**UVEITIS: SYSTEMIC & OCULAR APPROACHES TO MANAGEMENT**

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**Overview**

- Definition
- Etiology
- Signs/Symptoms
- Classification/Diagnosis
- Systemic Associations
- Lab Testing
- Treatment
- Follow-up

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**What is Uveitis?**

- Uveitis:
  - Generic, broad term referring to any inflammation of the uvea (iris, ciliary body, and choroid)
  - More precise terms include iritis and iridocyclitis
  - The inciting event -> release of chemotactic factors/mediators that increase vascular permeability -> breakdown of the blood-aqueous barrier -> macrophages/lymphocytes/proteins = CELLS & FLARE

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**Etiology**

- 3 main underlying causes are:
  - reaction to trauma
  - autoimmune
    - response to autoantigens
  - response to infectious agent

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**Uveitis - Signs and Symptoms**

- Patient symptoms are often very similar with all of the various etiologies
  - Can be some differences
- Anterior uveitis
  - pain, redness, photophobia
- Intermediate/Posterior uveitis
  - Floaters, mildly decreased vision from CME, etc
Patients with chronic uveitis are likely to be?

1. More symptomatic than acute uveitic pts
2. Less symptomatic
3. Symptoms are fairly equal between the two

Common patient symptoms include:
- pain - ciliary spasm
- red eye - ciliary flush
- tearing
- photophobia
- blurred vision
- Pupillary miosis

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Critical signs are cells and flare in the anterior chamber.
- Cells are lymphocytes or macrophages and indicate active inflammation in the iris and ciliary body.
- Flare is a result of protein leakage.

In the initial stages of an iridocyclitis, the patient's IOP will typically be?
1. Higher
2. Lower
3. No change

Keratic precipitates
- collections of inflammatory cells deposited on the endothelial surface of the cornea from the aqueous humor
- fresh KP's -> white and round
- older KP's -> pigmented or faded.
- Document size, color, distribution, and # of KP's

Accumulation of cells on the iris are referred to as iris nodules. Two types exist:
- Koeppe nodules are found on the pupillary border and Busacca nodules are on the anterior surface.
- Nodules on the pupillary border may result in posterior synechiae between the iris and lens.
Signs

- IOP must be monitored initially and at subsequent visits.
  - Usually a patient with acute uveitis will present with low pressure likely due to infiltration of the ciliary body and reduced aqueous secretion.
  - The pressure may be elevated secondary to inflammation in the trabecular meshwork or by blockage of the angle by cells and debris.
  - In addition, treatment with corticosteroids can result in glaucoma due to the patient being a steroid responder.

Which of the following is/are complications of long-standing uveitis?

1. Band keratopathy
2. Cataracts
3. Glaucoma
4. 2 & 3
5. All of the above

Signs - Long-Standing Uveitis

- Band keratopathy is also seen in chronic conditions such as uveitis.
  - It is the deposition of calcium at the level of Bowman's and in severe cases requires chelation therapy or mechanical scraping.

Signs - Long-Standing Uveitis

- Every patient with uveitis should have a DFE:
  - Posterior inflammation (vitreous) may be overlooked in a diagnosed case of anterior uveitis.
  - Macular area should be evaluated especially if there is any decrease in acuity.
  - CME frequently results from anterior uveitis and should be suspected if decreased VA.
  - Epiretinal membranes can form and distort the macular tissue.

Classification

- Classification is the key to the proper diagnosis and management of the uveitic patient.

- Most common classifications:
  - Anterior vs. Intermediate vs. Posterior vs. Panuveitis
  - Acute vs. Chronic
  - Granulomatous vs. Non-granulomatous
  - Infectious vs. Autoimmune
Classification of Uveitis

- 4 main questions we need answered
  - Where is the inflammation located?
  - Is disease acute or chronic?
  - Granulomatous or non-granulomatous?
  - Unilateral or bilateral?

Answers to the 4 questions

- 4 answered questions -> easier diagnosis and management
  - Anterior uveitis - etiology ???
  - Acute, unilateral, non-granulomatous anterior uveitis = Idiopathic, HLA-B27 uveitis, herpetic
  - Chronic, bilateral, granulomatous panuveitis = sarcoidosis, syphilis, TB

Duane’s Ophthalmology

- Most commonly encountered uveitic causes:
  1. Traumatic
  2. Post-surgical
  3. Anterior Idiopathic
  4. HLA-B27 associated uveitis
  5. JIA associated uveitis
  6. Fuch’s heterochromic iridocyclitis
  7. Posner-Schlossman syndrome
  8. Herpetic anterior uveitis
  9. Fars Planitis
  10. TB/Sarcoid/Syphilis

Anterior Uveitis Work-up

- After classification, 3 most common groups of uveitis include:
  1. Acute, unilateral (or bilateral), non-granulomatous anterior uveitis
     - Idiopathic, HLA-B27, Herpetic, Behcet’s
  2. Chronic, bilateral (or unilateral), non-granulomatous anterior uveitis
     - JIA, Fuch’s Heterochromic, Idiopathic, Herpetic
  3. Chronic, bilateral (or unilateral), granulomatous anterior uveitis
     - TB, Sarcoid, Syphilis, VKH

Which condition is NOT an HLA-B27 (+) condition linked with uveitis?

1) Ankylosing Spondylitis
2) Rheumatoid Arthritis
3) Reactive Arthritis (Reiter’s Syndrome)
4) Inflammatory Bowel Disease
1. Acute, unilateral (or bilateral), non-granulomatous anterior uveitis
   - Most common group
     - Idiopathic – most common cause of anterior uveitis
     - HLA-B27 – 2nd most common cause of anterior uveitis – nearly 20-50% of acute anterior uveitis pts are HLA-B27+
       - Ankylosing Spondylitis
       - Reactive Arthritis (Reiter's syndrome)
       - Psoriatic Arthritis
       - Inflammatory Bowel Disease
     - Herpetic
     - Behcet's

2. HLA-B27 (+) Associated Uveitis
   - Acute, rapid onset of unilateral pain and intense photophobia
   - Moderate to severe inflammatory reaction
     - 3-4+ cells
     - Hypopyon
     - Fibrin meshwork
     - Plasmoid aqueous
   - Aggressive treatment important
     - Average tx time = 6-10 weeks

3. HLA-B27 (+) conditions
   - Ankylosing Spondylitis
     - Low back pain
     - Diagnosis:
       - Abnormal S-I joint X-ray
       - Increased ESR
     - Treatment:
       - Exercise
       - Oral NSAID's

4. HLA-B27 (+) conditions
   - Reactive Arthritis (Reiter's syndrome)
     - “Can't see, can't pee, can't climb a tree”
     - Conjunctivitis/Uveitis
     - Urethritis
     - Arthritis - lower joints
     - Dermal skin lesions
     - Diagnosis:
       - Elevated ESR
     - Treatment:
       - NSAIDS

5. HLA-B27 (+) conditions
   - Inflammatory Bowel Syndrome
     - Ulcerative Colitis
     - Crohn's Disease
       - Stomach problems – diarrhea, bloody stools
     - GI referral – tx with diet change and immunosuppressives
   - Psoriatic Arthritis
     - Arthritis upper extremities
     - Characteristic skin lesions
**Herpetic Uveitis**

- HSV
  - H/O unilateral red eye
  - Corneal scarring
  - Active corneal disease
  - IOP increase & iris atrophy
- HZO
  - Characteristic skin lesions
  - Iris atrophy

An 8 y/o presents with a bilateral NG ant uveitis. The parents report she has had knee problems for the past 3+ years. Which of the following ocular findings is NOT part of the ocular triad you should look for to confirm your suspicion of JIA?

1. Corneal Ulcer
2. Cataract
3. Band Keratopathy
4. Glaucoma

**In the same 8 y/o, which lab test(s) would you run, and what results would confirm your suspicion of JIA?**

1. ANA (+), RF (+)
2. ANA (+), RF (-)
3. ANA (-), RF (+)
4. ANA (-), RF (-)
5. HLA-B27 (+)
6. HLA-B27 (-)

**2. Chronic, bilateral (or unilateral), non-granulomatous anterior uveitis**

- Most common cause
  - Juvenile Idiopathic Arthritis (JIA)
    - 80% of pediatric uveitis cases are associated with JIA
    - Slow, chronic onset; mild sx's, many chronic signs
    - ANA (+) triples the risk of uveitis – base f/u's on this
    - RF (-)
    - Tx: NSAID's, steroids, immunosuppresives

**JIA lab tests**

- ANA – very non-specific test
  - Used to confirm an autoimmune collagen vascular disease
    - Lupus and JIA
    - Weaker associations: Sjogren’s, RA, scleroderma, AS, MG
  - 15% of normals have a mildly elevated ANA (diabetics, elderly women)

- RF
  - 80% of RA pts are seropositive
  - Most often JIA patients are RF negative
    - ANA (+) and RF (-) -> significantly increased risk of uveitis in a suspected JIA patient
2. Chronic, bilateral (or unilateral), non-granulomatous anterior uveitis

- More common causes
  - Fuch's Heterochromic Iridocyclitis
    - Low-grade chronic uveitis with iris heterochromia
    - Usually unilateral - cataract & glaucoma
    - Uveitic eye is usually lighter in color
  - Idiopathic
  - Herpetic

3. Chronic, bilateral (or unilateral), granulomatous anterior uveitis

- Most common causes
  - Sarcoid
  - Syphilis
  - TB

A patient presents with a bilateral anterior uveitis w/ mutton-fat KP's. Which lab/radiology tests should be ordered for proper diagnosis?

1. PPD & chest X-ray
2. VDRL & FTA-ABS
3. HLA-B27
4. ACE
5. 1, 2, & 4
6. All of the above

Sarcoidosis

- Systemic granulomatous inflammation -> unknown etiology – Young, black, females
  - Pulmonary – 95%
  - Ocular – 60-70%
  - Skin
- Diagnosis
  - Serum
    - ACE, lysozyme, calcium
    - Chest X-ray, Gallium scan, biopsy of granulomas
- Treatment
  - Immune suppression

Which of the following indicates a patient has an active syphilis infection?

1. PPD
2. FTA-ABS
3. VDRL
4. ACE

Syphilis

- Infection with spirochete *T. pallidum*
  - Primary stage – Chancre
  - Secondary stage – rash palms of hands/soles of feet
    - Most ocular involvement
  - Latent and Tertiary Stage
- Diagnosis:
  - RPR or VDRL – general non-treponemal tests
  - FTA-ABS or MHA-TP – specific treponemal tests
- Treatment:
  - Penicillin
TB
- Infectious disease caused by *Mycobacterium tuberculosis*
  - Very rare
  - Exposure/Cough/Pulmonary involvement
  - Granulomatous anterior uveitis, Choroiditis, phlyctenular keratoconjunctivitis
- Diagnosis
  - PPD – not useful in uveitis patients
  - Chest X-ray/Sputum culture
- Treatment
  - Isoniazid, Rifampicin, Ethambutol, Pyrazinamide

Uveitis Work-up Rule of Thumb
- If the uveitis is:
  - Recurrent
  - Bilateral
  - Severe
  - Granulomatous OR
  - Resistant to standard treatment;
  - AND History does NOT point to a specific condition
  - Non-specific baseline eval
    - Work-up:
      - CBC
      - ESR/CRP
      - ANA/RF
      - HLA-B27
      - Lyme titer (depending on what area of the U.S.)
      - PPD/anergy panel and Chest X-ray
      - RPR or VDRL and FTA-ABS or MHA-TP
      - ACE

Lab Work Costs
- CBC - $9 - 12
- ESR - $5 - 7
- CRP - $18 - 24
- HLA-B27 - $36 - 49
- ANA - $15 - 21
- RF - $8 – 11
- ACE - $20 - 28
- VDRL/RPR - $6 -8
- FTA-ABS/MHA-TP - $18 - 25
- Lyme titer - $24 – 32
- Chest X-ray - $75 – 250
- Total = $216 - 443

Treatment of Uveitis
- Treat the disease properly
  - Minimize complications of the disease itself
  - Minimize complications of the treatment
- 2 main drugs/drops
  - Cycloplegics
  - Topical Corticosteroids
**Treatment**

- Cycloplegia:
  - used for reduction of pain,
  - break/prevent the formation of posterior synechiae
  - also functions in the reduction of inflammation

**Cycloplegics**

- Common cycloplegic agents include:
  - cyclopentolate 1-2% tid for mild-to-moderate,
  - homatropine 5% or
  - scopolamine 0.25% or
  - atropine 1% bid-tid for moderate-to-severe inflammation
  - most common is the use of Homatropine 5% bid
  - be careful using atropine as there is potential for severe systemic side effects
  - Also makes the iris essentially immobile

**Treatment**

- Steroids: necessary for the treatment of active inflammation
- Most common is the use of prednisolone acetate 1% (e.g. Pred Forte 1%)
  - Phosphate form -> does not penetrate cornea well
- Steroid medication that is felt to have less IOP response and report to not need as long of a taper is loteprednol etabonate (Lotemax)

**Treatment**

- Durezol (difluprednate ophthalmic emulsion) 0.05%
  - Dosing QID
  - Thought to be as potent or even more potent when compared to Pred Forte q2h
  - Minimal to no shaking of the bottle
  - No BAK

**Treatment**

- Topical administration is most common though periocular injections and systemic meds are useful for posterior uveitis and difficult cases
- Dosing is dependent upon severity of the inflammation
  - typically you want to hit the uveitis hard and fast!
    - E.g. 1 gtt q 2hrs until the inflammation is gone!
    - If you have a minimal anterior chamber reaction then steroid may not be necessary at all
NOTE: it is crucial to taper your steroid treatment!
- You will have a rebound inflammation if you simply remove your patient from their steroids...
- The taper will be dependent upon how long you have had them on the steroid to get rid of the inflammation!
- Typically, a slow taper is better in order to prevent rebound inflammation
- If the patient has been on the steroid for less than a week a faster taper can be considered.

NSAIDs:
- do not play an important role in the treatment of an acute uveitis
- may be used in the treatment of a chronic uveitis such as in a JRA patient who is using NSAIDs for the treatment of systemic pain.

Immunosuppressive agents (cytotoxic)
- reserved for sight-threatening uveitis that have not responded to conventional treatment
  - e.g. cyclophosphamide
- Antimetabolites (e.g. methotrexate) have been found useful in JRA related iridocyclitis and scleromalacia
- Cyclosporin has a very specific effect on the immune system and has been found useful in posterior and intermediate uveitis

Follow-up
- Every 1-7 days in acute phase depending upon severity and every 1-6 months when stable.
- On each f/u visit the AC reaction and IOP should be evaluated
  - DFE should be performed for flare-ups, when VA affected, or every 3-6 months.

If AC reaction improving, then steroid drops can be slowly tapered.
- cycloplegia can also be tapered as the AC reaction improves.
- slow taper recommended for chronic granulomatous uveitis.

Rules For Managing Uveitis
1. Remember the classifications.
2. Determine if there is corneal involvement & check IOP.
3. Determine the severity.
4. Is this a chronic problem?
5. Treat strongly.