregularities
  - h. Urticaria and other allergic, anaphylactic or hypersensitivity reactions
  - i. Infection, reduced symptoms from infection
  - j. Increased intracranial pressure with papilledema (pseudo-tumor cerebri), convulsions, vertigo, headache, insomnia, emotional disturbances
- 3. Long term
  - a. Osteoporosis, osteopenia (this begins by 3 months of steroid therapy)
  - b. Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, striae and may suppress reactions to intradermal skin tests (e.g., purified protein derivative test for tuberculosis infection)
  - c. Pancreatitis; abdominal distention; ulcerative esophagitis; increases in alanine transaminase, aspartate transaminase and alkaline phosphatase have been observed following corticosteroid treatment ("fatty liver")
    - i. In most cases, side effects are minor, not associated with any clinical syndrome and are reversible upon discontinuation
    - ii. Peptic ulcer with possible perforation and hemorrhage (risk appears to be associated primarily with concurrent use of non-steroidal anti-inflammatory drugs)
  - d. Reactivation of latent tuberculosis
  - e. Pathologic fracture of long bones, muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures

f. Fat redistribution, adrenal suppression, accelerated atherosclerosis, development of Cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth of children; decreased carbohydrate tolerance

### C. Intravitreal use

- 1. Endophthalmitis
- 2. Sterile, toxic-type reaction
- 3. Infectious
- 4. Vitreous hemorrhage
- 5. Retinal detachment

#### D. Topical use

- 1. Worsening of external infectious disease
- 2. Increased incidence and frequency of spontaneous subconjunctival hemorrhages

#### E. Regional use

- 1. Unintended injection into the choroidal or retinal circulation or emboli
- 2. Perforation of the globe with permanent loss of vision
- 3. Ptosis (more common with superior injections)
- 4. Proptosis
- 5. Orbital fat atrophy, fibrosis
- 6. Orbital fat prolapse (with inferior retroseptal injections)
- 7. Delayed hypersensitivity reactions
- 8. Subconjunctival hemorrhage
- 9. Chemosis
- 10. Infection
- 11. Pain from injection, syncope, scarring, Cushing Syndrome, pupillary dilatation

#### F. Intravitreal corticosteroid implants

- 1. Surgical complications
  - a. Approximately 100% of phakic patients will need cataract surgery at 2 years (sustained release implants)
  - b. Approximately 40% will need surgical intervention for glaucoma at 2 years, approximately 50% will need topical medication for glaucoma at 3 years (sustained release implants)
  - c. Vitreous opacities
  - d. Vitreous hemorrhage
  - e. Macular edema

- f. Retinal hemorrhage
- g. Hypotony
- h. Choroidal detachment
- i. Retinal detachment
- j. Sterile endophthalmitis
- k. Lens penetration
- 2. Rare complications
  - a. Late spontaneous dissociation of the implant from the anchoring strut
  - b. Conjunctival erosion of anchor suture with a high risk for endophthalmitis
- 3. Perioperative management
  - a. Maintenance of optimal immunomodulatory therapies preoperatively
  - b. Begin tapering concomitant immunomodulatory therapy when clinically optimal post-operatively
  - c. Monitor carefully for intraocular pressure rise and treat aggressively with MMT; engage glaucoma specialist early to manage and intervene surgically when appropriate to prevent irreversible optic nerve damage
  - d. Monitor cataract progression and intervene surgically when inflammatory status is stable and cataract is visually significant

# V. Describe the follow-up care

### A. Systemic use

- 1. Routine monitoring of blood pressure, weight, and response to therapy may vary, but generally every 4 to 6 weeks
- 2. Long-term use should be avoided
- 3. If long term therapy cannot be avoided, monitor bone mineral density initially, then approximately yearly, as well as cholesterol and lipids, and embark upon bone preservation strategies
- B. Topical, regional, intravitreal use
  - 1. Monitor IOP and cataract status

# VI. Describe appropriate patient instructions

- A. All patients should have blood sugar and blood pressure monitored, in conjunction with their primary care physician
- B. Use supplemental calcium and vitamin D to decrease the risk of osteopenia
- C. Maintain physical activity and optimal body weight

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Diagnosis and Management of Anterior Uveitis, Module #1, 2002.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel. Am J Ophthalmol 2000;130:492-513.
- 4. AAO, Focal Points: Steroid Therapy for Ocular Inflammatory Disease, Module #7, 2006.

# Methotrexate

# I. Pharmacology

# A. Mechanism of action

- 1. Methotrexate is an inhibitor of dihydrofolate reductase, an enzyme necessary in the metabolism of folic acid to folate cofactors, which are required in reactions including DNA replication and RNA transcription
- 2. Methotrexate thus reduces the growth of rapidly dividing cells
- 3. Increasing the rate of T-cell apoptosis
- 4. Increasing endogenous adenosine concentration
- 5. Altering cytokine production and humoral response

### B. Pharmacokinetics

- 1. Methotrexate absorption following oral administration varies greatly
- 2. In addition, methotrexate undergoes first pass metabolism in the liver, reducing bioavailability
- 3. Parenteral administration, particularly subcutaneous injection, is associated with greater bioavailability and reduced gastrointestinal side effects
- 4. The onset of action is slow, usually requiring 6 to 8 weeks to become effective and up to 3 to 4 months for full effect

# II. List the indications/contraindications

# A. Some uveitis specialists do not manage the administration of these agents themselves, but coordinate care of the patient with an internist/rheumatologist

### B. Indications

- 1. Noninfectious intraocular and scleral inflammatory disease
  - a. Nonresponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids
  - b. Incomplete response to other corticosteroid-sparing agents
- 2. Primary central nervous system- intraocular lymphoma
  - a. Treatment paradigm is complex but main point are:
    - i. High dose systemic therapy
    - ii. Intrathecal therapy
    - iii. Intravitreal therapy (especially in primary intraocular lymphoma)

### C. Contraindications

1. Infectious etiology

- 2. Liver disease
- 3. Renal insufficiency or other kidney disease (dosage adjustment required)
- 4. Allergy or sensitivity to agent or others in its class
- 5. Pregnancy (includes males impregnating others)
- 6. Breast feeding
- 7. Pulmonary disease
- 8. Hematologic abnormalities (relative contraindication)

# III. Describe the pre-procedure/therapy evaluation

- A. Renal function panel
- B. Complete blood count (CBC)
- C. Liver function tests
- D. Some clinicians perform hepatitis panel
- E. Chest x-ray

# IV. List the alternatives to this procedure/therapy

- A. Corticosteroids
- B. Calcineurin inhibitors
  - 1. Cyclosporine
  - 2. Tacrolimus
  - 3. Sirolimus
- C. Other antimetabolites
  - 1. Azathioprine
  - 2. Mycophenolate mofetil
- D. Alkylating agents
  - 1. Cyclophosphamide
  - 2. Chlorambucil
- E. Biologic agents approved for specific rheumatic diseases
  - 1. Anti-tumor necrosis factor alpha therapy
    - a. Etanercept (Enbrel®)
    - b. Infliximab (Remicade®)
    - c. Adalimumab (Humira®)
  - 2. Anti-CD-20 antibody Rituximab (Rituxan®)

# V. Describe the dosage

### A. For noninfectious intraocular inflammatory disease and scleritis

- 1. A typical initial dose is 7.5-15 mg/week
- 2. Maximum dosage varies per clinician and clinical response, but is typically in the range of 15 mg to 25 mg/week. (higher doses may be used cautiously)
- 3. Pediatric dosing 5-15 mg/m2
- 4. May be administered orally, intramuscularly or subcutaneously. Because of variable intestinal absorption mucosal irritation related side effects, parenteral administration may increase bioavailability and reduce gastro-intestinal side effects

# B. For primary central nervous system- intraocular lymphoma

- 1. High-dose systemic methotrexate alone or in combination with other chemotherapeutic agents
- 2. Intrathecal methotrexate via Omaya reservoir
- 3. Intravitreal methotrexate (400µg/0.1ml) with or without systemic treatment

# VI. List the complications of the procedure/therapy, their prevention and management

### A. Complications

- 1. Leukopenia
- 2. Elevation of liver enzymes
- 3. Pulmonary fibrosis
- 4. Headache
- 5. Nausea
- 6. Oral ulcers/stomatitis
- 7. Alopecia
- 8. Fatigue
- 9. Hypereosinophilia
- 10. Teratogenicity

#### B. Prevention

- Use of folic acid 1 mg/day usually decreases severity of side effects. May use higher doses (e.g., 2 mg/day)
- 2. Alcohol abstainence to obviate additive hepatotoxicity
- 3. Avoidance of other medications which affect liver
- 4. Appropriate contraception for women of childbearing age for at least 3 months after discontinuing the medication

5. Potential for sperm mutation: 4 months off drug for males prior to attempting conception

# VII. Describe the follow-up care

### A. Routine monitoring of

- 1. CBC
- 2. Liver function tests (LFT's: aspartate transaminase, alanine transaminase, total bilirubin)
- 3. Renal function

# B. Response to therapy may vary, but generally labs obtained every 4 to 8 weeks, more frequently with initiation of medication or with dosage changes

1. For stable dosage, monitoring every 8 weeks is now fairly standard based on reasonable data monitoring for cirrhosis

#### C. Reduce dose

1. LFT's > 2X upper limit normal on 2 separate occasions

### D. Interrupt therapy

- 1. WBC < 2500 cells/µl
- 2. Platelets < 75,000 cells/µl
- 3. LFT's > 5X upper limit normal

# VIII. Describe appropriate patient instructions

- A. Inform the ophthalmologist of any new symptoms while on the medication, including, but not limited to, the following
  - 1. Fever, chills, sore throat
  - 2. Cough
  - 3. Dark urine
  - 4. Black tarry stools
  - 5. Unusual bleeding
  - 6. Unusual tiredness or weakness
  - 7. Shortness of breath
  - 8. Yellowing of the skin or eyes
  - 9. Stomach or abdominal pain
  - 10. Muscle or joint pain

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Management of Chronic Uveitis, Module #11, 2007
- 3. Samson CM, Waheed N, Baltztzis S, et al. Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. Ophthalmology. 2001 Jun;108(6):1134-9.
- 4. Dev S, McCallum RM, Jaffe GJ. Methotrexate treatment for sarcoid-associated panuveitis. Ophthalmology. 1999 Jan;106(1):111-8.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel Am J Ophthalmol 2000;130:492-513.
- 6. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology 2008; 115: 1826-32.
- 7. Kemen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosupressive agents for ocular inflammtion : a critical assessment of the evidence. Am J Ophthalmol 2008; 146: 802-12.
- Gangaputra S et al. Methotrexate for Ocular Inflammatory Diseases. Ophthalmology 2009; 116:2188-2198.
- 9. Wessels JA, Huizinga TW, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2008;47: 249-55.
- 10. Chan ES, Cronstein BN. Methotrexate-how does it really work. Nat Rev Rheumatol. 2010 Mar;6(3):175-8.

# Azathioprine

# I. Pharmacology

# A. Mechanism of action

1. Azathioprine is a purine analog and prodrug, which is converted to 6-mercaptopurine, a competitive inibitor of pruine synthesis, that produces an immunosuppressive effect by inhibiting DNA and RNA synthesis in actively dividing cells, including lymphocytes

### B. Pharmacokinetics

- 1. Well absorbed orally
- 2. Crosses the placenta
- 3. Hepatically metabolized; then renally excreted
- 4. It may take several months to become maximally active

# II. List the indications/contraindications

# A. Some uveitis specialists do not manage the administration of these agents themselves, but coordinate care of the patient with an internist/rheumatologist

### B. Indications

- 1. Noninfectious intraocular inflammatory and scleral disease
  - a. Nonresponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids
  - b. Incomplete response to other corticosteroid-sparing agents
  - c. May be useful in intermediate uveitis; the Systemic Immunosuppressive Therapy for Eye Disease Cohort Study, indicated comparatively good results, for patients with mucous membrane pemphigoid (Pasadhika S et al)

# C. Contraindications

- 1. Infectious etiology
- 2. Hematologic disorders
- 3. Liver disease
- 4. Renal insufficiency or other kidney disease (dosage adjustment required)
- 5. Allergy or sensitivity to agent or others in its class
- 6. Pregnancy (includes males impregnating others)
- 7. Breast feeding
- 8. Homozygous thiopurine methyltransferase (TPMT) deficiency

# III. Describe the pre-procedure/therapy evaluation

- A. Renal function panel
- B. Complete blood count (CBC)
- C. Liver function tests
- D. Some clinicians perform hepatitis panel
- E. Chest x-ray
- F. Pretreatment testing for inherited thiopurine methyltransferase (TPMT) deficiency
  - 1. 89% wild type
  - 2. 11% heterozygous
  - 3. 0.3% homozygous

# IV. List the alternatives to this procedure/therapy

### A. Corticosteroids

- 1. Systemic administration
- 2. Local adminstration to the eye

### B. Calcineurin inhibitors

- 1. Cyclosporine
- 2. Tacrolimus
- 3. Sirolimus

### C. Other antimetabolites

- 1. Methotrexate
- 2. Mycophenolate mofetil

### D. Alkylating agents

- 1. Cyclophosphamide
- 2. Chlorambucil

### E. Biologic agents approved for specific rheumatic diseases

- 1. Anti-tumor necrosis factor alpha therapy
  - a. Etanercept (Enbrel®)
  - b. Infliximab (Remicade®)
  - c. Adalimumab (Humira®)

# V. Describe the dosage

A. 1 - 3.0 mg/kg/day (100-200 mg/day typical dose)

### B. Reduced dose

- 1. Heterozygous TPMT deficiency
- 2. Concomittant allopurinol

# VI. List the complications of the procedure/therapy, their prevention and management

- A. Leukopenia
  - 1. Potentially rapid bone marrow suppression if homozygous TPMT mutation
- B. Elevation of liver enzymes
- C. Possible increased long-term risk of malignancy (lymphoma, leukemia)
- D. Nausea
- E. Fatigue
- F. Teratogenicity: appropriate contraception for women of childbearing age

# VII. Describe the follow-up care

- A. Routine monitoring of CBC, liver function tests,renal function, response to therapy may vary, but generally every 4 to 6 weeks
- B. Decrease dose
  - 1. LFT's  $\geq$  3x upper limit of normal
- C. Interrupt therapy
  - 1. WBC  $\leq$  2,500 cells/mm3
  - 2. Platelet ≤ 75,000 cells/mm3
  - 3. LFT's  $\geq$  5x upper limit of normal

# **VIII.** Describe appropriate patient instructions

- A. Inform the ophthalmologist of any new symptoms while on the medication, including, but not limited to, the following
  - 1. Fever, chills, sore throat
  - 2. Dark urine
  - 3. Black tarry stools
  - 4. Unusual bleeding
  - 5. Unusual tiredness or weakness
  - 6. Yellowing of the skin or eyes
  - 7. Stomach or abdominal pain

8. Muscle or joint pain

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel Am J Ophthalmol 2000;130:492-513.
- 3. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology 2008; 115: 1826-32.
- 4. Kempen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosupressive agents for ocular inflammtion : a critical assessment of the evidence. Am J Ophthalmol 2008; 146: 802-12.
- 5. Fargher EA, Tricker K, Newman W, et al. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. J Clin Pharm Ther 2007;32:187-95.
- 6. Pasadhika S et al. Azathioprine for Ocular Inflammmatory Diseases. Am J Ophthalmol 2009; 148:500-509.

# Mycophenolate

# I. Pharmacology

# A. Mechanism of action

- 1. Mycophenolate mofetil, a prodrug of mycophenolic acid, is a selective inhibitor of de novo lymphocyte purine synthesis by reversibly and noncompetitively binding the enzyme inosine monophosphate dehydrogenase
- 2. The enzyme is predominantly active in T and B lymphocytes which are dependent on de novo purine synthesis accounting for the selectivity of the drug compared to azathioprine, which also inhibits purine synthesis
- 3. In addition, mycophenolate suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium, and decreases recruitment of leukocytes

### B. Pharmacokinetics

1. Well absorbed orally

# II. List the indications/contraindications

A. Some uveitis specialists would not manage the administration of these agents themselves but would coordinate care of the patient with an internist/rheumatologist

### B. Indications

- 1. Noninfectious intraocular and scleral inflammatory disease
  - a. Nonresponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids
  - b. Incomplete response to other corticosteroid-sparing agents

### C. Contraindications

- 1. Infectious etiology
- 2. Hematologic disorders
- 3. Liver disease
- 4. Renal insufficiency or other kidney disease (dosage adjustment required)
- 5. Allergy or sensitivity to agent or others in its class
- 6. Pregnancy (includes males impregnating others)
- 7. Breast feeding

# III. Describe the pre-procedure/therapy evaluation

### A. Renal function panel

### Uveitis

- B. Complete blood count (CBC)
- C. Liver function tests
- D. Some clinicians perform hepatitis panel
- E. Chest x-ray

# IV. List the alternatives to this procedure/therapy

- A. Corticosteroids
- B. Mycophenolic acid (Myfortis®) can be used in place of mycophenolate mofetil with a different dosing but a similar pharmacologic effect
- C. Calcineurin inhibitors
  - 1. Cyclosporine
  - 2. Tacrolimus
  - 3. Sirolimus

### D. Other antimetabolites

- 1. Methotrexate
- 2. Azathioprine

### E. Alkylating agents

- 1. Cyclophosphamide
- 2. Chlorambucil
- F. Biological agents approved for specific rheumatic diseases
  - 1. Anti-tumor necrosis factor alpha therapy
    - a. Etanercept (Enbrel®)
    - b. Infliximab (Remicade®)
    - c. Adalimumab (Humira®)

# V. Describe the dosage

- A. Initially 1 g twice a day (some clinicians begin with 500 mg twice daily and if tolerated, increase to 1 g twice daily)
- B. With failure to control disease and if medication well tolerated, may increase dose to 1500 mg twice daily (3 g daily total dose)

# VI. List the complications of the procedure/therapy, their prevention and management

- A. Gastrointestinal (GI) disturbance
- B. Leukopenia, pure red cell aplasia (PRCA)

- C. Possible increased long-term risk of malignancy (lymphoma, leukemia)
- D. Progressive multifocal leukoencephalopathy
- E. Nausea
- F. Fatigue
- G. Miscarriage
- H. Teratogenicity: appropriate contraception for women of childbearing age

# VII. Describe the follow-up care

- A. CBC assessment monthly to every two months
- B. Many clinicians perform liver function tests every three months during therapy as well

#### C. Reduce dose

- 1. LFT's > 2-3X upper limit of normal
- 2. Mild decrease platelet count

#### D. Interrupt therapy

- 1. WBC < 2500 cells/µl
- 2. Platelets < 75,000 cells/µl
- 3. LFT's > 5X upper limit normal

# VIII. Describe appropriate patient instructions

- A. Inform the physician of any new symptoms while on the medication, especially fever including, but not limited to, the following
  - 1. Fever, chills, sore throat
  - 2. Dark urine
  - 3. Black tarry stools
  - 4. Unusual bleeding
  - 5. Unusual tiredness or weakness
  - 6. Yellowing of the skin or eyes
  - 7. Stomach or abdominal pain
  - 8. Muscle or joint pain

#### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Management of Chronic Uveitis, Module#11, 2007.

- 3. Thorne JE, Jabs DA, Qazi FA. Mycophenolate Mofetil Therapy for Inflammatory Eye Disease. Ophthalmology 2005; 112:1472-1477.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel. Am J Ophthalmol 2000;130:492-513.
- 5. Teoh SC, Hogan AC, Dick AD ,et al. Mycophenolate mofetil for the treatment of uveitis. Am J Ophthalmol 2008; 146; 752-60.
- 6. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology 2008; 115: 1826-32.
- 7. Kemen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosupressive agents for ocular inflammtion : a critical assessment of the evidence. Am J Ophthalmol 2008; 146: 802-12.
- 8. Daniel E et al. Mycophenolate Mofetil for Ocular Inflammation. Am J Ophthalmol. 2010; 149(#): 423-432.

# Cyclophosphamide and chlorambucil

# I. Pharmacology

# A. Mechanism of action: alkylating agents

- 1. Cyclophosphamide
  - a. Following oral administration, it is metabolized in the liver to phosphoramide mustard and acrolein
  - b. Phosphoramide mustard inhibit T and B-cell proliferation by producing cross-linkage in DNA between guanine and thymidine with aberrant base pairing, DNA strand breakage and interruption of transcription
  - c. This results in cytotoxicity to both resting and dividing lymphocytes with suppression of both cellular and humoral immune responses
  - d. Acrolein is responsible for bladder toxicity
- 2. Chlorambucil
  - a. Nitrogen mustard derivative
  - b. Similar mechanism as cyclophosphamide with slower time of onset

# B. Pharmacokinetics

- 1. Well absorbed orally
- 2. Metabolized in liver
- 3. Renally excreted, but most is reabsorbed

# II. List the indications/contraindications

# A. Most uveitis specialists do not manage the administration of these agents themselves but coordinate care of the patient with an internist, rheumatologist or oncologist

# B. Indications

- 1. Noninfectious intraocular and scleral inflammatory disease
  - In certain conditions such as necrotizing scleritis or granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis), cyclophosphamide is indicated as first line therapy where it is particularly efficacious for the eye and for saving the patient's life. Similarly, chlorambucil has been shown to induce long- term remission (cure) in patients with otherwise intractable sight-threatening non infectious uveitis such as Behcet's disease, sympathetic ophthalmia and serpiginous choroidopathy
  - b. Nonreponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids
  - c. Incomplete response to other corticosteroid-sparing agents

#### C. Contraindications

- 1. Infectious etiology
- 2. Allergy or sensitivity to agent or others in its class
- 3. Pregnancy (includes males impreganating others)
- 4. Breast feeding
- 5. Hematologic disorders (relative contraindication)
- 6. History of prior cancer

# III. Describe the pre-procedure/therapy evaluation

- A. Renal function panel
- B. Complete blood count (CBC)
- C. Urinalysis
- D. Liver enzymes

# IV. List the alternatives to this procedure/therapy

A. Corticosteroids

#### B. Calcineurin inhibitors

- 1. Cyclosporine
- 2. Tacrolimus
- 3. Sirolimus

#### C. Antimetabolites

- 1. Methotrexate
- 2. Azathioprine
- 3. Mycophenolate mofetil

#### D. Other alkylating agents

- 1. Chlorambucil
- E. Biologic agents approved for specific rheumatic diseases
  - 1. Anti-tumor necrosis factor alpha therapy
    - a. Etanercept (Enbrel®)
    - b. Infliximab (Remicade®)
    - c. Adalimumab (Humira®)
    - d. Rituximab (Rituxan®)

# V. Describe the dosage

# A. Cyclophosphamide

- 1. 1 3 mg/kg/day orally, 3-12 months
  - a. 100-150 mg/day typical initial dose increased to a maximum 200mg/day if uveitis remains active
- 1000 mg/m2 body surface area intravenous initial dose, then tailored dose based upon dynamics of the hemogram (treat to target; see below) every 7-21 days thereafter IV pulse therapy for 6-12 months
- 3. Dosage adjusted based on tolerance and laboratory values
  - a. Target leukocyte count 3,000-4,000 cells/µl off steroids
- 4. Maximum cumulative cyclophosphamide dose in the range of 35gm before risk of secondary leukemia substantially increases

# B. Chlorambucil

- 1. Long-term, low-dose therapy, 12 months
  - a. 0.1-0.2 mg/kg/day orally, single undivided dose
  - b. Dosage adjusted based on tolerance and laboratory values
    - i. Target leukocyte count 3,000-4,000 cells/µl off steroids
- 2. Short-term, high-dose therapy, 3-6 months
  - a. Initial daily dose 2 mg/day for 1 week
  - b. Increase dose by 2 mg/day each week until
    - i. Inflammation suppressed
    - ii. Leukocyte count reaches 2500 cells/ µl
    - iii. Platelets drop below 125,000 cells/ µl

# VI. List the complications of the procedure/therapy, their prevention and management

# A. Leukopenia or bone marrow suppression

- B. Infection
  - 1. Pneumocystis carinii prophylaxis
    - a. Trimethoprim-sulfamethoxazole, one tablet, single strength, daily
- C. Hemorrhagic cystitis (increases risk of subsequent bladder cancer)
- D. Gonadal suppression and permanent infertility
  - 1. Banking of sperm, eggs, embryos before treatment
- E. Pulmonary fibrosis
- F. Rash

- G. Long-term risk of secondary malignancy (bladder, lymphoma, leukemia, skin cancer)
- H. Nausea
- I. Fatigue
- J. Hair loss does occur with both but may more pronounced with Cyclophosphamide
- K. Teratogenicity: appropriate contraception for women of childbearing age

# VII. Describe the follow-up care

- A. Routine monitoring of CBC weekly, renal function, urinalysis with microscopic examination generally every 4 weeks once on stable regimen
- B. Dose titrated to leukocyte count of 3000-4000 cells/µl
- C. Discontinue therapy
  - 1. WBC  $\leq$  2,500 cells/ µl
  - 2. Hematuria

# VIII. Describe appropriate patient instructions

- A. Inform the ophthalmologist of any new symptoms while on the medication, including, but not limited to, the following
  - 1. Fever, chills, sore throat
  - 2. Dark urine
  - 3. Blood in urine (hematuria)
  - 4. Black tarry stools
  - 5. Unusual bleeding
  - 6. Unusual tiredness or weakness
  - 7. Yellowing of the skin or eyes
  - 8. Stomach or abdominal pain
  - 9. Muscle or joint pain
- B. Take dose of cyclophosphamide in early morning with at least 2 L fluid per day, maintain good urine flow
  - 1. This reduces contact time of acrolein metabolite with bladder wall
- C. Avoid live virus vaccines
- D. Appropriate follow up with reumatologist or oncologist

### Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis,

2013-2014.

- 2. AAO, Focal Points:Management of Chronic Uveitis, Module#11, 2007.
- 3. AAO, Focal Points: Scleritis and Episcleritis: Diagnosis and Management, Module 4, 2009.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel Am J Ophthalmol 2000;130:492-513.
- 5. Kemen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosupressive agents for ocular inflammtion : a critical assessment of the evidence. Am J Ophthalmol 2008; 146: 802-12.
- 6. Goldstein DA, Fontanilla FA, Kaul S, et al: Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threateining ocular inflammation. Ophthalmology 109:370, 2002.
- 7. Pujari SS, et al. Cyclophosphamide for Ocular Inflammatory diseases. Ophthalmol, 2010; 117(2): 356.
- 8. Hemady R, Tauber J, Foster CS. Immunosuppressive drugs in immune and inflammatory ocular disease. Surv Ophthalmol 1991; 35;:369-85.

# Cyclosporine

# I. Pharmacology

# A. Mechanism of action

- 1. Cyclosporine is a non-cytotoxic immunmodulatory agent which selectively and reversibly inhibits helper/inducer CD4+ T- lymphocyte mediated immune responses
  - a. Cyclosporine binds to cyclophilin
  - b. The cyclosporine-cyclophilin complex then binds to and inhibits calcineurin
  - c. Calcineurin catalyzes reactions necessary for early activation of T-cells particularly the expression and production of cytokines such as interleukin-2 (IL-2)
- 2. Cyclosporine does not affect suppressor T-cells or T-cell independent, antibody-mediated immunity

### B. Pharmacokinetics

- 1. Different formulations have different bioavailabilities, therefore consistency in the formulation used is needed (see dosages)
  - a. The USP modified microemulsion formulation (Neoral, Gengraf) has greater oral bioavailability than unmodified cyclosporine A (Sandimmune)
  - Unmodified cyclosporine A is the only liquid formulation. (There are 2 oral solution formulations, and 2 soft gelatin capsule formulations: the Sandimune oral solution and soft gel capsules both have decreased bioavailability compared to the Neoral formulations)
- 2. When converting from one formulation to another, a dosage adjustment is needed
- 3. Cyclosporine crosses the placenta and is found in breast milk
- 4. Food consumed with cyclosporine affects absorption
  - a. The liquid formulation can be diluted with orange or grape juice, or chocolate milk
  - b. Taking cyclosporine with meals of a relatively uniform composition from day to day may result in more even drug levels
  - c. Food generally enhances absorption

# II. List the indications/contraindications

A. Some uveitis specialists do not manage the administration of these agents themselves, but coordinate care of the patient with an internist/rheumatologist

### B. Indications

- 1. Noninfectious intraocular and scleral inflammatory disease
  - a. Nonresponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids

- b. Incomplete response to other corticosteroid-sparing agents
- c. Cyclosporine is frequently used in combination with systemic steroids in patients who need a rapid control of inflammation

#### C. Contraindications

- 1. Infectious etiology
- 2. Poorly controlled or difficult to control hypertension
- 3. Renal insufficiency or other kidney disease
- 4. Allergy or sensitivity to agent or others in its class

#### D. Relative contraindications

- 1. Pregnancy
- 2. Breast feeding
- 3. Advanced age (increased risk of renal dysfunction)

# III. Describe the pre-procedure/therapy evaluation

- A. Renal function panel and estimated creatinine clearance. An average of 3 baseline measurements has been suggested
- B. Liver function panel
- C. Serum cholesterol and triglycerides
- D. Complete blood count (CBC)
- E. Blood pressure (BP). An average of 3 baseline measurements has been suggested

# IV. List the alternatives to this procedure/therapy

- A. Other calcineurin inhibitors (tacrolimus) and agents that interfere with signals leading to IL-2 production (sirolimus)
  - 1. Competes with tacrolimus
  - 2. Synergistic with sirolimus

#### B. Antimetabolites

- 1. Methotrexate
- 2. Azathioprine
- 3. Mycophenolate mofetil
- C. Alkylating agents
  - 1. Cyclophosphamide
  - 2. Chlorambucil

#### D. Biologic agents approved for specific rheumatic diseases

- 1. Anti-tumor necrosis factor alpha therapy
  - a. Etanercept (Enbrel®)
  - b. Infliximab (Remicade®)
  - c. Adalimumab (Humira®)
  - d. Rituximab (Rituxan®)
- 2. IL-2 antagonists
  - a. Daclizumab
  - b. Basiiliximab

# V. Describe the dosage

- A. 2.0 to 5 mg/kg/day, typically in two divided doses with adjustment depending on clinical response and toxicity
  - 1. USP modified cyclosporine is typically 4.0 mg/kg/day
  - 2. Unmodified cyclosporine A is typically 5 mg/kg/day
  - 3. Maintenance doses are usually one half the typical dose
  - 4. Doses more than 200 mg/day in adults have a higher incidence of side effects
  - 5. Decrease dose 20% when moving from unmodified to modified cyclosporine, and increase dose 20% when moving from modified to unmodified cyclosporine
  - 6. Taper dose by 20% every 2 to 3 weeks when decreasing therapy to prevent rebound of inflammation
  - 7. Caution with doses in patients who are markedly underweight or overweight

# VI. List the complications of the procedure/therapy, their prevention and management

### A. Hypertension

- 1. Antihypertensive medication may be necessary
- 2. Angiotensin converting enzyme inhibitors preferred
- 3. Calcium channel blockers may increase blood cyclosporine levels
- 4. Avoid diuretics as dehydration may affect kidney function
- B. Reduction in estimated creatinine clearance
  - 1. Dosage reduction required if declines by more than 20%
- C. Hirsutism
- D. Gingival hyperplasia
  - 1. Prophylactic dental cleaning and daily gum massage and flossing

- E. Trembling and shaking of hands/paresthesia
- F. Acne or oily skin
- G. Headache
- H. Leg cramps
- I. Nausea
- J. Infection
- K. Malignancy
- L. Central nervous system dysfunction or peripheral neuropathies
- M. Osteoporosis

# VII. Describe the follow-up care

- A. Routine monitoring of BP, renal function generally every 4 to 6 weeks initially, then at least every 3 months
- B. Magnesium levels if patient having cramps or neurological symptoms
- C. Uric acid may rise during early treatment
- D. Liver enzymes may rise during early treatment
- E. Cholesterol may rise during prolonged treatment
- F. Whole blood drug levels may be checked as an indicator of compliance, bioavailability, or in suspected toxicity, however most clinicians do not routinely check levels and do not use them for treating to a target level.
- G. Reduce dose
  - 1. Systemic BP>140/90 Hg or clinically significant increase in blood pressure above baseline if not controlled by antihypertensive medication
  - 2. Decrease in renal function as measured by estimated creatinine clearance by >20% from baseline
- H. Taper and discontinue drug
  - 1. BP not controlled despite antihypertensive therapy
  - 2. Estimated creatinine clearance decreased by 30% since baseline
- I. Reliance on normal BP ranges and normal creatinine ranges without considering age, sex, body weight, and baseline values may lead to underestimation of toxicity

# VIII. Describe appropriate patient instructions

- A. Certain foods and medications can result in an increase in blood levels
  - 1. Macrolide antibiotics erythromycin and clarithromycin (not azithromycin)
  - 2. Cholesterol drugs atorvastatin, lovastatin, simvastatin (not pravastain or rosuvastatin)
  - 3. Grapefruit juice (if taken at the same time as the medication)
  - 4. Drug interactions summarized at http://medicine.iupui.edu/clinpharm/ddis/

(http://medicine.iupui.edu/clinpharm/ddis/)

a. Ketoconazole - has been used to reduce needed dose of cyclosporine

# B. Inform the ophthalmologist of any new symptoms while on the medication

- 1. Especially
  - a. Fever, chills, sore throat
  - b. Headache
  - c. Confusion, depression
  - d. Muscle and joint aches
  - e. Changes in urine production or color
  - f. Changes in gums
  - g. Numbness or tingling in hands or feet
- C. Inform ophthalmologist of any new medications added to regimen
- D. Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) due to increase in risk of renal toxicity

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Management of Chronic Uveitis, Module #11, 2007
- Ramadan AM, Nussenblatt RB, de Smet MD. Long-term follow-up of patients with chronic uveitis affecting the posterior pole treated with combination cyclosporine and ketoconazole. Ophthalmology.1997;104:706-11.
- Nussenblatt RB, de Smet MD, Rubin B, et al. A masked, randomized, dose-response study between cyclosporine A and G in the treatment of sight-threatening uveitis of noninfectious origin. Am J Ophthalmol. 1993;15:115-91.
- Jabs DA, Rosenbaum JT, Foster CF, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel Am J Ophthalmol 2000;130:492-513.
- 6. Murphy CC, Greiner K, Plskova J et al. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. Arch Ophthalmol 2005; 123: 634-41.
- 7. Hesselink DA, Baarsma GS, Kuijpers RW, et al. Experience with cyclosporine in endogenous uveitis posterior. Transplant Proc 2004; 36 (2 Suppl.): 372-377S
- 8. Kemen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosupressive agents for ocular inflammtion : a critical assessment of the evidence. Am J Ophthalmol 2008; 146: 802-12.
- 9. Kaçmaz, RO et al. Cyclosporine for Ocular Inflammatory Diseases. Ophthalmol, 2010; 117(#): 576-584.

# **Biologic response modifiers**

# I. Pharmacology

- A. Biologics Response Modifiers (BRM's) area newer class of agents used to treat systemic autoimmune diseases and have been recently exploited for the treatment of noninfectious uveitis. They include
  - 1. Recombinant cytokines and monoclonal antibodies directed against specific cell-surface markers on lymphocytes
  - 2. Cytokines or their receptors which selectively suppress the inflammatory cascade
    - a. The major classes of biologics relevant to ocular inflammatory disease include
      - i. Tumor necrosis factor (TNF)-alpha inhibitors
      - ii. Antilymphocyte drugs
      - iii. Cytokine receptor blockade
      - iv. Recombinant human cytokines/cytokine analogues
      - v. Costimulation modulators
      - vi. Selective lymphocyte elimination drugs

### B. Rationale for use

- Inhibition of tumor necrosis factor (TNF)-alpha has been shown in several studies in the rheumatology and dermatology literature to favorably impact diseases such as rheumatoid arthritis (RA), ankylosing spondylosis, psoriasis, and inflammatory bowel disease, among others
- Anti-CD20 monoclonal antibodies, widely expressed on B-cells, have been used to treat B-cell malignancies as well as systemic autoimmune diseases such as RA, classically thought to be T-cell mediated
- 3. Blockade of the interleukin-2 (IL-2) receptor on T lymphocytes, and so, II-2 mediated proinflammatory responses has been used in solid organ transplantation and other immunologically mediated conditions such as multiple sclerosis (MS), and psoriasis
- 4. Recombinant human cytokines and their analogues such as the interferons (INFs) have been used in the treatment of hepatitis C, neoplastic diseases and autoimmune diseases such as MS
- 5. Costimulation modulators bind to antigen presenting cells and prevent them from delivering costimulatory signals to T cells thereby preventing T cell activation
- 6. Small studies and case series, as well as some clinical trials, have suggested a similar benefit in some forms of ocular inflammatory disease
- 7. However dosing, duration of therapy, and agent choice are still largely based on anecdotal evidence and clinician choice
- 8. Effects of these agents may be reduced over time, based on anecdotal evidence

# C. Mechanisms of action

- 1. TNF-alpha inhibitors
  - a. Soluble TNF receptor
    - i. Etanercept is a fusion protein consisting of two human extracellular TNF binding domains complexed to the Fc portion of human immunoglobulin G (IgG), it can bind well to soluble TNF- $\alpha$  but not as effectively to to trans-membrane TNF- $\alpha$
  - b. Anti-TNF antibodies
    - Infliximab is a chimeric IgG monoclonal antibody containing human and murine portions, directed against TNF-alpha, it competitively and irreversibly inhibits both soluble and transmembrane forms of TNF-α.Adalimumab is a recombinant IgG containing 100% human peptide sequences, and is directed against TNF-alpha, targets and neutralizes membrane bound TNF-α.
- 2. Anti- CD20 monoclonal antibody
  - a. Rituximab is a chimeric monoclonal antibody directed against CD20-positive cells, largely expressed on B-lymphocytes
    - i. The role of B-cells and their interactions with T-cells may be more critical in the pathogenesis of inflammatory conditions previously thought to be exclusively T-cell mediated, including noninfectious uveitis
- 3. Cytokine receptor blockade
  - a. Daclizumab is a human-murine monoclonal antibody directed against the alpha subunit of the IL-2 receptor complex on T-lymphocytes (also known as the Tac or CD25 subunit) which inhibits IL-2 mediated proinflammatory immune responses including T-cell and macrophage activation. Daclizumab is no longer available in the United States
- 4. Recombinant human cytokine/cytokine analogues
  - a. The mechanism of action of interferons is poorly understood but these agents are known to have antiviral, antineoplastic, and antiangiogenic effects
    - i. Recent case series in Europe suggest efficacy of interferon alpha 2a in the treatment of the mucocutaneous, articular, and ocular manifestations of Behcet disease
- 5. Costimulation modulators
  - Orencia is a fusion protein of immunoglobulin bound to the extracellular domain of CTLA-4, a molecule which binds B7 on antigen presenting cells, effectively preventing binding of the APC to T-lymphocytes and preventing T cell activation

# II. List the indications/contraindications

- A. Most uveitis specialists do not manage the administration of these agents, but refer the patient to an internist/rheumatologist
- B. Note that the employment of these medications is off label for ocular disease
- C. Indications
  - 1. Noninfectious ocular inflammatory disease
- a. Nonresponsive or incompletely responsive to corticosteroids, or recurrence with tapering of corticosteroids
- b. Incomplete response to other corticosteroid-sparing agents
- c. Systemic disease such as Crohn disease for which a TNF antagonist may be indicated
- d. TNF antagonism appears to be particularly effective in the management the ocular manifestations of Behcet disease

### D. Contraindications

- 1. Infectious etiology of intraocular inflammatory diseases
- 2. Infection elsewhere (e.g., active tuberculosis, untreated latent tuberculosis)
- 3. Allergy or insensitivity to agent or others in its class
- 4. Pregnancy (Category B)
- 5. Breast feeding
- 6. Moderate to severe congestive heart failure
- 7. Multiple sclerosis or other demyelinating diseases
- 8. Moderate or severe heart failure

## III. Describe the pre-procedure/therapy evaluation

- A. Chest X-ray
- B. Purified protein derivative
- C. Rule out possibility of multiple sclerosis
- D. Metabolic panel
- E. Complete blood count (CBC)
- F. Query on history or risks for heart failure
- G. Antinuclear antibodies

## IV. List the alternatives to this procedure/therapy

- A. Corticosteroids
- B. Calcineurin inhibitors
  - 1. Cyclosporine
  - 2. Tacrolimus
  - 3. Sirolimus
- C. Antimetabolites
  - 1. Methotrexate

- 2. Azathioprine
- 3. Mycophenolate mofetil

### D. Alkylating agents

- 1. Cyclophosphamide
- 2. Chlorambucil

## V. Agents

### A. TNF-alpha inhibitors

- 1. Etanercept (Enbrel®)
  - a. 25 mg subcutaneously (SC), once or twice weekly
  - b. Two randomized, placebo-controlled trials have now demonstrated that this agent, although very effective for rheumatoid and psoriatic arthritis, is no better than placebo for the treatment of uveitis
- 2. Infliximab (Remicade®)
  - a. 3-10 mg/kg intravenous (IV) infusion
    - i. Anecdotal reports have used higher doses in nonresponsive cases. There is not enough experience in ocular disease to establish either the safety or efficacy of this dosing at this time. However, the body of case cohort reports continues to grow, and this drug is now approved in Japan for the treatment of patients with Behcet's Disease and its associated uveitis
  - b. Timing between infusions varies but generally at weeks 0, 2, 6, and every 8 weeks thereafter. For uveitis, every 4 weeks is preferred, with a beginning dose of 5 mg/kg
- 3. Adalimumab (Humira®)
  - a. 40mg SC every other week or weekly as clinically indicated

### B. Anti- CD20 monoclonal antibody

- 1. Rituximab (Rituxan®)
  - a. 1g twice 2 weeks apart, IV infusion

### C. Recombinant human cytokine/cytokine analogues

- 1. IFN alpha 2a (Roferon-A®)
  - a. 3-9 million international units/day, 3 times weekly, subcutaneous injections

## VI. List the complications of the procedure/therapy, their prevention and management

### A. TNF alpha inhibitors

- 1. Infusion reactions other than hypersensitivity reactions
- 2. Hypersensitivity reactions

- 3. Exacerbation of demyelinating disease
- 4. Exacerbation of tuberculosis and other latent infections (e.g., histoplasmosis)
- 5. Heart failure
- 6. Production of neutralizing antibodies
- 7. Drug induced lupus
- 8. Neoplasia (acute leukemia, infliximab)
- 9. De novo uveitis (etanercept)

### B. Anti-CD20 monoclonal antibody

- 1. Hypersensitivity reactions
- 2. Infusion reactions other than hypersensitivity reactions

### C. Interleukin-2 receptor blockade

- 1. Psoriasiform skin rashes
- 2. Lymphadenopathy
- 3. Peripheral edema (mild)
- 4. Infections (usually mild, may be severe with concomitant cytolytic therapy)
- 5. Neoplasia (one case, possibly related to treatment)

### D. Recombinant human cytokine/cytokine analogues (IFNs)

- 1. Arthralgia, fever, first week of therapy very common
- 2. Erythema, discomfort at injection site
- 3. Leukopenia
- 4. Alopecia
- 5. Depression
- 6. Cotton wool spot retinal, venous occulsion, retinal hemorraghe

### VII. Describe the follow-up care

A. Patients treated with biologic response modifiers generally have blood work at time of each infusion, approximately every 8 weeks

## VIII. Describe appropriate patient instructions

- A. Inform the physician of any new symptoms while on the medication
  - 1. Fever, cough, sore throat
  - 2. Allergic reactions
  - 3. Numbness, weakness

- 4. Shortness of breath
- 5. Swelling, fluid retention
- 6. Rash

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. Lim L, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. Clin Experiment Ophthalmol. 2006;34:365-374.

# Intravitreal antiviral therapy

## I. List the indications/contraindications

### A. Indications

- 1. Cytomegalovirus (CMV) retinitis
  - a. For induction treatment
  - b. Intolerance to systemic medication
  - c. In resource poor settings where systemic treatment cannot be afforded
  - d. Failure to respond to systemic ganciclovir or foscarnet
- 2. Acute retinal necrosis (ARN) syndrome
  - a. Herpes simplex retinitis
  - b. Varicella zoster retinitis
- 3. Progressive outer retinal necrosis syndrome

### B. Contraindications

1. Allergy or sensitivity to agent or others in its class

## II. Describe the pre-procedure/therapy evaluation

- A. Comprehensive eye examination
- B. Optional
  - 1. Aqueous or vitreous sampling for PCR to identify viral etiological agent prior to intravitreal injection though both frequently performed concurrently in the appropriate clinical context

## III. List the alternatives to this procedure/therapy

A. Intravenous (IV) therapy and oral therapy in conjuncation with intravitreal antiviral therapy is usually appropriate therapy

## IV. Dosage of agents commonly used in USA

## A. Ganciclovir

- 1. Intravitreal injection
  - a. CMV retinitis
    - i. 0.2 to 5 mg in 0.05-0.1ml 1-2 times weekly for 2-3 weeks followed by weekly injections

- i) 5 mg is the highest dose reported in the literature
- ii) 2 mg is the conventional dose and has pharmacokinetic data regarding vitreous levels
- iii) Vitreous levels will rise if 2 mg dose given 3 times weekly for more than 2 weeks
- iv) 0.2 mg is the originally dose described as effective when given weekly
- v) Dose should be titrated to location and extent of retinitis
- ii. Alternative, 2.5 mg in 0.05ml once weekly
- b. Necrotizing retinitis due to simplex or zoster in immunocompetent patients
  - i. Single dose (0.2 to 2 mg ) followed by IV or oral therapy may be adequate for ARN, but can be repeated depending on the clinical response
  - ii. Not all clinicians admit patients for IV therapy if intravitreal is used, but rather cover with high dose oral antivirals
  - iii. Dose of oral or IV antivirals may need to be adjusted in patients with kidney problems
- c. Progressive outer retinal necrosis and necrotizing herpetic retinitis in immunosuppressed individuals may require combinations of antiviral agents and routes of administration, including intravenous and intravitreal therapy

### B. Foscarnet

- 1. Intravitreal injection
  - a. CMV retinitis
    - i. 1.2 to 2.4 mg in 0.05-0.1ml every 2-3 days for up to 2 to 3 weeks followed by weekly injections as needed
      - i) This is the highest reported dose in the literature
      - ii) Originally described as effective when given in doses of 1.2 to 2.4 mg weekly
  - b. Necrotizing retinitis due to simplex or zoster
    - i. Single dose followed by IV or oral therapy may be adequate for ARN but may be repeated depending on the clinical response
    - ii. Not all clinicians admit patients for IV therapy if intravitreal is used, but rather cover with oral antivirals
  - c. Progressive outer retinal necrosis and necrotizing herpetic retinitis in immunocompromised individuals may require combinations of antiviral agents and routes of administration, including intravenous and intravitreal therapy

## V. Describe the technique

- A. Topical anesthesia with 2% lidocain gel
- B. Lid speculum, 5% povidone iodine solution eye drops, post-injection topical antibiotic

(controversial), post-injection fundoscopy

- C. Injection given through pars plana, 3.5mm (for pseudophakic) to 4mm (for phakic) posterior to the limbus
- D. Check intraocular pressure (IOP) afterwards and confirm light perception, if elevated, consider anterior chamber (AC) tap
- E. Some clinicians will perform AC tap initially with the first injection to use fluid for diagnostic testing (polymerase chain reaction (PCR) and/or local antibody production)

## VI. List the potential complications of the procedure/therapy, their prevention and management

- A. Retinal detachment
- B. Endophthalmitis
- C. Cataract
- D. Increased IOP

### VII. Describe the follow-up care

A. Frequent serial eye examinations to confirm response

## VIII. Describe appropriate patient instructions

- A. Inform the ophthalmologist of any new symptoms following the treatment
  - 1. Especially decreased vision, pain, increasing redness (other than subconjunctival hemorrhage)
- B. Do not rub the eye or get water in it for 24 hours

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Necrotizing Herpetic Retinopathies, Module 10, 2008.
- 3. Kirsch LS, Arevalo JF, Chavez de la Paz E, et al. Intravitreal cidofovir (HPMPC) treatment of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. Ophthalmology. 1995 Apr;102(4):533-42.
- 4. Arevalo JF, Garcia RA, Mendoza AF. European Journal of Ophthalmology. Sept/Oct; 15(5):610-618.
- 5. Tibbetts MD et al. Treatment of Acute Retinal Necrosis. Ophthalmology 2010; 117: 818-824.
- 6. Gore DM et al. Progressive Outer Retinal Necrosis: Outcomes in the Intravitreal Era. Arch Ophthalmol. 2012; 130(6): 700-706.

# Cataract extraction for uveitis patients

## I. List the indications/contraindications

### A. Indications

- 1. Decreased visual acuity explained by cataract
- 2. Inability to examine posterior segment in potentially progressive posterior segment disease
- 3. Lens-induced inflammation
- 4. Consider age of patient
  - a. Urgent if in amblyogenic age group
  - b. Can often be deferred in middle childhood and teen years until more mature

### B. Contraindications

- 1. Active anterior segment inflammation (other than that associated with lens induced inflammation, in which cataract extraction is therapeutic)
- 2. Active surface infection
- Concurrent ocular pathology that is likely to prevent functional vision improvement for the patient even with successful cataract surgery; surgery should be done only if necessary to allow visualization of the patient's fundus for treatment purposes

## II. Describe the pre-procedure/therapy evaluation

### A. History

- 1. Course of visual loss (rapid, gradual)
- 2. Previous best corrected acuity
- 3. Previous eye surgery/trauma

### B. Medical history

- 1. Type of uveitis
- 2. Previous work-up
- 3. Response to treatment, including elevation in intraocular pressure with corticosteroids
- C. Medications (ocular and systemic)
- D. Comprehensive eye examination including refraction and dilated fundus examination
  - 1. Special attention should be paid to
    - a. Concurrent corneal disease that might require combined penetrating keratoplasty with cataract extraction
    - b. Elevated intraocular pressure (IOP)/glaucoma requiring surgery

- c. Posterior synechiae requiring attention during surgery
- d. Presence of phacodonesis
- e. Zonular integrity
- f. Presence of cystoid macular edema, which should be treated prior to surgery
- 2. If no view of posterior segment, B-scan is required to rule out retinal detachment, intraocular mass

### E. Decision regarding whether to implant intraocular lens (IOL)

- 1. Degree of flare chronically present in the anterior chamber is associated with the presence of posterior synechiae
  - a. Whether this is a risk factor for subsequent posterior synechiae formation after cataract surgery is unknown
- 2. The ability of the ophthalmologist to prevent active inflammation is most likely the key factor in successful IOL implantation in uveitis patients
- 3. Uveitic diagnosis such as juvenile idiopathic arthritis (JIA) and chance of recurrent disease
  - a. Many uveitis specialists consider a diagnosis of JIA a relative contraindication to IOL implantation
  - b. As adults, former JIA uveitis patients can be considered for an implant, depending on uveitis status
- 4. Patient compliance

### F. Managing expectations - the following should be discussed PRIOR to surgery

- 1. The reason for surgery (i.e. visual rehabilitation versus improved visualization of posterior pole) and expected outcome
- 2. Prolonged follow-up and increased need for medications in perioperative period
- 3. Increased likelihood of additional procedures (i.e. injections, imaging, lasers)

## III. List the alternatives to this procedure/therapy

- A. Refraction
- B. Observation
- C. Dilation may help with small central posterior subcapsular cataracts

## IV. Describe the technique

### A. Pre-procedure

- 1. Commonly followed rule-of-thumb is no active anterior segment inflammation for 3 or more months. Disease control during this period is generally maintained with chronic topical or periocular corticosteroids, or with immunomodulatory therapy
- 2. Days to 1 week prior to surgery, patient should have an examination to confirm the eye is quiet. At

this time, periocular, systemic or intraocular corticosteroids may be administered

- 3. Topics NSAID therapy may be use adjunctively as prophylaxis against macular edema
- 4. 1 day prior to surgery, it may be helpful to prescribe corticosteroid eyedrops hourly while awake

### B. Special considerations during procedure

- 1. Intraoperatively, methylprednisolone is often given intravenously to minimize the likelihood of a postoperative flare
- 2. Consider clear corneal incision for preservation of conjunctiva for future glaucoma procedures, which are more common in uveitis patients
- 3. Consider placing suture, as these patients will be on frequent topical steroids and may have delayed wound healing

### C. Postoperative management

- 1. Oral corticosteroids may be tapered and discontinued based on the degree of intraocular inflammation
- 2. Topical corticosteroids are generally given frequently while awake for several days postoperatively, and then tapered according to disease activity
- 3. Postoperative cycloplegia is generally helpful to minimize the likelihood of posterior synechiae (iris will stick to the lens capsule) and provide comfort

## V. List the postoperative complications of the procedure/therapy and their management

### A. Uveitis flare up

- 1. Prevention
  - a. Increase anti-inflammatory drug agents preoperatively
  - b. Remove all nuclear and cortical material
- 2. Management
  - a. Aggressively reduce the inflammation and quickly taper as tolerated
  - b. Identify any retained nuclear or cortical particles; may need to have nuclear pieces removed surgically

### B. Retinal detachment

1. Obtain retina subspecialist consultation

### C. Endophthalmitis

- 1. Obtain retina subspecialist consultation
- 2. Use intravitreal antibiotics
- D. Increased IOP
  - 1. Aqueous suppressants

### E. Corneal decompensation

- 1. Topical corticosteroids
- 2. Hypertonic saline
- 3. Consider toxic reaction versus endothelial damage due to procedure

### F. Ptosis

- 1. Observation
- 2. Referral to an oculoplastic subspecialist

### G. Cystoid macular edema

- 3. Topical corticosteroids
- 4. Nonsteroidal anti-inflammatory drugs (NSAIDs)
- 5. Regional corticosteroids
  - a. Kenalog appropriate for periocular injection
  - b. Preservative-free triamcinolone acetonide for intraocular injection

### H. Wound leak

- 1. Aqueous suppressants
- 2. Bandage contact lens
- 3. Patch eye
- 4. Suture the wound in operating room

### I. Posterior capsular opacification

- 1. Neodymium yttrium-aluminum-garnet (Nd:YAG) capsulotomy
- 2. This therapy may need to be repeated

### J. Iridocapsular synechiae

- 1. Drops of intermediate duration
- 2. Possibly Nd:YAG lysis
- 3. This therapy may need to be repeated

### K. IOL capture

- 1. Observation
- 2. If significant dislocation occurs, reposition lens

### L. Capsular distension syndrome

- 1. Observation
- 2. Nd:YAG capsulotomy (of anterior capsular edge versus posterior capsule)

## VI. Describe the follow-up care

### Uveitis

- A. Postoperative examination within 1 day and then as dictated by the examination findings depending on presence of uveitis and other complications
- B. Topical ± systemic corticosteroids as needed for disease control
- C. Topical antibiotics
- D. Protect eye (shield, eyeglasses)
- E. Limit strenuous activity for initial postoperative period

## VII. Describe appropriate patient instructions

- A. Inform the ophthalmologist of any worsening in visual acuity, pain, redness of eye
- B. Stress compliance with medications, limitations, and follow up visits
- C. Provide instructions for contacting office in emergency, including after hours

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Uveitis in Children, Module #4, 1995, p.7-8, 13.
- 3. Alio JL, Chipont E, BenEzra D, et al. Comparative performance of intraocular lenses in eyes with cataract and uveitis. J Cataract Refract Surg. 2002;28:2096-108.

# Glaucoma surgery for uveitis patients

## I. List the indications/contraindications

### A. Indications

- 1. Increased intraocular pressure (IOP) unable to be controlled medically that is high enough to cause optic nerve damage
- 2. Need for local corticosteroid treatment in known steroid responder

### B. Contraindications

- 1. Active anterior segment inflammation or active scleritis (relative contraindications that require assessment of relative risks and benefits)
- 2. Active surface infection
- 3. Poor visual potential (relative contraindication)

## II. Describe the pre-procedure/therapy evaluation

- A. History
  - 1. Course of pressure rise (rapid, gradual) and maximum pressure
- B. Previous eye surgery/trauma medical history
- C. Medications (ocular and systemic)
- D. Comprehensive eye examination including refraction and dilated fundus examination
  - 1. Special attention should be paid to
    - a. Concurrent conjunctival disease
    - b. Cataract that would require concurrent extraction
    - c. Depth of anterior chamber
    - d. Presence and degree of posterior synechiae
  - 2. Extra special attention should be paid to the status of the conjunctiva
  - If no view of posterior segment, B-scan is required to rule out retinal detachment and intraocular mass
- E. Decision regarding type of surgery
  - 1. Filtering procedure (trabeculectomy)
  - 2. Seton (tube shunts)
    - a. Preferred surgery in the setting of uveitis
    - b. Lower failure rate than trabeculectomy in uveitis patient, in which scarring is more common.
    - c. Other, less commonly used procedures

- i. Goniotomy in children
- ii. Laser cyclodestruction; caution in patients with iridocyclitis at risk for later hypotony, e.g., juvenile idiopathic arthritis (JIA)
- iii. Gonioscopic stripping of angle membranes if present

### F. Preoperative management

- 1. Whenever possible, uveitis should be inactive for 3 months preoperatively
  - a. This may require repeat corticosteroid injections, long term topical corticosteroid use, often with immunosuppressive medication as well
  - b. A vigorous inflammatory response should be anticipated postoperatively
    - i. Discuss realistic outcome expectation with patient and family, including need for addition surgery
- 2. Combined glaucoma and elective cataract surgery may exacerbate the amount of postoperative inflammation

## III. List the alternatives to this procedure/therapy

- A. Oral or topical medications
- B. Laser trabeculoplasty is relatively contraindicated

## IV. Describe the technique

### A. Anesthesia

- 1. Topical
- 2. Peribulbar
- 3. Retrobulbar
- 4. General
- B. Pathologic examination should be carried out on removed tissue including iris and/or trabecular meshwork

## V. List the postoperative complications of the procedure/therapy, their prevention and management

- A. Uveitis flare up
  - 1. Control inflammation preoperatively, whenever if possible
  - 2. Oral, periocular, intravenous, and/or topical corticsoteroids are used for preoperative, intraoperative and postoperative disease control
  - 3. Treat as appropriate, often requires intraocular corticosteroid postoperatively or prolonged use of systemic corticosteroids

### B. Acute endophthalmitis

- 1. Treat blepharitis pre-operatively
- 2. Add preoperatively 5% povidone-iodine solution to conjunctival fornix
- 3. Obtain retina subspecialist consultation
- 4. Use intravitreal antibiotics

### C. Delayed endophthalmitis

- 1. Avoid inferior placement of filters
- 2. Prompt treatment of conjunctivitis or blebitis
- 3. Topical corticosteroid use not proven as a risk factor, although frequent follow-up should be considered
- 4. Tap and inject with broad spectrum antibiotics vs. pars plana vitrectomy (PPV)

### D. Retinal detachment

1. Obtain retina subspecialist consultation

### E. Hypotony

- 1. Adequate control of postoperative inflammation
- 2. Try increased topical and regional corticosteroids (difluprednate)

### F. Choroidal effusion and choroidal hemorrhage

### G. Increased IOP

- 1. Aqueous suppressants
- 2. May be hypertensive phase of seton, suture lysis

### H. Corneal decompensation

- 1. Placement of seton tubes away from iris (risk of peripheral anterior synechiae (PAS)) and cornea (risk of endothelial cell decompensation)
- 2. Topical corticosteroids
- 3. Hypertonic saline
- 4. Consider toxic reaction versus endothelial damage due to procedure
- 5. Consider repositioning of seton tube

### I. Ptosis

- 1. Avoid excessive pressure from speculum
- 2. Observation
- 3. Obtain oculoplastic subspecialist consultation

### J. Cystoid macular edema

- 1. Topical corticosteroids
- 2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

3. Regional corticosteroids

### K. Epiretinal membrane development

- 1. Difficult, but strict control of inflammation may help
- 2. Surgical removal if indicated

### L. Wound leak

- 1. Adequate suturing in operating room
- 2. Aqueous suppressants
- 3. Bandage contact lens
- 4. Patch eye
- 5. Wound revision

### M. Peripheral anterior synechiae around tube with pupil distortion

- 1. Proper tube placement
- 2. Avoidance of other elective surgeries such as cataract extraction
- 3. Avoidance of strong dilators postoperatively
- 4. Observation
- 5. Sweeping of iris adhesions with a needle

### N. Overfiltration with low intraocular pressure

- 1. Continued treatment of uveitis to prevent ciliary body dysfunction
- 2. Filter or tube closure if necessary

### VI. Describe the follow-up care

- A. Postoperative examinations frequently during first 90 days, based on condition afterwards
- B. Topical corticosteroids frequently
- C. Oral corticosteroids as needed for disease control
- D. Topical antibiotics
- E. Protect eye (shield, eyeglasses)
- F. Limit strenuous activity for initial postoperative period

## VII. Describe appropriate patient instructions

- A. Inform the ophthalmologist of any worsening in visual acuity (VA), pain, redness of eye
- B. Stress compliance with medications, limitations, and follow up visits
- C. Provide instructions for contacting office in emergency, including after hours

### Additional Resources

- 1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.
- 2. AAO, Focal Points: Management of Glaucoma Secondary to Uveitis, Module #5, 1995.

# Complications of uveitis

## I. Calcific band-shaped keratopathy

### A. Calcium deposits in the epithelial basement membrane and the Bowman layer

- 1. Common in the interpalpebral zone, often extending into the visual axis
- 2. Removal with epithelial debridement and chelation with sodium ethylenediaminetetraacetic acid (EDTA)

### II. Cataract

### A. Chronic or recurrent uveitis, causes

- 1. Intraocular inflammation
- 2. Corticosteroid use
- B. Surgical management when visually significant or precluding view of posterior pole (see section on Cataract extraction in uveitis patient)

### III. Glaucoma

- A. Uveitic ocular hypertension intraocular pressure (IOP) 10 mm Hg or greater above baseline without evidence of glaucomatous optic nerve damage
  - 1. Treat inflammation
  - 2. Consider steroid response if IOP increase occurs after 3 weeks of corticosteroid treatment
  - 3. Consider alternative cause, such as viral or toxoplasma
- B. Uveitic glaucoma progressive neuroretinal rim loss and/or development of typical, perimetric, glaucomatous field defects

### C. Secondary angle-closure glaucoma

- 1. Acute
  - a. Choroidal inflammation with anterior rotation of ciliary body and lens iris diaphragm
    - i. Vogt-Koyanagi-Harada disease (VKH)
    - ii. Sympathetic ophthalmia
    - iii. Posterior scleritis
  - b. Clinical findings
    - i. Complaint of pain
    - ii. Elevated IOP
    - iii. No posterior synechiae

- iv. Severe inflammation
- c. Ultrasound biomicroscopy (UBM) to detect choroidal thickening and anterior rotation of the ciliary body
- d. Treatment
  - i. Aggressive corticosteroid therapy
  - ii. Aqueous suppressants
  - iii. Peripheral iridotomy or iridectomy is NOT effective
- 2. Subacute angle closure
  - a. Significant posterior synechiae, pupillary block, and iris bombé
    - i. Lead up may be subacute, but rise in IOP may be acute or hyperacute
  - b. Management
    - i. Peripheral iridotomy (PI) with the Nd:YAG or argon laser
      - i) Multiple and large
      - ii) Intense topical corticosteroid following procedure
      - iii) Consider argon laser pre-treatment to shrink iris tissue, vessels before YAG
    - ii. Surgical iridectomy
      - i) Failure of laser PI
      - ii) Darker irides
      - iii) Consider histology of iris specimen
- 3. Chronic angle closure
  - a. Chronic peripheral anterior synechiae (PAS) and secondary angle-closure glaucoma
    - i. Topical aqueous suppressants often inadequate
    - ii. May require goniosynechialysis and trabeculectomy with mitomycin C or glaucoma tube shunt placement

### D. Secondary open-angle glaucoma

- 1. Acute, typically attributed to trabeculitis
  - a. Associated with infectious uveitis
    - i. Toxoplasma retinochoroiditis
    - ii. Necrotizing herpetic retinitis
    - iii. Herpes simplex and zoster iridocyclitis
    - iv. Cytomegalovirus Iridocyclitis
    - v. Fuchs heterochromic iridocyclitis
  - b. Responds to topical cycloplegics, corticosteroids, and treatment of infections

2. Chronic - inflammatory debris clogging the angle or direct damage to the trabecular meshwork

### E. Corticosteroid-induced ocular hypertension and glaucoma

- 1. Common with more potent topical corticosteroids
  - a. Difluprednate
  - b. Prednisolone acetate
- 2. Periocular, intravitreal steroids, and steroid implants
- 3. Less common with oral and nasal corticosteroids, but still needs monitoring

### F. Combined-mechanism uveitis glaucoma

### G. Management

- 1. Control intraocular inflammation when attributed to trabeculitis
- 2. Control IOP with topical and additional systemic therapy, if required
- 3. Prevent glaucomatous optic nerve damage
  - a. Gonioscopy to assess angle (should be repeated at least annually and whenever IOP elevates)
  - b. Optic nerve evaluation (disc photos and OCT nerve fiber layer)
  - c. Automated visual fields
- 4. Prostaglandin analogs do not generally exacerbate intraocular inflammation, especially when used concomitantly with IMT and corticosteroids
- 5. May require surgical intervention to prevent vision loss and allow for treatment of uveitis

## IV. Hypotony

### A. Decreased aqueous production

- 1. Acute inflammation of the ciliary body resolves with treatment
  - a. Intensive corticosteroid
  - b. Cycloplegia
- 2. Chronic ciliary body damage with atrophic or absent ciliary processes
  - a. PPV in patients with ciliary processes on UBM or traction from cyclitic membranes
  - b. PPV with silicone oil requires reinjection in ~50% 1 year
- 3. Often associated with serous choroidal detachment

### V. Cystoid macular edema

- A. Common cause of visual loss in uveitis
- B. Quantified by spectral-domain OCT and fluorescein angiography

- C. Severity of CME does not necessarily correspond to the level of inflammation
- D. Increased incidence in smokers, especially in intermediate and panuveitis

### E. Treatment

- 1. Control of inflammation with corticosteroids and IMT
  - a. Periocular therapy
    - i. Superotemporal posterior sub-Tenon injection of 20-40 mg of triamcinolone acetonide delivers corticosteroid closest to the macula
    - ii. Injections may be repeated
  - b. Intravitreal therapy
    - i. Preservative-free triamcinolone acetate or triamcinolone acetonide (Triesence)
    - ii. Preserved triamcinolone acetate (Kenalog) NOT approved for intravitreal injection
    - iii. Drug is eliminated more quickly from the vitreous cavity of vitrectomized eyes
    - iv. Maximum visual improvement and reduction of CME after intravitreal triamcinolone injection occurs within 4 weeks
    - v. The fluocinolone acetonide implant dramatically reduces uveitic CME but with high rate of cataract formation and glaucoma
    - vi. Intravitreal bevacizumab effective in short term and repeat injections are required
    - vii. Intravitreal methotrexate effective in short term
  - c. Topical ketorolac and nepafenac can be beneficial in treating pseudophakic CME
  - d. Oral acetazolamide shown to be effective in reducing uveitic CME; useful with concomitant ocular hypertension
  - e. Topical difluprednate for CME in phakic and pseudophakic patients
- 2. Surgical therapy for uveitic CME is still controversial, likely helpful where traction is a component of condition

## VI. Vitreous opacification and vitritis

- A. Common in *Toxoplasma* retinitis and pars planitis.
- B. Visual acuity improved in majority of patients undergoing PPV

## VII. Rhegmatogenous retinal detachment

### A. 3% of patients with uveitis

- 1. Panuveitis and infectious uveitis are the entities most frequently associated with RRD
- 2. Pars planitis and posterior uveitis can also be associated with rhegmatogenous or tractional retinal detachments

3. Worse prognosis than in non-uveitic eyes

## VIII. Retinal neovascularization

- A. Associated with chronic inflammation or capillary nonperfusion
  - 1. Pars planitis
  - 2. Sarcoid panuveitis
  - 3. Retinal vasculitis

### B. Treatment is directed toward the underlying etiology.

- 1. Control inflammation
- 2. Scatter laser photocoagulation of areas with documented ischemia by fluorescein angiography
- 3. Intravitreal VEGF inhibitor in conjunction with control of inflammation

## IX. Choroidal neovascularization (CNV)

### A. More common posterior uveitis and panuveitis

- 1. Ocular histoplasmosis syndrome
- 2. Punctate inner choroidopathy (PIC)
- 3. Multifocal choroiditis
- 4. Serpiginous choroiditis
- 5. VKH syndrome

### B. Treat inflammation and CNV

- 1. Ensure complete control of underlying inflammation
- 2. Focal laser photocoagulation of peripapillary, extrafoveal, and juxtafoveal CNV
- 3. Intravitreal bevacizumab injections
- 4. Pars plana vitrectomy and subfoveal CNV extraction in selected cases

### Additional Resources

1. AAO, Basic and Clinical Science Course. Section 9: Intraocular Inflammation and Uveitis, 2013-2014.