I have no financial conflicts to report
940-1010 Ali-ibn-Isa described uveitis with poliosis
1906 Vogt published first case
1926 Harada described a posterior uveitis with exudative RD associated poliosis and pleocytosis in the spinal fluid
1929 Koyanagi described 6 cases of iridocyclitis associated with poliosis, vitiligo, and added dysacusia and alopecia
1939 Babel called it V-K-H Syndrome (VKH?)

Posterior uveitis, serous retinal detachment, and CSF pleocytosis in the absence of extraocular manifestations
Harada’s Syndrome is not recommended terminology
VK Syndrome.....

More common in darkly pigmented races
~8% of uveitis in Japan is VKH
Unusual in persons on northern European descent
Many of the patients seen in the USA have American Indian or Eskimo heritage
Age: 2nd to 4th decade of life most common
Etiology

- Exact etiology is unknown
- Thought to be an inflammatory condition directed against melanin containing cells
- Thought to be a cellular immune response because of close contact between lymphocytes and uveal melanocytes
- IL-2 dependent T cells found with specificity to melanin containing cells

- T lymphocyte is predominant infiltrating cell in the choroid (CSA and Neoral!)
- Peripapillary choroid is the predominant site of granulomatous inflammatory infiltration
- Larger proportion of CD4 compared with CD8
- Clinical and pathological similarity to Sympathetic Ophthalmia
- HLA – DR4

Animal Studies

- Animal studies have shown that a VKH-like disease is inducible in rats by immunization with peptides derived from proteins of the tyrosinase family, which are found in melanocytes
- Rats develop uveitis 12 to 21 days after immunization, followed by fundus depigmentation at 2 to 3 months.
- Histopathologically, the rats had granulomatous inflammation in the choroid and iris, similar to that observed in patients with VKH disease
Animal Studies
- A VKH like syndrome occurs naturally in the Akita dog.
- Deafness in dogs associated with merle and white colored dogs (Malamute).
- EMO “foot in mouth disease” at Ophthalmologic veterinarian meeting in Vegas!

Histopathology
- Granulomatous panuveitis
- Diffuse nodular lesions of epithelioid cells surrounded by lymphocytes and plasma cells
- No sparing of choriocapillaris
- More scarring

VKH Stages
- Prodrome Phase
- Meningeal Phase
- Ophthalmic Phase
- Convalescent Phase
- Chronic/recurrent Phase
Characteristics of patients with VKH seen at the NEI.


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Females 59 (78.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White/Native American ancestry</td>
<td>17 (22.7)</td>
</tr>
<tr>
<td>African-American/Native American ancestry</td>
<td>39 (52.0)</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Oriental</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Age (mean, yr)</td>
<td>32.8 ± 12.6</td>
</tr>
<tr>
<td>Duration of disease (mean, mo)</td>
<td>29.0 ± 50.7</td>
</tr>
</tbody>
</table>

Systemic manifestations
- Ocular only 12 (16.9)
- Ocular + cutaneous 10 (14.1)
- Ocular + neurologic 30 (42.3)
- Ocular + cutaneous + neurologic 19 (26.7)

Prodromal Stage
- Prodromal stage: patient may complain of headache, orbital pain, stiff neck, vertigo and sometimes fever
- Also reported: sensorimotor hemisyndrome, cognitive brain dysfunction, mild facial weakness
- Spinal Fluid: Mostly lymphocytes and monocytes with normal CSF to serum glucose level (will ultimately disappear)
  - Can show melanin-laden macrophages

Meningeal Phase
- Acute onset in previously healthy patient
- Last 1-4 weeks
- Gradually merges into ophthalmic phase
- Highly variable course
- 50% in VK and 90% in Koyanagi’s
Neurologic findings
- Encephalitis and Meningitis (25-70%)
- CSF Pleocytosis (97% within 4 weeks)
- Cranial Nerves 3, 4, 5, 6, 8
- Hemiparesis and Hemiplegia
- Dysarthria and Aphasia
- Papillary
- Transverse Myelitis
- Papilledema
- Psychosis

Auditory Problems
- Usually involves higher frequencies
- Detailed auditory testing needs to be performed
- Some will have tinnitus without an objective decrease in hearing
- Intermediate cells in the stria vascularis of the mammalian cochlea are melanocytes
- Melanin may protect against trauma to the cochlea (aminoglycosides/loud noise)
How many senses do we have?
Skin lesions

- Sensitivity to touch of both hair and skin during prodromal phase
- Convalescent Stage
  - Alopecia (70%)
  - Vitiligo (63%) axilla too
  - Poliosis (90%)
- Hispanic people have a lower incidence of dermatologic involvement

Who loves ya?

Worst "comb-over"... ever! Notice the alopecia and poliosis (ie. white hair)
Bilateral disease
- May present unilateral but 94% have involvement of both eyes two weeks after presentation
- Granulomatous Inflammation with mutton fat KP
- Sugiura’s sign (perilimbal vitiligo)
  - Occurs in Asian patients ~85%

Early finding can be shallowing of the AC because of swelling of the ciliary processes along with mild IOP↑
- UBM has shown ciliochoroidal detachment
- Can have hypotony too
- Glaucoma associated with this can be very difficult to control
Anterior ocular findings

- Thickened iris can occur
  - Makes PI's difficult and close quickly
  - Iris often adheres to the lens completely allowing angle closure with a plateau iris

Anterior Findings

Scleritis

- Rare presentation in dark skinned people
- Scleral perforation
- Presumably at site of emergence of scleral nerves
Posterior Eye Findings

- Disc edema/papillitis (87% of patients)
- Severe vitreous inflammation
- Multifocal choroiditis
- Exudative retinal detachment
- Dalen-Fuchs nodule equivalents
- Perivasculitis
**Convalescent Phase**

- Resolution of ocular findings over 12 months
- Cutaneous findings (55%)
  - Vitiligo
  - Alopecia
  - Poliosis
- Dysacousia, Deafness & Vestibular (75%)
- Chorioretinal scarring
Massive chorioretinal scarring

As disease process begins to wane, a characteristic depigmentation of the posterior portion globe occurs (Asian patients)

Less pigmented patients in US get a pronounced “Blonde” fundus

**Sunset Glow Fundus**

- Massive chorioretinal scarring
- As disease process begins to wane, a characteristic depigmentation of the posterior portion globe occurs (Asian patients)
- Less pigmented patients in US get a pronounced “Blonde” fundus
Acute stage: multifocal punctate hyperfluorescent lesions at the level of RPE that gradually enlarge and pool in the subretinal fluid. 70% have disc leakage. Vascular leakage, sheathing and staining are rare. CNV occurs in up to 11% of eyes.
RB - 16 yr old identical twin with complete alopecia, hearing loss and High School Prom date concerns. Her identical twin sister had no disease.
**Ultrasonography**

- Diffuse thickening of the posterior choroid with low to medium reflectivity
- Serous RD around the posterior pole or inferiorly
- Vitreous opacities without PVD
- Posterior thickening of the sclera or episclera
- Scleritis, TB, Sarcoidosis, Leukemia, and Lymphoma can appear similar

**MRI**

- Discriminates choroid from sclera so can tell between VKH and primary scleral disease
Criteria for VKH

- 1 – No trauma history
- 2 – No laboratory evidence for another disease
- 3 – Bilateral ocular disease
  - Early manifestations – diffuse choroiditis with RD
  - Late manifestations – depigmentation or pigment clumping
- 4 – Neurologic/Auditory findings
  - Meningismus, HA/NA, Tinnitus, CSF pleocytosis
- 5 – Cutaneous findings
  - Alopecia, Poliosis or Vitiligo

Complete – Criteria 1-5 must be present
Incomplete – Criteria 1-3 must be present plus 4 (neurologic) or 5 (cutaneous)
Probable (ocular only) – Criteria 1-3 present

Highly variable course over many years

VKH clinical diagnosis

- Complete – Criteria 1-5 must be present
- Incomplete – Criteria 1-3 must be present plus 4 (neurologic) or 5 (cutaneous)
- Probable (ocular only) – Criteria 1-3 present


- 1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
- 2. No clinical or laboratory evidence suggestive of other ocular disease entities
- 3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)
  a) Early manifestations of disease
  (1) Evidence of diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction or optic disc hyperemia) which may manifest as (a) focal areas of subretinal fluid or (b) bullous serous retinal detachment
  b) Late manifestations of disease
  (1) History suggestive of prior presence of early findings noted in 3a and either (2) or (3) below, or multiple signs from 3.
  (2) Ocular depigmentation: either (a) nummular chorioretinal depigmented scars or (b) retinal pigment epithelium clumping and/or migration or (c) recurrent or chronic anterior uveitis
  (3) Neurological/auditory findings (may resolve by time of evaluation)
  a) Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back; or a combination of these factors); Note that headache alone is not sufficient to meet the definition of meningismus
  b) Tinnitus
  (c) Cerebrospinal fluid pleocytosis
- 4. Neurological/auditory findings (may resolve by time of evaluation)
  a) Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back; or a combination of these factors); Note that headache alone is not sufficient to meet the definition of meningismus
  b) Tinnitus
  (c) Cerebrospinal fluid pleocytosis
- 5. Intergumentary findings (not preceding onset of central nervous system or ocular disease)
  a) Alopecia, or
  b) Poliosis, or
  b) Vitiligo
Initial and aggressive treatment appears to be associated with a shorter duration and less progression of the disease. Inside the United States, high dose oral corticosteroids (1-2 mg/kg) and if fail then IV. Outside the United States, clinicians may frequently admit patients to the hospital for IV as first-line. Anecdotal evidence that early, aggressive tx reduces recurrences and the development of complications. Whether this is true remains to be proved in a prospective clinical trial.

Patients are treated with tapering steroids on average for 6 months. Severe cases need a treatment for 1 year with a slow gradual taper. Periocular and intraocular steroids. Cataract (aphakia) and Glaucoma Rx. Other IMT added for long term control: Cyclosporin, Imuran, Cyclosporine (Neoral) and Tacrolimus (FK-506) and Cellcept (mycophenolic acid) are considered good options based on etiologic mechanism.
50 – 60% retained 20/50 or better in one eye
25-45% retained 20/50 or better in both eyes
45% had worse than 20/200 in one eye
25% had worse than 20/200 in both eyes
Bilateral granulomatous uveitis that occurs after either intentional or unintentional penetrating trauma to one eye.

Trauma to the exciting eye results in an inflammatory response to that eye as well the sympathizing eye.

1000AD Agathias: “The right eye when diseased often gives its suffering to the left”

1583 Bartisch: “When one eye is injured the other good eye is besides in danger”

1818 Wardrop: Noted veterinary practice of destruction of the injured eye to preserve the good one

1830 McKenzie: Clinical description named the entity

1905 Fuchs: Classic histologic studies

Louis Braille (1809-1852):
Devised the writing system of Braille in the early 1800’s
Penetrating injury to OS at age 2 by a leather awl.
Gradually lost his sight in OD and blind by age 4 of SO!
Heard a lecture by Charles Barbier at age 12 about a “Soldiers, silent 12 dot system to be able to speak in the dark.”
Braille invented a 6 dot system.
Epidemiology

- M>F
- 16% eye injuries in Civil War got SO
- None in WWII, Korean or Vietnam Wars
- 2-5/1000 Nonsurgical penetrating injuries
- 1/10,000 surgical cases

- Anesthetic
  - Mortality: 1.4/1000-1/5000
  - Morbidity: MI 1.3/1000, urine 2.3/1000

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Number of Procedures</th>
<th>Years Studied</th>
<th>Types of Anesthesia</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurtner &amp; Billet</td>
<td>N/A</td>
<td>1946-54</td>
<td>General-100% Local-96% General-88%</td>
<td>N/A*</td>
</tr>
<tr>
<td>Quigley</td>
<td>42,001</td>
<td>1952-72</td>
<td>Local-50% General-60%</td>
<td>0.10%</td>
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<tr>
<td>Patrascu et al</td>
<td>31,322</td>
<td>1962-71</td>
<td>Local-50% General-49%</td>
<td>0.08%</td>
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<tr>
<td>Becker et al</td>
<td>10,278</td>
<td>1962-77</td>
<td>Local only</td>
<td>0.00%</td>
</tr>
<tr>
<td>Kaplan &amp; Rehn</td>
<td>214,000</td>
<td>1956-78</td>
<td>N/A</td>
<td>3%</td>
</tr>
<tr>
<td>Lang</td>
<td>14,889</td>
<td>1977-79</td>
<td>Local-50% General-50%</td>
<td>0.015%</td>
</tr>
</tbody>
</table>

*Three million deaths per year in ophthalmology in the United States.
Sympathetic Ophthalmia

- It can begin several days after the injury to decades later
- 30-80% by 3 months
- 50-90% by 1 year
- 0.2-0.5% of eyes with nonsurgical trauma develop SO
- Vitrectomy probably has highest risk of the surgical procedures (0.06-0.1%)

Prospective surveillance for SO in the UK and Ireland
23 were identified over 15 months
Most frequent cause of SO in this group was retinal surgery
Earliest onset of symptoms was 3 weeks
Only 33% developed in the first 3 months
Less than half in one year

First described in 1905 by Fuchs
Massive lymphocytic infiltration, and nests of macrophages, epithelioid cells, plasma, eosinophils and multinucleated giant cells
Sparcs choriocapillaris
Dalen-Fuchs nodules: contain macrophages, epithelioid cells and RPE cells and occur between Bruchs membrane and the RPE
Early in the disease CD4+ cells predominate, as the disease becomes chronic CD8+ cells predominate…‘A pile of canon balls’

**Histopathology**

- Zonal granulomatous reaction to the lens is often found in association with SO
Animal Model
- Experimental Autoimmune Uveitis (EAU) is often considered an animal model for SO
- Circulating anti-S-antigen antibodies have yet to be detected in patients with SO

Presentation
- Photophobia and accommodation
- Granulomatous mutton fat KP
  - Can be nongranulomatous early
- Moderate to severe vitritis
- Multiple yellow-white lesions in the periphery
  - Sometimes become confluent
  - Clinical appearance of Dalen-Fuchs nodules
Clinical spectrum ranges from mild to very severe

- Swelling of the disc
- Circumpapillary choroidal lesions
NLP OS due to multiple vitreoretinal surgeries OS. New onset blur OD.
Similar to VKH
ON leak, papillitis
Dalen Fuch (drusen like)
Multiple choroidal leaks (not retinal vasculature)
No exudative RD
Lens Induced: Zonal, unilateral, granulomatous, choriocapillaris involved, no Dalen Fuchs
VKH: Skin, hearing, hair, CNS, involve choriocapillaris
Post operative endophthalmitis

Differential Dx of SO
"If vision is still unimpaired, applying appropriate treatment at the appropriate time in order to preserve vision with God’s help.”

Bartisch 1583

- Remove Blind, Painful, Unsightly inciting eye prior to or within 2 weeks to prevent SO
- No benefit if greater than 2 weeks
- Don’t remove inciting eye with useful vision it may be the better seeing eye
- Prednisone (taper over 6 months)
- Regional Steroids
- CSA, Cytoxan, MTX
Debate between enucleation and evisceration

- Started in 1972 in a report by Green et al
- 4 cases of SO were noted after evisceration (2 before 1949)
- No mention of total number of eviscerations

Debate between enucleation and evisceration

- Levine 1999 looked at 90 eviscerations done in the Cleveland area
- 51 reported for follow up and no SO cases were reported
- Surveys to oculoplastics (61%), uveitis (37), ophthalmic pathology (41%)
  - 5 cases of SO out of 841 eviscerations
  - 2 nontraumatic, 3 traumatic

Debate between enucleation and evisceration

- Theoretical increased risk of SO with evisceration
- No hard proof one way or the other because it is so rare
- Has been postulated that the risk of eviscerating an unknown malignancy is higher than SO
Dr. Frederick Blodi’s caveat made in 1963 regarding this subject is still the most appropriate:

- "Whether we want to take the risk of this rare—but certainly occurring—severe complication [SO], against an alleged cosmetic advantage, is up to the conscience of every ophthalmologist".

Debate between enucleation and evisceration