Uveitis Update:

A Clinicians Guide to Diagnosis and Treatment

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Mark Dunbar: Disclosure

- Consultant for Allergan Pharmn
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  - Carl Zeiss Meditec
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  - Reed Exhibitions

Mark Dunbar does not own stock in any of the above companies

Case: 40 yo male

- Pain, redness, floaters LE X 1 wk
- 2 previous episodes: 1st time RE, 2nd LE
- VA: 20/20 OU
- 2++ injection LE
- K- scattered KP LE
- AC- 2+ cell, tr flare LE

Diagnosis: Anterior Uveitis

But what is the etiology?
Are you obligated to work it up?
What would you like to know?

Classification of Uveitis

1987 Intl. Uveitis Study Group (IUSG)

Location

- Anterior uveitis
  - iritis
  - iridocyclitis
- Intermediate uveitis = Pars Planitis
- Posterior uveitis
- Panuveitis

Uveitis Classifications

- Intermediate: Vitreous and peripheral retina
  - Pars Planitis
  - Cyclitis
  - Vitritis
- Posterior
  - Retinitis
  - Choroiditis
  - Retinochoroiditis
Uveitis Classifications

- Panuveitis
  - Involvement of the entire uveal tract
- Endophthalmitis
  - Inflammation involving all intraocular tissues except the sclera
- Panophthalmitis
  - Involves entire globe – often with orbital extension

Anterior Uveitis: Etiologies

- Idiopathic: most common
- Exogenous
  - Infections
  - Non-infectious
    - Surgical
    - Traumatic
    - Chemical
    - Allergic
- Endogenous: immunological reaction

Uveitis By The Numbers

- HLA-B27 related acute anterior uveitis is the most common cause
  - 15.2% of all uveitis cases
- Intermediate uveitis accounts for 7.9% of all cases
- Toxoplasmosis is the most common type of posterior uveitis
  - 4.6% of all cases

Developing a Diagnosis

- Is the disease acute or chronic?
  - Acute: < 6 weeks, chronic: > 6 weeks
- Is the inflammation granulomatous or nongranulomatous?
- Is the disease unilateral or bilateral?
- Where is the inflammation located in the eye?

Developing a Diagnosis

- What are the demographics of the patient?
- What associated symptoms does the patient have?
- What associated signs are present on the physical exam
- How did the disease respond to previous therapy

Making a Diagnosis

Case History: Most important!
- Onset: sudden vs insidious
- Course: short, chronic
- Activity: mild, severe
- Single vs repeated
- Unilateral vs bilateral
- Medical history
**Anterior Uveitis**
- Case History
  - Age, sex, race
  - Pets
  - h/o trauma
  - Dietary habits
  - Systemic disease history
  - Medications
  - IV drug abuse
  - Foreign travel
  - Joint pain/peripheral extremity pain
  - Oral/genital ulcers

**Medical History**
- Arthritis/joint pain
- Which joints involved?
- Back pain, stiffness
- Inflammatory bowel disease
- Skin rashes
- Ulcerative lesions in mouth
- Recent viral illness

**Acute Anterior Uveitis**

**Clinical Signs**
- Redness/ciliary injection
- AC reaction
  - Cells & Flare
- KP’s
- Band keratopathy
- Iris nodules
  (Koeppe, Busacca)

**Variable presentation**
- Granulomatous
  - insidious onset
  - eye more white
- Nongranulomatous
  - Acute onset
  - Red eye
  - No nodules
  - More symptoms
Granulomatous
- Indicates disease may be systemic in nature
- Mutton-fat KP
- Koeppe nodules, Busacca nodules
- Cell and flare
- Posterior synechia

Granulomatous disease may present in a nongranulomatous manner with fine KP and no iris nodules...

nongranulomatous disease will not present in a granulomatous fashion

When do you do a medical work up?

1st time: unilateral, nongranulomatous uveitis and no other significant clinical finding, laboratory work-up is not indicated

Bilateral granulomatous, or any recurrent uveitis (otherwise unremarkable exam) work-up should be conducted
Treatment of Uveitis
- Depends on severity
- Typically Rx topical steroids
- Cycloplegics
- May need IOP lowering medications

Treatment for Mild/Moderate Anterior Uveitis
- Optional depending on symptoms
- Prednisolone acetate, 1% qid
- Cycloplegia depending on Sx
- Oral aspirin or ibuprofen (2 tab q4h)
- Beta blockers if IOP elevated
- Re-evaluate 3-7 days
  - Or prn if worsening

Treatment for Severe Anterior Uveitis
- Prednisolone acetate, 1% q2 to q3h
- Durezol q2h to q 3h – more potent
- Homatropine 5% or Scopolamine 0.25% bid
- Oral aspirin or ibuprofen (2 tab q4h)
- Dark glasses
- Beta blockers if IOP elevated
- Re-evaluate 1-2 days

How Long to Use Medications?
- Depends on the initial severity:
  - If A/C reaction is improving, medication can be continued or reduced
  - D/c cycloplegics when cellular reaction is subsiding and flare is absent
  - Continue steroids until cellular reaction is minimal or absent
  - Steroid should be tapered slowly – one drop per week

How Long to Use Medications?
- Most anterior uveitis will clear within 6 weeks
- Chronic anterior uveitis may require long-term use of low-dose topical steroid
- If pt is a steroid responder, treat IOP (stay away from PGA’s)
- Follow-up should be every 1-6 months depending on findings

Laboratory Tests
- ANA
  - JRA
  - SLE
- ESR - Systemic inflammation
- CXR - Sarcoid, TB
- FTA-ABS - Syphilis
- RPR – Active Syphilis
- PPD - TB
Laboratory Tests
- RF - JRA
- ACE - Sarcoid
- HLA typing
  - Autoimmune
  - Genetic make-up
  - Reiter's, Spondylopathies, Bechet's
- Limited gallium scan - Sarcoid

Back to Our Patient
40 yo male
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Diagnosis

More History
- Past history: inflammatory bowel disease

Does this help you?

Back to Our Patient
40 yo male
- Diagnosis: Anterior Uveitis associated with HLA-B27

HLA-B27 Associated
Anterior Uveitis
- Can occur alone as a distinct entity
- Acute
- Unilateral
- Pain, redness
- 1 to 2 day prodrome
- Men > women
- Nongranulomatous

HLA-B27 Associated
Anterior Uveitis
- Recurrent
- One eye then the other
- Abundant fibrin (no M&F KP)
- Posterior synechia
- May last 2-3 months with Tx
- History: Back pain, Arthropathies, Bowel disease
Other Diseases Assoc with HLA-B27 + Uveitis
- Ulcerative Colitis/ Crohn’s Disease
- Ankylosing Spondylitis

Human Leukocyte Antigen-B27–Associated Uveitis: Long-term Follow-up and Gender Differences
AJO March 2008
- 177 HLA-B27 (+) patients: 54% Male, 46% Female
- Evaluated b/w January 1995 and December 2005
- Average age at onset of AAU was 36 years
- HLA-B27–associated systemic disease developed earlier in males than in females (31 vs 37 years; \( P = .021 \))
  - AAU, HLA-B27–associated systemic disease were more frequent in males than in females (25/75 [33%] males vs nine/54 [17%] females; \( P = .030 \))
  - Over time, males and females risk of developing HLA-B27–associated systemic disease was equal
  - Bilateral uveitis developed more frequently in Females 11/35, [31%] vs. males (6/45 – 13%)

Ulcerative Colitis Crohn’s Disease
- HLA-B27 +
- Inflammatory bowl disease
- Uveitis more common with associated arthritis
- 5-12% develop anterior uveitis
- Non-granulomatous
- Episcleritis
- Idiopathic, chronic, relapsing disease

Ankylosing Spondylitis
- M > F; 20-30 yo
- Unilateral > bilateral
- Acute, intermittent uveitis
- Non-granulomatous
- H/o back pain
- Posterior synecia
- Cataracts
- Secondary Glaucoma

Ankylosing Spondylitis Work Up
- HLA B27 - + in over 90% of pts
- Sacro-iliac X-ray
- ESR - increased during attack

57 y/o White Female
- Blurred Vision at near
- “Has a problem with one of her eyes that has always aroused suspicion when she has had her eyes checked in the past”
- Has been on eye drops at various times - on and off
- VA: 20/20 OU distance: J 3 at near OU
**Fuch’s Heterochromic Iridocyclitis**
- Minimal symptoms - often misdiagnosed
- 90% unilateral
- Fine stellate KP dispersed on entire cornea
- Mild AC reaction
- Iris atrophy - “loss or relief”
- Glaucoma
- Treat glaucoma, not uveitis

**Posterior Uveitis**
- Known disease entities:
  - Often have characteristic picture
  - Lab testing often helps in refinement - confirming diagnosis

**Ocular Toxoplasmosis**
- Intracellular protozoan parasite
  - *Toxoplasmosis gondii*
- Prevalence: 10-90% of pop (30% USA)
- #1 cause of retinochoroiditis
- #2 HIV opportunistic pathogen (encephalitis)
- Significant cause of birth defects or spontaneous abortion

**Posterior Uveitis**
- Anatomical perspective
  - May affect varying layers/structures at different stages
  - Presentations can vary
    - +/- vitritis, +/- choroid
Epidemiology of Toxoplasmosis
- As many as 2 billion people worldwide have *T. gondii* antibodies
- In the US, it is estimated that 22.5% of people are systemically infected
  - Around 2% of these people have ocular involvement
- Prevalence varies greatly between geographic regions and population groups
  - In southern Brazil the systemic infection rate is around 98%, with 17.7% ocular involvement

Toxoplasmosis gondi: 3 Forms of Parasite
- Tachyzoite (trophozoite)
  - Invasive form of parasite
  - Responsible for acute infection
- Bradyzoite (tissue cysts)
  - Encysted form of parasite
  - Cysts may contain 50-3000 bradyzoite
  - Protected from immune host response
- Sporozoite (oocysts)

Toxo: Human infestation
- Ingestion of undercooked meat, chicken
  - Humans eat flesh of an intermediate host which contains tissue cysts
    - Steak tartare, undercooked hamburgers
- Ingestion of oocytes:
  - Humans accidentally contaminate their hands when disposing cat litter - then transfer the oocysts onto foods
  - Kids infested by eating dirt
- Transplacental: tachyzoites cross placenta

Toxoplasmosis Stages in Humans:
- Acute: asymptomatic
  - Ingested by humans
  - Parasite penetrates intestinal mucosa, disseminated throughout body
  - Rapidly multiply in various tissues
    - Predilection for brain, eye, muscle
  - Host defense reacts to produce anti-toxoplasma antibodies

Toxoplasmosis Stages in Humans:
- Chronic (inactive)
  - Cysts form slowly metabolizing inactive parasites (bradyzoites)
- Recurrent
  - Cell walls rupture, releasing active parasites (tachyzoites)
  - May result from immunosuppression
  - Invade/destroy healthy cells resulting in recurrence
### Toxoplasmosis:
#### Congenital vs Acquired
- Most congenital infections are mild
- Severe infections can present with convulsions, calcification of arterioles, or mental retardation
- Higher risk for ocular involvement (~70%)
- Higher rate of macular involvement
  - Worse Visual prognosis

- Acquired infections can present with flu-like symptoms, but many cases are asymptomatic
  - New evidence shows that most toxo cases are acquired postnatally
  - Risk factors for more severe ocular disease include immune status and older age

### Serologic Evidence of Infection
- **IgG**
  - The major immunoglobulin class for serum detection of *T. gondii* infection
- **IgM**
  - Appears 1st week after infection, peaks at 1 month, and usually disappears after 9 months
  - May still be detected in serum more than 2 yrs after infection
  - Can also be naturally occurring, has been found in noninfected people, so may not be the most reliable confirmation
- **IgA**
  - Appears 2-4 weeks after infection, peaks around 2-3 months, disappears within 7-9 months
  - May be a more reliable measure of recent infection

### Ocular Toxoplasmosis:
#### Course of Disease
- Many cases are subclinical, with a healed chorioretinal scar being the only sign of initial infection
- Ocular involvement may not become clinically apparent for months to years after initial infection
- Recurrences are common
  - Develop adjacent to an old scar
  - Netherlands study of 154 pts found that 79% had recurrences within a 5 yr follow-up
    

### Active Toxoplasmosis
#### Clinical Findings:
- Anterior Chamber Cells: Spill over
- Prominent vitritis, “Headlights in a fog”
- Focal area of necrotizing retinitis
  - Often adjacent to old scar - satellite lesion
  - Fluffy white
  - Single solitary lesion (can be multifocal)
  - Macular edema/CME
  - Sclerosed or sheathed vessels

- Focal intense retinal inflammation at the border of an old pigmented retinochoroidal scar
- Clinical presentation can also include granulomatous uveitis, CME, and CNV
Active Toxoplasmosis Clinical Course

- Healthy patients: retinitis heals 1-4 mo
- Virulent organisms may last up to 2 yrs
- Dependent upon host immune system

10 yo ↓ VA RE (20/200)
Flunked school screening
New floaters LE

3 Morphologic Forms

- Large destructive lesions (> 1 DD)
- Punctate inner retinal lesion
  - single or multifocal, mild vitritis
- Punctate outer retinal lesion
  - multifocal gray white
  - Deep retina
  - little to no vitritis
  - slow resolution

4½ months
**Toxoplasmosis: Detection**
- Sabin-Feldman Dye Test: IgM, IgG abs
- ELISA: IgG and IgM antibodies
- Indirect fluorescent antibody test (IFA)
- Diff. Agglutination test AC/HS test
- Uncertainty: FTA-ABS, PPD (anergy) CXR, *Toxocara* ELISA, HIV

**Indications for Treatment**
- Lesion involving or threatening macula
- Lesion involving or threatening optic nerve
- Severe vitritis resulting in reduced acuity
- Smaller peripheral lesions do not need Tx

**Active Toxoplasmosis Treatment**
Depending upon severity:
- Sulfonamides
  - Sulfadiazine, sulfamethazine
- Pyrimethamine (Daraprim)
- Trimethoprim/Sulfamethoxazole (Bactrim)
- Clindamycin
- Corticosteroids
  - Not to be used alone
- Azithromycin

**Toxoplasmosis Drugs**
- Trisulfapyrimidines 1 g qid X 3-4 wks
  - Sulfadiazine, sulfamethazine
  - Lack of bioavailability has led to use of bactrim instead (sulfa + trimethoprim)
  - Inhibits *Pneumocystis c.* (# 1 AIDS OI)
- Pyrimethamine (Daraprim)
  - 50 mg qid loading dose followed by 25 mg bid X 3-4 wks
  - Folic acid antagonist
  - Synergistic w/ sulfadiazine (given in combo)
    - Most common prescribed combination
  - Toxic so given as 3rd drug when other 2 are nonresponsive
  - Causes thrombocytopenia and leucopenia
    - Given with folic acid
- Trimethoprim/Sulfamethoxazole (Bactrim)
  - Trimethoprim 160 mg
  - Sulfamethoxazole 800 mg
  - Less toxic than Pyrimethamine (Daraprim) and Sulfadiazine
  - Work synergistically by blocking the sequential steps in the folic acid pathway
  - 3% experience side effects
    - GI, skin rashes
  - Reduced the rate of recurrences (AJO 7/2002)
Toxoplasmosis Drugs

- Clindamycin 300 mg q 6 hrs
  - Expensive - not approved by FDA for Toxo
  - Macrolide, binds to 50S ribosome
  - Diarrhea 25%

Active Toxoplasmosis
Survey of Uveitis Specialists
AJO 7/2002

When to treat?
- 15% Treat all cases
- Majority Tx based on location or severity of inflammation

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<thead>
<tr>
<th>Location</th>
<th>1991</th>
<th>2001</th>
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<tr>
<td>Parapapillary</td>
<td>78%</td>
<td>85%</td>
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<tr>
<td>Maculopapillary bundle</td>
<td>93%</td>
<td>88%</td>
</tr>
<tr>
<td>Parafoveal</td>
<td>98%</td>
<td>94%</td>
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Active Toxoplasmosis
Treatment Survey AJO
7/2002

<table>
<thead>
<tr>
<th>Drug</th>
<th>1991</th>
<th>2001</th>
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</thead>
<tbody>
<tr>
<td>Pyrimethamine</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td>Sulfonamides</td>
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</tbody>
</table>
  - Sulfadiazine        | 81%  | 55%  |
  - Triple Sulf          | 10%  | None |
| Combination Tx's      |      |      |
  - Bactrim             | 5%   | 32%  |
  - Pyrimethamine/Sulfadoxine | None | 1% |

Other Parasitic Agents
1991 2001
- Clindamycin 55% 45%
- Macrolides
  - Spiramycin None 3%
  - Azithromycin None 1%
- Prednisone 95% 82%

Active Toxoplasmosis Treatment 1991 vs 2001

- Regimen 1: (32%) 29%
  - pyrimethamine, sulfadiazine, folic acid, pred
- Regimen 2: (27%) 13%
  - pyrimethamine, sulfadiazine, folic acid, clindamycin prednisone
- Regimen 3: (16%) (1%)
  - sulfadiazine, clindamycin, prednisone
- Regimen 4: (6%): clindamycin, pred(10%)

Outbreak of Acquired Toxoplasmosis

- Municipal drinking water source of outbreak
- 100 pts with acquired and 12 pts congenital toxo identified
- 21 eyes of 20 patients had retinitis

Outbreak of Acquired Toxoplasmosis

- Campos dos Goytacazes, northern Rio de Janeiro, Brazil
- Reports of uveitis consistent with toxoplasmosis led to a survey of the prevalence and risk factors for Toxoplasma gondii infection in 1997–1999
- Random survey pop at selected schools and army battalion
- 1436 serum samples were tested

Outbreak of Acquired Toxoplasmosis

- Age adjusted results:
  - 84% of the population in the lower socioeconomic group was seropositive
  - 62% Middle class
  - 23% Upper socioeconomic groups, respectively (p<0.001).
- Drinking unfiltered water was found to increase the risk of seropositivity
- May indicate the potential importance of oocyst transmission in H2O