UVEITIS

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Uveitis Definitions:

**Uvea (Latin = grape)**
Middle pigmented, vascular layer: iris, ciliary body and choroid (the layer between retina & Sclera)

**Itis (Latin = inflammation)**

Uveitis can and frequently does involve adjacent structures: Cornea, sclera, vitreous retina, optic nerve
**Uveitis Definitions:**

**Uvea (Latin = grape)**

Middle pigmented, vascular layer: iris, ciliary body and choroid (the layer between retina & Sclera)

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**Uveitis Classification:**

(Historically: Anatomy, Clinical Course, Etiology, Histology)

**SUN** Standardization of Uveitis Nomenclature Working Group 2005

**Etiology**

- Noninfectious/ autoimmune
- Infectious

**Basic 4 anatomical classifications of Uveitis (focus of inflammation)**

1. **Anterior** A/C iritis/iridocyclitis/keratouveitis
2. **Intermediate** Vitreous Pars planitis/posterior cyclitis/hyalitis
3. **Posterior** Retina and Choroid retinitis, choroiditis, neuroretinitis,
4. **Panuveitis** A/C/Vitreous/ Retina & Choroid
Uveitis Classification:

**SUN** Standardization of Uveitis Nomenclature Working Group 2005

**Onset:** Sudden/Insidious

**Duration:**
- Limited: less than 3 months
- Persistent: more than 3 months

**Course:**
- Acute: sudden onset and limited duration
- Recurrent: repeated episodes with periods of inactivity greater than 3 months
- Chronic: Episodes & relapse less than 3 months

**Remission:** Inactive disease for greater than 3 months after stopping TX

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Uveitis Classification:

**SUN** Standardization of Uveitis Nomenclature Working Group 2005

Anterior Chamber Cells

1X1mm high mag. & high intensity light count the cells

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in field</th>
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<tbody>
<tr>
<td>0</td>
<td>&lt;1</td>
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<tr>
<td>0.5+</td>
<td>1-5</td>
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<tr>
<td>1+</td>
<td>6-15</td>
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<tr>
<td>2+</td>
<td>16-25</td>
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<tr>
<td>3+</td>
<td>26-50</td>
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<tr>
<td>4+</td>
<td>&gt;50</td>
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(divide beam ½ if easily over 10 or 20 can help with speed/accuracy)
Uveitis Classification:

**SUN** Standardization of Uveitis Nomenclature Working Group 2005

Anterior Chamber Flare

Grade
- 0 none
- 1+ faint
- 2+ Moderate (but iris and lens clear)
- 3+ Marked (iris and lens hazy)
- 4+ Intense (fibrin or plasmoid aqueous)
**Uveitis Classification:**

**Vitreous Haze** (better indicator of disease activity)
NIH/SUN grading Indirect exam with 20D lens
- 0 = No Flare,
- 1+ = Clear disc and vessels but hazy NFL
- 2+ = Disc outline clear, but hazy vessels
- 3+ = Only Disc visible with blurred margins and detail,
- 4+ = NO view of Disc

**Vitreous Cell** (no current SUN consensus)
- 1X0.5mm high mag. & high intensity light count the cells
- Cells in vitreous strands are likely inactive, those in clear moving fluid active
- 0 = 0
- 0.5+ = 1-5
- 1+ = 6-10
- 2+ = 11-20
- 3+ = 21-50
- 4+ = >50
  (divide beam ½ and double if hard to count)
How (and why) Classify inflammation?

1. Granulomatous or Nongranulomatous
   Based on Appearance of precipitates on corneal endothelium
   1. Granulomatous KP
      1. Less common, but more useful
      1. Larger, yellowish, glassy or greasy appearance = Mutton or meat Fat keratic precipitates, may have serrated borders, collections of plasma cells, lymphocytes and giant cells
      2. Useful because can give diagnostic clue: Sarcoidosis, Lens induced uveitis, Vogt-Koyangi-Harada (VKH), Syphilis, TB, Uveitis associated with MS, IOFB, Sympathetic Ophthalmia
   2. Nongranulomatous KP
      1. More common, less useful
      1. Fine, white colored collections of plasma cells
      2. Can be seen in any form of uveitis
Herpes Uveitis

Anterior Uveitis is the most common type of uveitis over 80%
Herpes simplex or Herpes zoster cause 5-10% of anterior uveitis and is the most common cause of anterior infectious uveitis.

Suggestive Clinical Picture:
Active Skin lesions
Active keratitis and/or corneal anesthesia
Nearly always unilateral
SLE:
active keratitis/scarring/or normal cornea
Usually granulomatous
Iris atrophy or synchie
Can have elevated IOP
Herpes Uveitis

Diagnosis:
Usually Clinical, but can confirm with A/C tap of fluid for PCR or culture

Treatment:
1. Topical Steroids and cycloppegia
2. Oral Acyclovir
3. As needed IOP lowering drops

Herpes Related Uveitis
Glaucomatocyclitic crisis
Posner Schlossman

Clinical Picture/SLE:
Adults, unilateral
Mild, non-granulomatous anterior uveitis
Patchy iris atrophy or loss of iris color
PSC cataract
MARKEDLY ELEVATED IOP

Pathology/associations:
Elevated levels of protoglandins cause increase in Aqueous production
Inflammation causes scaring in TM which decreases aqueous drainage
Associations with Rubella virus/toxocariasis/toxoplasmosis

Treatment
1. Control IOP (meds or surgery)
2. If needed cataract surgery
3. Usually steroids not used long-term
Glucomatocyclitic crisis
Posner Schlossman
### What is Intermediate Uveitis?

1. IU is defined by inflammation concentrated in the anterior vitreous and the vitreous base overlying the ciliary body and peripheral retina, pars plana and accounts for 15% of all cases of uveitis.

   1. Anterior vitreous cells are seen
      1. The cells aggregate = **snowballs**
      2. These aggregates coalesce = **snowmen**
      3. Inflammatory exudate from the pars plana or snowballs or snowmen falling onto the pars plana = **snowbanking**

   2. Retinal phlebitis may occur
   3. Anterior cells may occur
      1. These are usually spillover from the vitreous.

### What is Pars Planitis?

Pars Planitis is IU of unknown cause making up 85-90% of the cases of IU.

- It is the most common type of IU, but is a DX of exclusion.
- Age range 5-40
  - Bimodal: 5-15 years and 20-40 years
- Men = women
- Associated with HLADR15
  - Coding for one of the two HLA-DR2 subtypes
- MS is associated with HLA-DR2
What are the Clinical Findings of Pars Planitis?

80% bilateral, often asymmetric

Children:
- Redness, photophobia, discomfort, a/c reaction

Teenagers and adults:
- More insidious, usual complaint is floaters
  - Spillover a/c reaction
  - Vitreous cells: snowballs
  - Inferior peripheral retinal vessel sheathing (phlebitis)

**CME (10%) most common cause of ↓ acuity**

NVE of snowbanking in 5-10%
- Can evolve into VH, tractional RD or RRD (10%)
- PSC cataracts (15%) and ERMs (5-10%)

IU associated with MS

15% of IU eventually develop MS
- Preceding MS, by 5-10 years

Patients with MS
- IU or retinal periphlebitis may be seen in 5-20%
- Not associated with optic neuritis, systemic exacerbations or disease severity
- IU is milder in MS patients
  - CME less common, treatment less frequently needed
  - Interferon TX of MS does not appear to effect IU

IU and MS patients share HLA-DR2 haplotype
What in the Differential Diagnosis and work up of Pars Planitis?

DDX:
- Syphilis, Lyme, Sarcoid, IU associated with MS, and toxocariasis, in older patient remember intraocular lymphoma

W/U:
- Presence of Clinical Findings
- R/O: Sarcoid, Lyme, Syphilis, toxocarasis

Clinical Course:
- 10% short mild course, 30% smoldering up and down course, 60% have mild but chronic course
Uveitis associated with Juvenile Rheumatoid Arthritis

Juvenile Rheumatoid Arthritis (JRA)

Most common disease associated with iridocyclitis in children. JRA has three types.

20% have Systemic onset (Still Disease).
- Age under 5, fever, rash, lymphadenopathy, and hepatosplenomegaly.
- Joint involvement is minimal or absent initially.
- Eye disease rare – less than 6%

40% have Polyarticular onset
- Five or more joints involved within 6 weeks
- Eye disease uncommon – 7-14%

40% have Pauciarticular onset
- Four or less joints involved within 6 weeks (some have no joint symptoms)

Type 1: girls under five ANA+ chronic uveitis in 25%
Type 2: older boys, 75% are HLA-B27+, usually acute and recurrent rather than chronic
Uveitis associated with Juvenile Rheumatoid Arthritis

JRA associated Uveitis

Risk factors for uveitis: female, pauciarticular, ANA+, most are RHF –

Eye findings: OFTEN WHITE & QUIET
OFTEN FOUND ON ROUTINE EXAMS
Fine KP, cell and flare, posterior synechiae cataract, band keratopathy
Symptoms due occur in some: pain, photophobia and ↓ VA

These findings or history in children = workup for JRA, ANA testing and referral to PCP comfortable with this type of evaluation or to Rheumatologist that sees children.

Uveitis associated with Juvenile Rheumatoid Arthritis

Management – Medical

Topical Steroids mild cases short course
Treat for cell only, watch for complications
Pupil dilation important even with flare, use short acting dilator QHS to prevent synechiae

Periocular steroids
Children go to OR for this

Systemic steroids
Should be managed by PCP → pediatrician
All must be vigilant for systemic and ocular complications

Systemic immunosuppression
Managed by pediatrician or pedi rheum or pedi oculist or adult rheum
Weekly methotrexate can be PO or IM
**Uveitis associated with Juvenile Rheumatoid Arthritis?**

Management – Surgical

**Cataracts**

Inflammation controlled for 3 months

This will be a challenging surgery

To do it well or refer to someone who can

Ideal Referral Surgeon (may not be typical cataract-jock)

Good with parents and kids

Comfortable with uveitic cataracts

Surgery will likely be done in hospital

**Role of IOL?? This is evolving**

young with active no, older and controlled yes

**Glaucoma**

Medical first:

Beta blocker, diamox ok, no alphagan in the very young

Surgery last:

May have to be done with inflammation in order to control IOP

Filters with anti-metabolite or valve/tubes

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**Uveitis associated with Juvenile Rheumatoid Arthritis?**

Management – Surveillance

Patients with JRA (girls, ANA +, pauciarticular)

Tables (AAP and AAO)

**Keys: less than 7, pauciarticular disease, and ANA+**

| JRA Subtype at Onset | <7 Years  
Age of Onset | ≥7 Years |
|---------------------|---------|---------|
| Pauciarticular +ANA | Every 3–4 months  
1 | Every 6 months |
| Pauciarticular -ANA | Every 6 months  
1 | Every 6 months |
| Polyarticular +ANA | Every 3–4 months  
1 | Every 6 months |
| Polyarticular -ANA | Every 6 months  
1 | Every 6 months |
| Systemic | Every 12 months  
1 | Every 12 months |

1 All patients are considered at low risk 7 years after the onset of their arthritis and should have yearly ophthalmologic examination indefinitely.

2 All patients are considered at low risk 4 years after the onset of their arthritis and should have yearly ophthalmologic examinations indefinitely.

3 If no uveitis 4 years after onset of arthritis, should have ophthalmologic examination every 6 months.
Uveitis associated with Sarcoidosis

Sarcoidosis accounts for 3-10% of all uveitis
15-50% of patients with sarcoidosis have uveitis

Sarcoidosis is a systemic disease

10x more common in blacks
Primarily thoracic (90%), but can effect brain, bones, joints, liver
Uncommon in young children, but skin/joint >> chest findings

Key pathological lesion
noncaseating epitheloid cell granuloma or tubercle

Epitheloid cell is a polyhedral mononuclear histiocyte
Tubercle = epitheloid cells + multinucleated giant cells of Langhans type (nuclei at the periphery in an incomplete circle + rim of lymphocytes)

Uveitis associated with Sarcoidosis

Possible genetic link:
Increased HLA-DRB1 in biopsy proven cases

Presence of peripheral anergy
Due to depression in delayed-type hypersensitivity
However, at the target organ site (eye)
Active T-lymphocyte (CD4+) and ΜΦ response leading to granuloma
**Uveitis associated with Sarcoidosis**

**Acute Systemic Sarcoidosis and iridocyclitis**
- Löfgren syndrome
  - Erythema nodosum, febrile arthropathy, bilateral hilar adenopathy, acute iritis
  - responsive to systemic steroids
- Heerfordt Syndrome (uveoparotid fever)
  - Uveitis, parotitis, fever and facial palsy

**Chronic Sarcoidosis**
- 2 years duration, thoracic findings, chronic uveitis
- Thoracic/pulmonary disease major cause of morbidity
- Mortality is 5-10% (neurosarcoidosis)

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**Eye Findings**
- Skin involvement is common
- Orbital and eyelid granulomas
- Conjunctival nodules
- Lacrimal gland infiltration cause of dry eye

**Uveitis**
- Can involve all structures
- May begin as acute nongranulomatous but 60% become chronic granulomatous
Uveitis associated with Sarcoidosis

Main Uveitic Findings
- Mutton-fat KP
- Koepppe and Busacca iris nodules
- Snowballs in the inferior anterior vitreous

Other findings
- Corneal: nummular infiltrates & endothelial opacification
- Angle: posterior and anterior synchiae

Posterior Segment findings – less common than A/C
- Retinal and choroidal granulomas usually ¼ DD in size
- Irregular nodules along venules = candelwax drippings or taches de bougie
- Retinal periphelbitis presents as sheathing
- CME is common
- Disc edema, NVD, NVE can occur

Uveitis associated with Sarcoidosis?

Diagnosis
- Because of its variety of presentation and frequency, it should be considered in every case of uveitis
- If suspicion is strong
  - CXR best screening test (positive in 90%) or CT
  - Lysozyme, ACE are supportive but not diagnostic
- If clinical picture is strong and above are inconclusive consider
  - Gallium scan of head and neck especially used with ACE
  - Steroid treatment make this unreliable
  - Biopsy is useful especially of conjunctival or lacrimal nodules, which are easier than bronchial sample
Uveitis associated with Sarcoidosis?

1. Treatment
   1. Steroids: (Topical, Periocular and Systemic)
   2. Systemic immunosuppresion
      1. MTX or azathioprine, cellcept, infliximab
   3. Remember it is a systemic dz, so get PCP involved in evaluation and management of systemic effects

Sarcoidosis
Sympathetic Ophthalmia (SO)

Rare bilateral, nonnecrotizing granulomatous after injury/surgery to one eye (the exciting eye). Followed by a latent period and the development of uveitis in the uninjured eye (the sympathizing eye).

Lower incidence because we are better surgeons
Better wound closer and techniques (more enucleations vs eviscerations)

Cause of SO is not known, but theories include:
- Hypersensitivity to melanin and melanin-associated protein
- An infectious causal agent
- Sensitivity to retinal S antigen or retinal or uveal proteins

Possible Genetic risk:
- HLA-DR4, HLA-DRw53, HLA-DQw3
- In UK and Japan also see HLA-DRB1*04 and HLA-DQB1*04
- These and VKH are nearly the same
Sympathetic Ophthalmia

Incidence
- 0.2-0.5% in nonsurgical trauma
- 0.01-0.03% in surgical trauma
- Vitrectomy has now emerged as the main surgical risk for the development of SO
  - 1980’s 0.01-0.06%
  - Now may be as high as 0.06-0.12%

Risk factors:
- Old: males, children, elderly
- Newer: no difference in the sexes, lower in kids, still high in the elderly
  - Increased history of previous eye surgery and trauma

Timing of onset
- Traditional: 80% in 3 months, 90% in one year
- Recent: 30% in 3 months, 50% in one year

Sympathetic Ophthalmia

Histopathological Features
- Diffuse granulomatous uveal involvement
- Absence of reaction at the choriocapillaris
- Phagocytosis of uveal pigment by epithelioid cells
- Extension of the granulomatous process into scleral canals and the optic disc

Clinical Features, asymmetrical bilateral panuveitis worse in exciting eye

Unaffected eye
- Can occur within 10 days after injury or surgery, slight redness, mild photophobia, mild problems with near vision
- Progression to panuveitis
  - Mutton fat KP, iris nodules, PAS, vitritis, choroiditis, ERD, papillitis

Injured or operated eye
- Early Panuveitis,
**Sympathetic Ophthalmia**

**Diagnosis**
- Bilateral uveitis following trauma or surgery → **Think SO**
  - Inflammation may occur between 10 days to 50 years following the triggering event, but usually within the year

**Management**
- The course of SO is chronic with frequent exacerbations
  - Topical, systemic or periocular steroids
  - Cycloplegia
  - May need antimetabolite level immunosuppression: cyclosporin
- Overall current treatment for SO is effective and results in good vision over many years
- Removal of blind exciting eye within two weeks of event has been shown to decrease risk of SO or if eye becomes blind after SO develops removal may decrease severity of SO,
  - However, if exciting eye still sees (even LP) most will leave eye because of effective treatment of SO
- Prognosis is reasonable with 50% of patients having 20/40 in at least one eye
Uveitis and Closing Pearls

When seeing a patient with Uveitis:

1. Could it be an infection?
2. Could it be caused from a systemic disease?
3. With Initial Treatment decisions:
   1. Deal with inflammation & IOP
4. With chronic treatment decisions
   1. Deal with Inflammation
   2. Deal with the side effects of the medication to TX the inflammation (toxicity and IOP)
   3. Deal with the IOP from uveitis or meds to treat uveitis
   4. Deal with side effects of uveitis
      1. Eye: cataracts and glaucoma
      2. Systemic: uveitis or TX of uveitis

Questions??
**Vogt-Koyangi-Harada (VKH) Disease**

1. Rare cause of Panuveitis even among the mostly commonly effected groups
   1. Asian & American Indian's between 30-50 years of age
   2. Dark skinned people: Hispanics
2. Cause not known
   1. However, reaction to melanin-associated protein, melanocytes or RPE
3. Overall the bilateral granulomatous panuveitis resembles SO, however these patients have no history of ocular injury or surgery
VKH – 4 Phases

1. Prodromal
   1. Flu symptoms
   2. CNS signs: nuchal rigidity, seizures, coma, loss of consciousness, paralysis, optic neuropathy, CSF → transient pleocytosis
   3. Skin signs in 30% of patients
      1. Alopecia, vitiligo, poliosis
   4. Hearing complaints in 30% of patients
      1. Deafness or tinnitus

2. Uveitic (1-2 days after CNS signs)
   1. Symptoms: photophobia, redness, blurry vision and ocular pain
   2. Signs: bilateral a/c and vitreous cell and Exudative RD – these can be shallow and have a cloverleaf pattern around posterior pole, optic nerve head swelling

3. Chronic or convalescent
   1. Resolution of ERD and gradual depigmentation of the choroid
      1. Producing the orange-red discoloration = sunset-glow fundus
   2. Discrete, round depigmented lesion develop in the inferior peripheral fundus = resolved Dalen Fuchs nodules
   3. Peripapillary atrophy can be seen
   4. Skin changes usually occur weeks to months after the beginning of the uveitic phase, but can occur at the onset
      1. Perilimbal vitiligo (Sugiura’s sign) in more than 75% of cases
      2. Vitiligo, alopecia, and poliosis in 30%

4. Recurrent phase
   1. Increased risk with incomplete treatment of uveitic and chronic phases
   2. Signs: granulomatous anterior uveitis: KP, iris nodules and depigmentation and atrophy
   3. Vision loss due to: Cataracts 50%, glaucoma 33%, CNVM 10%
VKH – Diagnosis and Treatment

1. Diagnosis based on Clinical picture
2. Consider SO
3. Work-up
   1. FA – Multiple areas of focal leakage in early angiogram
   2. LP – lymphocytosis in pt with bilateral panuveitis is very helpful
   3. HLA- haplotyping is helpful
      1. HLA-DR1 & 4 is strongly associated (84%) with VKH in hispanics in SoCal
         1. With HLA-DR1 having a higher relative risk than HLA-DR4
         2. HLA-DRB1*04 and HLA-DQB1*04
4. Treatment
   1. Steroids: topical, periocular and systemic
      1. Taper slowly over 3 months to minimize risk of recurrent phase
      2. If steroids not effective in making eyes completely quiet, must move on to stronger immunosuppressive cyclosporine or MTX.
Behcet Disease (Adamantiades-Behcets)

1. Chronic relapsing occlusive vasculitis
   1. Eastern Mediterranean and Pacific rim of Asia
   2. Old Silk Route established by Marco Polo
   3. Turkey: 100-300/100,000, Japan:8-10/100,000 in Japan, 0.4/100,000 in US
   4. Four classic lesion:
      1. Aphthous oral lesions
      2. Skin lesions, erythema nodosum
      3. Genital lesions
      4. Intracocular inflammation
   5. HLA typing
      1. HLA-B51

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<thead>
<tr>
<th>Clinical criterion</th>
<th>Typical frequency in BBP (%)</th>
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<tr>
<td>1. Recurrent oral ulcer</td>
<td>At least 3 episodes per year, minor aphthous, major aphthous or herpetiform ulceration.</td>
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<tr>
<td>2. Recurrent genital ulcer</td>
<td>70–80</td>
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<tr>
<td>3. Eye disease</td>
<td>Uveitis, retinal vasculitis, cells in the vitreous</td>
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<tr>
<td>4. Skin disease</td>
<td>Erythema nodosum, folliculitis, acneiform lesions outside adolescence, papulo-pustular lesions</td>
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<tr>
<td>5. Positive pathergy test</td>
<td>Vesicular lesion larger than 2 mm, 24-48h after skin prick with 20-22 gauge needle penetrated to 5 mm</td>
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*BBP = Behcet's disease