Ocular Immunology
Uveal Disease
Clinical Applications

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Neurology and Immunology

- Represent the most complex body systems
- Immunology is playing an increasingly important role in understanding disease processes with potentially new treatment options.

Basic Processes

- Defend host from infection (present in all organisms) may become dysfunctional
- House cleaning (autoimmune)
  - Clear metabolic debris
  - Clear environmental waste

"Microbes inhabit just about every part of the human body, living on the skin, in the gut, and up the nose. Sometimes they cause sickness, but most of the time, microorganisms live in harmony with their human hosts, providing vital functions essential for human survival." *

*Coombs & Gell Classification
Hypersensitivity

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Mediators</th>
<th>Clinical examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Allergy (immediate)</td>
<td>IgE IgG4</td>
<td>Anaphylaxis, Asthma ...</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic (Ab Dependent / receptor mediated)</td>
<td>IgG IgM</td>
<td>Complement Thrombocytopenia / Graves</td>
</tr>
<tr>
<td>III</td>
<td>Immune Complex</td>
<td>IgG Complement Neutrophils</td>
<td>RA SLE</td>
</tr>
<tr>
<td>IV</td>
<td>Delayed Hypersensitivity (DH) (self-mediated)</td>
<td>T-Cells</td>
<td>Contact dermatitis, transplant rejection</td>
</tr>
</tbody>
</table>

Vertebrate Immune System(s)

Innate
Adaptive
Complement

Vertebrate Immune System(s)

Innate
Adaptive
Complement
Vertebrate Immune System(s)

- **Innate**
  - Natural & stereotypical
  - 1st & immediate line of defense
  - Cutaneous
    - Barrier: stratum corneum (cuticular layer) impermeable to water etc
    - Keratinizing stratum epithelium cells / molecules send alarm when invaded
  - Mucosa (eye)
    - Leukocytes (PMN in tears) & molecules with antimicrobial properties (pH / lysozymes etc)

- **Adaptive**
  - Acquired, specific, remembered & tolerizable
  - 1st exposure not immediate (hrs to days to build response); 2nd is quicker
  - Spleen & lymphoid tissues, including, thymus, bone, marrow, & mucosa-associated lymphoid tissue, generates antigen specific lymphocytes & supporting cells:
    - T - cells
    - B - cells
    - Antigen-presenting Cells (dendritic)
    - Macrophages

Innate Vs. Adaptive

- **Innate**
  - Stereotypical response to patterns of repeating surface molecules of pathogens
  - Macrophages / neutrophils "pattern recognition receptors" stimulate release of chemical mediators that initiate plain vanilla inflammatory response
    - Alpha lipotrieholic acid (gm + bacteria)
    - Lipopolysaccharide (gm – bacteria)
    - Killer lymphs lyse virus

- **Adaptive**
  - Specific
  - Develops memory
  - Humoral arm recruits innate immunity.
  - Tolerizable (recognizes self & can be regulated)
  - Normal (ideal) combined host response is
    - Predictable, appropriate and specific
    - Measured & of finite duration ending with little or no damage to host.

Complement System

- Complex array of serum-borne molecules with enzyme activity generated in cascade fashion. Straddles innate and adaptive since it can be activated by either bacterial products or antigen-antibody interactions. Has different pathways:
  - **Alternate:** Bacterial triggered immunoglobulins: facilitate phagocytosis.
  - **Classic:** Direct lysis
Afferent Limb:

- Exogenous antigen (pathogen) gain access to body penetrating skin, mucous membrane or directly into blood (periodontal, eye / life support tubes)
- Professional APCs (bone marrow derived mature dendritic cells) capture the antigen
- Sensitize lymphocytes

Immunity Induction

Afferent Limb:

- Professional APCs (bone marrow derived mature dendritic cells) capture the antigen and:
  - 1st ….. ingest & process antigenic material to present to T lymphs

Immunity Induction

Afferent Limb:

- Cleave material into epitopes / antigenic material.
- Protein based antigens are loaded into class I (peptide fragments) or class II (peptides) MHC-HLA encoded molecules located w/i the APC.
- Non protein based antigens’ fragments of lipids / carbs are loaded onto conventional or atypical class I
- Migrate to cell surface.

Generic Immune Reflex Arc

Central processing limb occurs when antigen-specific T & B cells activate, clone & differentiate into effectors (T cells / Abs)

Effferent limb begins as effectors disseminate & find offending antigen / pathogen

Immunity Induction

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- Migrate to cell surface.

HLA (Human Leukocytic Antigen) alleles

- HLA = MHC (human major histocompatibility complex)
- Short arm of Chromosome 6
- Distinguishes self from non – self & presents foreign proteins to stimulate T – cells.
- Class I
  - Found on all somatic cells
  - bind endogenously synthesized proteins from viral infected cells
  - presents to CD 8 T-cells
- Class II
  - Binds exogenously engulfed proteins from APC
  - Presents to CD4 T-cells

Afferent Limb:

- 2nd …., those with class I or II encoded molecules that have migrated to cell surface
  - detach from surrounding cells / matrix either through cell adhesion molecules or response to chemotactic factors that encourage migration into lymphatics.
  - travel to draining lymph nodes (spleen for blood / some ocular borne)
Afferent Limb:

- Acquire co-stimulatory signals needed to arouse naïve lymphocytes (T-cells)
- Present antigenic fragment loaded onto HLA coded marker molecule and simultaneously stimulate T-cell with co-stimulatory molecules
  - cytokines (cell mediators including interleukins, chemokines, colony-stimulating factors, interferons, & growth / trophic factors) IL-12 or IL-10
  - cell surface ligands (B7.1, B7.2, ICAM (intercellular adhesion molecule)…

Central Processing Limb:

**Professional APCs**

Guide replication / differentiation of T & B Cells creating a large range of functionally distinct effector modalities.

- B lymphs
  - produce IgM
  - differentiate into plasma cell progeny that produce: IgG1, IgG2, IgG3, IgA1, IgA2 and IgE.
- T cells develop into
  - CD8+ cytotoxic
  - CD4+ (T helper)

Central Processing Limb:

- Effector arm initiated with
  - Exquisite antigen specificity
  - Regulator T-cells (TH2 variety) modulates response for a more eye tissue friendly response
  - T & B cell memory is developed

Generic Immune Reflex Arc

Central processing limb occurs when antigen-specific T & B cells activate, clone & differentiate into effectors (T'cells / Abs)

Effector limb begins as effectors disseminate & find offending antigen / pathogen

TH1 cells

- secrete IL-2, IFN-γ (cytokine), and lymphotoxin.
- IFN-γ induces B cell production of proinflammatory Abs & complement fixation.

TH2 cells

- secrete cytokines IL-4, IL-5, IL-6, IL-10 & IL-13 which promote B cell differentiation that produce non-complement fixing Abs (IgG Abs as well as IgA & IgE.)
- Mitigate TH1.

Generic Immune Reflex Arc

Central processing limb occurs when antigen-specific T & B cells activate, clone & differentiate into effectors (T'cells / Abs)

Effector limb begins as effectors disseminate & find offending antigen / pathogen
Immunity Expression

Efferent Limb:

Multi-step process whereby effectors are delivered to an antigen localized site via peripheral circulation to destroy / eliminate the pathogen / antigen.

Antigen localized by

- Ab binding
- Antigen sensitized T-cells

Efferent Limb

Ab binding.

- alone maybe sufficient to eliminate antigen (viruses)
- inflammatory response initiated by Ab then interacts with complement or Fc-receptors on macrophages, neutrophils, etc. Antigen is
  - lysed
  - phagocytized

Fragment crystallizable.

Efferent Limb

Professional APCs (bone marrow derived) are involved in induction of immunity

When APC = viral infected epithelial cell
CD 8+ T cells will lyse antigen if MHC-HLA is class I but the epithelial cell will likely be destroyed.
OK for epithelial cells but t-cell cytotoxicity is not user friendly for eye tissue.

Non-professional APCs (local epithelial cells, fibroblasts etc) can present antigenic peptides i.e. expression of immunity.

Efferent Limb

Where localized antigen is recognition by sensitized t-cell, HLA-MHC bound antigenic peptides must be presented. (specific response)

CD4+ T TH1 type expression

- Natural killer cells and TH1 type CD4+ T cells secrete IFN-γ that will recruit non-professional APCs from parenchymal tissue that will respond to class II HLA molecules.
- Secretes IL 2
- lymphotoxins

Non-complement fixating reactions

TH2 modulates TH1 to reduce the immunopathologic burden. However the reverse is also true.

CD4+ T TH2 type CD 4+ T

- IgE dependent. Responsible for skin & mucous membrane immediate allergic reactions type I
- Secretes cytokines IL-4, IL-5, IL-6, IL-10 & IL-13. Non-complement forming reactions

Micro environment controls immune expression: start, stop & limit.

- Regional APCs
- Tissue trophic T & B cells
- Microvasculature
- Secondary lymphatics
- Parenchymal cells
- Neurotransmitters

How?

T Cells may not be activated (anergy)
- Locally produced (parenchymal) TGF-β or IL-10 transform T cells into suppressor cells.
Regulation

Systemic Suppressor cells & cytokine interactions

− Afferent
− Central
− Efferent

Regional Immunity

• Mucosal
  − GI
  − Conjunctival
• Brain (e.g. respiratory ctr)
• Maternal / Fetal Interface
• Intraocular

Regional (Ocular)

Three types

• Epithelial (periocular)
  − TH1 cell
  − Most violent
  − Rapid neutralization of pathogen
  − Pathogens capable of penetrating intact skin
• Mucosal (conjunctiva)
  − TH2 cell
  − IgA
  − IgE producing B cells
• Immune privilege (extreme form of regional control)
  − Eye (intraocular) ACAID

• anterior chamber
  • associated immune deviation

Features that contribute to Ocular Immune Privilege

1. Microanatomical Factors
2. Molecules Expressed on Ocular Parenchymal cells
3. Soluble Factors in the Ocular Microenvironment

Microanatomical factors

Immune Privilege

• Blood ocular barrier is selectively permeable
• Antigens are presented in the spleen NOT lymphatic system therefore favors less traumatic humoral response than cell mediated.
• Tolerance promoting APCs. MHC II identify self vs non-self.

Microenvironment Tolerance

Central processing (spleen / thymus)

• Cell types differ from generic
  − CD8+ T cells produced (gentle)
    • Precursors to cytotoxic T cells
  − Precursors to suppressor T cells
  − Does NOT produce CD4+ T cells that mediate delayed hypersensitivity (DH) / graft rejection.
  − Atypical APCs activate subsets of T & B lymphs
    • TH2 (not TH1) cells types react to second An exposure
    • B cells produce NON-compliment fixation Abs.

Microanatomical factors

Immune Privilege

• APCs derived from bone marrow or recruited local uveal tissue macrophages behave different when exposed to aqueous
  − deficient in production of IL-12
  − deficient expression of CD40
  − Secrete TGFβ
  − Via TM pass to spleen white pulp (less aggressive immune expression); NOT lymphatics!
Microenvironment Tolerance Efferent

- Characterized by **lack of**
  - compliment fixing Abs
  - IFNγ that mediates delayed hypersensitivity (therefore limits delayed hypersensitivity)
- Local control therefore
  - Creates an intraocular environment inhospitable to dh.
  - Promotes systemic response to eye derived Ans that is selectively deficient in dh

2. Molecular features that promote Immune Privilege

- Expressed on parenchyma *(not professional APCs)*
  - Low Class I MHC & NO Class II MHC resulting in feeble T-cell immunity.
  - Ocular tissue & cornea express ligands for CD95 (aka – death receptor protein) that stimulate apoptosis of activated T-cells who express **surface molecule CD95**

3. Soluble Factors Immune Privilege

- Aqueous Humor inhibits T-cell activation but allows activated T-cells to function
- AH prevents killer T-cells from lysing targets.
- Abs cannot activate complement fixing abiility.
- Endothelium most tolerant.

Immune Privilege
The Good & The Bad

- Reduces inflammation to limit collateral damage preserving vision.
- ACAID is responsible for high rate of K transplant (PKP / DSEK). Selectively improving ACAID w/o compromising eye will decrease rejection rate.
- Allows tumor growth with little immune response.
- Likely prevents killing HSK virus resulting in recurrent manifestations.

Autoimmunity (dysfunctional)
Inflammatory Uveal Disease
Pathology

- Infectious
  - Endogenous
  - Exogenous
- Granulomatous
  - Large white cells
    - Macrophages
    - Monocytes
    - Epithelioid cells
  - Ab/An complexes
  - TB / sarcoid
- Non-infectious / autoimmune
- Non-Granulomatous
  - Small white cells
    - Lymphocytes
    - Monocytes
    - Fibrin
    - Streptococcal

Infectious Etiology

Must treat infection!!!  
But also limit collateral damage from immune response.

- Exogenous
  - Compromised globe / barrier.
  - Trauma
  - Collagenase secreting organisms
  - Immune response produces metalloproteases.
    - Saprophytic organisms i.e. staph
    - Pseudomonas or Neisseria
- Endogenous
  - Blood / neuron borne
  - TB
  - Syphilis / Lyme (Borrelia Burgdorfei)
  - Candidiasis (other fungal)
    - Histo
    - Toxo
    - Herpes (Simplex / vericella)

Infectious Etiology

Index of suspicion is elevated.

- Exogenous
  - History of compromised globe / barrier
    - Surgical trauma
    - Non surgical trauma
    - Evidence on physical examination (PE).
    - External / slit lamp
      - DFI
- Endogenous
  - Blood / neuron borne
  - H/O risk exposure to TB
  - Social hx Syphilis / Lyme (Borrelia Burgdorfei)
  - Immune compromise or chronic exposure
    - Candidiasis (other fungal)
    - Toxo
    - Hx / PE Herpes (Simplex / vericella)
    - Unresponsive to Tx

Non - Infectious Etiology

Limit collateral damage from immune response.

- Collateral damage
  - Secondary Glaucoma from PAS / PS / debris
  - CME
  - Optic neuritis / disc edema
  - Retinal ischemia from vasculitis (NVE)
  - Direct tissue damage
- Histopathology
  - Auto immune (dysfunctional)
  - Posterior and some anterior uveitis’ are T+ cell mediated diseases with both Th1 & Th2 phenotypes involved.
  - Enhanced cytokine activity
Non-Infectious Etiology

DDX

- Predicts tissue damage
- Along with initial presentation and clinical course, DDX dictates type & aggressiveness of treatment
- Word of caution!!
  - white cells without sx's, response to tx or apparent etiology may need to r/o systemic lymphoma (CLL / non – Hodgkin's).

Assessment
(infectious & non-infectious)

- AC / PC / vitreal cell classification
- No standard
- Grade each modified Schlagel
  - Rare 1 cell searched
  - Occasional 1-3 in beam
  - 1+ = 4-10 in beam
  - 2+ = 11-15
  - 3+ = 16-30
  - 4+ = too many to count
- DFE!!
- Differentiate cell type, fibrin & protein (flare)
  - White cell (large / small)
  - Pigment cell vs melanin
  - Red cells
- Example
  - AC 2+ small white cells with 1+ pigment and 1+ flare
  - PC 1+ small white cell
  - Dark adapt & use bright non-conical beam

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Non-Infectious Etiology

Trauma ? Collagen Vascular Sarcoïd Idiopathic

Why not all traumas induce uveitis

Lupus
Spondyloarthritis RA

DDX Pars Planitis

HLA related dx

Trauma & uveitis

- Traumatic uveitis is self limiting.
  - Compliant treatment should yield quiescence without recrudescence.
- If not consider:
  - Social implications
  - Trauma incited dysfunctional (auto) immune uveitis
  - Tailored systemic work-up

DDX

- Systemic work up yield?
  - Variable data from studies
  - Referral centers higher yield?
  - Better understanding of uveitis will reduce idiopathic %.
  - Yabuki et al reported 1999 Dev in Ophthalmology Uveitis Update with respect to idiopathic specific uveitis syndromes "it has been elucidated that the patients with these syndromes have characteristic genetic backgrounds, especially HLA (human leukocyte antigens) alleles."
**DDX**

**Systemic work up yield?**

  - 60.1% yield
  - 400 consecutive patients
  - 51.4 % anterior uveitis
  - Bechet's > 60% but panuveitis

- Rosenbaum Arch Intern Med. 1989 May;149(5):1173-6 (Oregon)
  - 40% yield
  - Retrospective 236 consecutive charts
  - 53% anterior uveitis showed causal systemic relationship
  - Reiters, Sjogrens, sarcoid, & ankylosing spondylitis.

**When is a systemic work up indicated?**

- Bilateral
- Recurrent or non – responsive to tx
- Severe
- Hx
  - Joint or skeletal pain / deformity
  - Dematologic features
  - Social (risk for STDs) TB (urethritis)
  - GI (diarrhea)
  - Ethnic risk(s)

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**Cases #1**

- 50 y/o CAM c/o OD painful photophobia & globe sensitive to touch
- 20/20 OD OS with small pupils + LRAPD & light – near disassociation; Motility / VF full
- Sclera showed diffuse injection
- OD AC rxn 2+ cell / flare
- + serum VDRL & FTA – Abs
- Hx intercourse c prostitute x 1 mo ("only once")
- 1x10^9 units IV Pcn G x 10 days

**Case #2**

- 60 y/o NAM c/o OS painful photophobia & globe sensitive to touch; recurrent following successful tx with oral NSAID (Indomethacin 50 mg x3 x 1 mo)
- 20/30 OD 20/25 OS
- Motility / VF full / pupils normal s APD
- OD Sclera diffuse injection c AC 2+ cell / flare
- OD inferior infiltrate dx staph marginal keratitis
- Poor response to topical pred / e-mycin ung / moxi gtts
- Progressed to Wesley immune ring
- Dx changed to HSV; responded well to acyclovir 800x5x4 mos then maintenance dose.

**Cases 2a ...... 2f**

- 30-65 y/o male c/o mild to 4+ photophobia often asymmetric (including unilateral)
- VA 20/20 20/25
- Motility / VF wnl
- May have h/o trauma; if so non resolving uveitis
- AC 1+3+ white cell (large / small), 1+ flare
- May have ciliary flush. Few have scleral injection.
- Poor response to topical steroids (including Pred Forte) or recrudescent.

**Cases 2a ...... 2f**

- Lab w/u is negative:
  - RPR / MHA-TP
  - PPD or Quantiferon Gold
  - ACE / serum lysozyme (maybe CXR)
  - RF
  - ESR / CBC c diff
  - ANA (SS / DS DNA)
Cases 2a .... 2f

- 2nd level w/u is negative:
  - Lyme titer
  - ANCA c/p
  - HLA – B27

Empirically tx for HSV
(? AC tap c PCR)
Acyclovir 800x5x4 mos
(or equivalents Famciclovir 500 x2)

Case #3

- 65 y/o AAM c/o OD painful photophobia & globe sensitive to touch; h/o ulnar drift and morning joint pain.
- 20/20 OD OS with motility / VF full / pupils wnl -RAPD
- Scleral diffuse injection OD 2-3+cell mild flare.
- Labs ordered: CBC c diff, RF, ANA, ESR, ACE, Lysozyme, HLA, ANCA, & claimed – PPD in recent past. RF = 500. Dx RA already being seen by Rheumatology. They weaned of oral Pred (steroid responder) and started Imuran because of scleral uveitis.

Case #3 cont’d

- responded poorly to immunosuppressant tx (Imuran max daily dose, fundus nodule noted and Quantiferon Gold ordered and was positive.
- ID consulted but since chest CT negative and patient denied night sweats, weight loss and lethargy, was started on INH 300 mg daily. Simultaneously was started on anti-TNF Humira sub c q 2 wks. Sclerouveitis resolved.

Case #4

- 44 y/o AAM c/o blurred vision x 2 weeks (far and near)
- VA 20/40 20/20
- Pupils sluggish no RAPD
- AC OD 2+ large white cell 1+ flare
- AC OS 1+ large white cell 1+ flare
- No synechiae posterior or peripheral (gonio!)
- Large pigmented KP bilateral
- Venous sheathing
- Med Hx: HTN on lisinopril 40mg once daily

Case #4

- DDX: sarcoid, TB, luetic
- Labs:
  - ACE 45 (lab normal 52)
  - Quantiferon Gold neg
  - RPR and MHA-TP neg
- Necrotizing (caseating) vs non - cheesy granulomas
Case #5

- 23 y/o male just discharged from army c/o acute photophobia x 2 wks (thought it would “go away on its own”).
- VA 20/25 OD OS
- Pupils sluggish; motility VF normal
- AC 2+ cell 1+ fibrin 2+ flare OU
- Medical Hx: normal exiting PE at discharge

Case #5

- What question can you ask this young veteran that would significantly help your DDx?
- What is your treatment?

HLA (Human Leukocytic Antigen) alleles

- HLA = MHC (human major histocompatibility complex)
- Short arm of Chromosome 6
- Distinguishes self from non–self & presents foreign proteins to stimulate T–cells
  - Class I
    - Found on all somatic cells
    - Bind endogenously synthesized proteins from viral infected cells
    - presents to CD8 T-cells
  - Class II
    - Binds exogenously engulfed proteins from APC
    - Presents to CD4 T-cells

HLA related diseases

Reiter’s Syndrome (Reactive Arthritis)

- Hans Reiter discovered in young Prussian army soldier
- Systems (recurrent)
  - Peripheral & axial arthritis
  - Enthesitis (lower’s heel)
  - Urethritis / prostatitis
  - Mucocutaneous lesions histopathologically same as psoriasis
  - Ocular (uveitis / conjunctivitis)
  - Aortic insufficiency & neuropathies
- Histopathology
  - Exposure to Chlamydia?

HLA related diseases

Behcet’s Disease (BD).

- Affects all body systems
- Aphthous ulcers
- Ocular (uveitis)
- Dermatologic
- Genital ulcerations

- HLA – BS1 Middle – far east
- HLA – BS101 98% expresses in Japanese, Greek & Spanish
  - BUT not BD in Japanese
  - Immigrants to Hawaii: no difference with controls
  - Likely environmental factor
    - Syphilis
    - Organophosphates
    - Heavy metals
    - MICA gene another candidate
    - Polymorphism (GCT/AGC)n
    - 74% + HLA BS1
    - Also – HLA BS1 BD cases

HLA related diseases

Sarcoidosis

- Affected systems
  - Lungs
  - Ocular (uvea retina)
  - Cardiac
  - Derm
  - Lymph
  - Etc.
- Histopathology
  - Accumulation of Activated CD4+ T–cells
  - Alveolar macrophages
  - Granulomas ectopic source of ACE

- HLA – BS – DR 3, 5 & 6 Caucasians
- HLA – DR52 Japanese

- HLA – B8 – DR3, 5 & 6 Caucasians
- HLA – DR52
- Japanese
HLA related diseases

VKH (Vogt Koyanagi Harada)

- Affected systems
  - Panuveitis
  - Hearing loss
  - Tinnitus
  - Alopecia
  - Vitiligo
  - Poliosis
- Histopathology
  - Selective destruction of melanocytes (CD4+ >> CD8+) expressing CD25 & CD26 antigens.
  - CD4+HLA-DR+ lymphocytes found in aqueous.

HLA related diseases

Ankylosing Spondylitis (AS)*

- Affected systems
  - Inflammatory arthritis
  - Axial Skeletal
  - AAU that is recurrent non-granulomoutous in 30%.

HLA related diseases

Juvenile Arthritis (JRA/JCA)

- Affected systems
  - Inflammatory arthritis
  - Axial Skeletal
  - Iris granulomas
  - < 16 yrs
  - (JCA European definition different)
- HLA DR8, DR5, & DR6
- HLA Class II
- HLA B27 only in males
- Large variability in study results

HLA related diseases

Acute Anterior Uveitis (AAU)

- Affected systems
  - Fulminant irido (cyclitis)
  - Acute few month subsides
  - Recurrent
  - Difficult to tx
- Histopathology
  - Fibrin
  - Sticky PAS / PS
- HLA B27
- MICA – A4 allele found in Caucasians even if neg for HLA – B27

HLA related diseases

Birdshot Retinochoroidopathy

- Multiple chorio retinal lesions
- HLA – A 29
- Specifically two peptides derived from carboxy – terminal sequence of the human retinal soluble antigen that is bound to HLA – A29

HLA related diseases

Sympathetic Ophthalmia (SO)

- VERY similar to VKH panuveitis.
- Fuch Dalen spots ?
- No ethnic predilection
- HLA – DR 4
<table>
<thead>
<tr>
<th>HLA related diseases OHS</th>
<th>HLA related diseases Spondyloarthropidies</th>
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<tbody>
<tr>
<td>• Chorioretinal disease</td>
<td>• Ankylosing Spondylitis</td>
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<tr>
<td>• No cells in AC PC or</td>
<td>• Reiter’s (reactive arthritis)</td>
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<tr>
<td>vitreous; if so, consider</td>
<td>• Chohn’s</td>
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<tr>
<td>different DX!</td>
<td>• Ulcerative Colitis</td>
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<tr>
<td></td>
<td>• Psoriatic Arthritis</td>
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<td>• Behcet’s Disease</td>
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<td></td>
<td>• SLE</td>
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<td>• Lenssen et al 1995 AJO reported</td>
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<td>66% HLA B27 uveitis had spondyloarthritis compared to 6% who were HLA B27 negative.</td>
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