Infectious Uveitis: From Diagnosis to Specific Therapy

13 June 2017
08:00 - 09:30hrs
Room 116

HAND-OUTS
Fuchs uveitis

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3. Hôpital La Pitié-Salpêtrière, Paris, France

Fuchs Heterochromic uveitis described in 1906 by Fuchs represents between 1.2 - 4.5% of 1,2 uveitis. Unilateral in more than 90% of cases, its evolution is chronic and insidious. It is easily identified in its complete form (described below), whose main features are mild intraocular inflammation with diffuse keratic precipitates (KPs), heterochromia, absence of synechiae and vitritis 1,3:

Signs:
Absence of acute functional signs, patients complain of floaters and visual blur. In day light heterochromia is more easily identifiable than at slit lamp, the eye is white At slit lamp: presence of small, white, stellar keratic precipitates (KPs) small and /or medium-sized KPs may have a granulomatous aspect, dispersed throughout the endothelial surface. No peri-keratic circle is observed. The flare and cells in the aqueous are discrete and automated photometry shows hardly values above normal (average 11 ± 5 photons / ms preoperatively normal <8) 4.

The iris atrophy is diffuse and leads to iris heterochromia. It is often absent in brown irises reason why Fuchs heterochromic uveitis in now often called Fuchs uveitis. Atrophy of the anterior surface of the iris with the attenuation of the iris crypts can lead to a velvet aspect. Atrophy of the posterior surface of the iris can produce discrete diffuse transilluminable area. After aqueous tap, cataract surgery or minor trauma, angle bleeding may occur, which is the Amsler sign. 5,6. In rare cases, crystals iris can be found in these patients (Russell bodies), they reflect light during an examination at the slit lamp 7-8. They represent plasma cells filled with antibody 7,9. It may rarely involve small iris nodules on the collar (Busacca nodules) or more frequently on the sphincter (Koeppe nodules). They are usually smaller than in cases of sarcoidosis. In children, the form is often incomplete and heterochromia often only occurs in adulthood. There is no irido-crystalline synechia. They can however be found in a holder eye Fuchs uveitis 10 after postoperative inflammation of the anterior segment. 11,12.

The appearance of a posterior capsular cataract over the years is the rule. Vitreous inflammation is an important component of diagnosis and has been described in 74% of cases but could be present in all cases 13. Anterior vitreous condensations are sometimes dense.

Elevated intraocular pressure is common and secondary glaucoma is present between one third and one half of the long course and its frequency is increased after cataract surgery 1,3,10,12,14-17. Different mechanisms have been implicated in its genesis: trabeculitis which gives
a hypertonia that responds to transient corticosteroid therapy, abnormal angular vessels, trabecular sclerosis, angle lesions, or cortico-induced glaucoma.

Chorioretinal scars were found in the context of Fuchs uveitis by Fuchs himself and by many authors. These lesions are generally small, atrophic and/or pigmented.

<table>
<thead>
<tr>
<th>Diagnostic Signs of Fuchs Heterochromia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of hyperemia</td>
</tr>
<tr>
<td>Unilateral in more than 90% of cases</td>
</tr>
<tr>
<td>Iris heterochromia (not always in brown iris)</td>
</tr>
<tr>
<td>Diffuse KPs, including stellar KPs</td>
</tr>
<tr>
<td>Flare and cells (+) in aqueous</td>
</tr>
<tr>
<td>No posterior synechiae</td>
</tr>
<tr>
<td>(Nodules of Koepp small size)</td>
</tr>
<tr>
<td>Vitreous Inflammation</td>
</tr>
<tr>
<td>Subcapsular cataract</td>
</tr>
<tr>
<td>Secondary glaucoma (often with late onset)</td>
</tr>
<tr>
<td>Amsler sign</td>
</tr>
<tr>
<td>Chorioretinal scars</td>
</tr>
<tr>
<td>Insidious evolution</td>
</tr>
<tr>
<td>Favorable prognosis</td>
</tr>
</tbody>
</table>

Physiopathogeny:

Many theories regarding the etiology and pathogenesis of Fuchs uveitis have been proposed. In the past, Fuchs uveitis related to toxoplasmal toxocariosis, or herpes infection, however now the rubella virus and cytomegalovirus (CMV) are selected as the main causes of this uveitis. Local synthesis of IgG1 has been described in 9/11 patients with Fuchs uveitis. Aqueous is the seat of lymphocytic infiltrates cytotoxic CD8 and clonal composition of these TL (CD8+CD28-) showed a restriction translating one antigenic immune response. In contrast to several autoimmune forms of uveitis, Fuchs uveitis could not be linked to HLA antigens. Recently rubella has been implicated in the genesis of Fuchs uveitis. Of 52 eyes with Fuchs uveitis, 52 (100%) had increased anti-rubella specific GIs in the HA and 28% of the HA tested were positive in rubella PCR, demonstrating the extreme sensitivity of this test. However controls aqueous taken during intermediate uveitis complicating multiple sclerosis also had elevated rubella specific IgG in 73% of cases which demonstrates the lower specificity of this test. But since these results were confirmed by others.
We previously found in our European study that 93% have a significant Goldmann-Witner-Desmonts coefficient (GWc) (>3) for rubella, whereas the GWc for HSV or toxoplasmosis were insignificant. In this study, the vaccination status of the patients was not mentioned, indeed an English group described that after the introduction of rubella in the national immunization program in 1969, the number of patients seen with Fuchs uveitis had dropped 4.48% patients/year (born between 1919-1958) was 1% in the cohort born after 1958. Another author recently mentioned that a subgroup of young patients with Fuchs uveitis had been vaccinated within the question whether a live attenuated vaccine or subclinical infection before vaccination could induce Fuchs uveitis.

A recent article by Dr. Chee (Singapore) group showed the presence of CMV in 23/104 (22.8%) patients with unilateral hypertensive anterior uveitis (without rubella). Of these 23 patients, 18 had an array of Posner-Schlossman syndrome, but 5 had a typical clinical picture of Fuchs uveitis. These data suggest that CMV may also be a significant causative agent of Fuchs uveitis, particularly in Asia. However this might differ in Europe, in our referral hospitals for uveitis in Brussels, Fuchs uveitis is relatively common like previously described, while only 2 patients were found to have a PCR and/or a CWc positive for CMV (unpublished data). Moreover, in our recent study including 15 patients with CMV anterior uveitis, 14 patients had a Posner Schlossman uveitis while only one patient had a Fuchs uveitis.

**Diagnostic:**

The diagnosis is essentially clinical. In some incomplete Fuchs uveitis, it is now reasonable to perform an aqueous tap in order to detect the presence of a viral genome (mainly rubella or CMV) and to measure the production of specific antibodies to calculate the Goldmann-Witmer coefficient. The combination of these two tests would increase the chances of diagnosis.

**Evolution:**

Fuchs uveitis is a chronic disease without spontaneous remission. It has a low inflammatory activity and a slow evolution, which does not require anti-inflammatory). The chronicity of the functional discomfort and the aspects of precipitates and vitreous condensations are sometimes the occasion of an over-treatment using long-term immunosuppressors.

Factors that lead to decreased visual acuity and influence prognosis are either cataracts that occur in all cases over a long period of time or glaucoma or, to a lesser extent,
the presence of vitreous opacities that are mainly bothersome. Of these complications, it is the glaucoma that is often difficult to treat and which can be source of severe loss of visual function. Macular edema does not complicate this chronic pathology and is only observed in some cases after cataract intervention.

**Treatment:**

Due to the low rate of inflammatory activity of the anterior segment, no local or systemic anti-inflammatory treatment is necessary. At the same time, as there is no formation of synechiae, their prevention by topical mydriatic treatment is also unnecessary. The favorable visual prognosis has been reported in several studies after cataract surgery in cases of Fuchs uveitis. The cataract surgery is usually phacoemulsification with the implant in the bag without oral corticosteroid therapy. The maximum medical treatment of secondary glaucoma is unsatisfactory in more than half the cases (50 to 73%) requiring filtration surgery often associated with antimitotic.

**Conclusion:**

Fuchs heterochromia is one of the most frequent intraocular inflammations, but often under diagnosed, especially when heterochromia is not present or is mild. Nevertheless, it is very important to rapidly suspect Fuchs uveitis in order to avoid many complementary examinations and especially to avoid local or systemic corticotherapy or even immunosuppressive treatment which are sometimes prescribed in the long term by mistake. Its diagnosis remains until today, essentially clinical. Nevertheless, rubella and to a lesser extent CMV, have been demonstrated as probably implicated as causative agent of FUCHS UVEITIS.

**References**


4. Tran VT, Guex-Crosier Y, Herbort CP. Effect of cataract surgery with intraocular lens implantation on inflammation in chronic uveitis: A


Anterior Uveitis

- Most frequent intraocular inflammation
- Multifactorial etiology
  - Assoc. with systemic dx. (HLA-B27)
  - Infect associated
  - "Idiopathic"
- Often unilateral
- Recurrent
- Impact on Visual acuity
- Therapy: respect. its etiology

Viral associated uveitis

Herpetic anterior uveitis: Mixing classical and newer entities

Financial Disclosures
Uwe Pleyer

- Abbott S, L
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- Amgen C
- Bayer/Schering C, S
- BMBF S
- Bausch & Lomb C, S, L
- Cellseed S
- Centocor C
- Deutsche Forschungsgemeinschaft S, C
- Esba Tech S
- Novartis S, C, L
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Es liegt kein finanzielles Interesse an einer der genannten Produkte oder Instrumente vor.

Uwe Pleyer
Humboldt-University, Berlin

Herpetic anterior uveitis: Mixing classical and newer entities

Uwe Pleyer
Humboldt-University, Berlin
Infectious diagnosis

"Koch Postulates"

1. The microorganism must be found.
2. The microorganism must be isolated from a diseased organism and grown in culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified.

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Diagnostic approach

[SUSPECT/EXCLUDE INFECTIOUS ETIOLOGY!]

- Fuchs uveitis syndrome (FHC)
- HSV, VZV
- Sarkoidosis
- Lues, Tbc, Toxoplasmosis
- VKH Syndrome
- HLA-B27 assoc.
- Posner Schlossman Syndrome
- Juvenile idiopathic Arthritis
- M. Behcet

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Herpetic anterior Uveitis
(HSV, VZV, EBV, CMV)

**Signs**

- Low grade inflammation
- With - w/o keratitis
- Chronic-undulating course
- Unilateral (90%)
- All Ages
  Peak age > 50 y.

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Herpetic anterior Uveitis
(HSV, VZV, EBV, CMV)

**Signs**

- Granulomatous / nongranulomatous uveitis
- Distorted pupilla (sphincter atrophy)
- Iris changes
- Depigmentation (Heterochromia)
- Reduced cornea sensitivity (with keratitis)

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Herpetic anterior Uveitis
(HSV, VZV, EBV, CMV)

**Signs**

- Initial: IOP increase (trabeculitis)
- Pigmented endothelial precipitates
- "Kirchenfensterphänomen" (nekrot. vasculitis)
- Moderate response to topical steroids

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Herpetic anterior Uveitis
(HSV, VZV, EBV, CMV)

**Signs**

- Approx. 30% in Zoster Ophthalmic
- (Non)-granulomatosus uveitis
- Variable course
- More severe clinical course!
- Hypopyon + hyphema

**Complications**

- Iris atrophy (20%)
- Sec. glaucoma
- Cataract
- Phthisis bulbi
Herpetic anterior Uveitis
Differential diagnosis: HSV - VZV

<table>
<thead>
<tr>
<th>Signs</th>
<th>HSV Anterior Uveitis</th>
<th>VZV Anterior Uveitis</th>
<th>HSV versus VZV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival redness</td>
<td>6/46 (13%)</td>
<td>23/37 (62%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>1/55 (1.8%)</td>
<td>20/37 (54%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous keratitis</td>
<td>2/56 (3.6%)</td>
<td>12/37 (33%)</td>
<td>0.073</td>
</tr>
<tr>
<td>KPs present</td>
<td>47/56 (84%)</td>
<td>29/37 (76%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Cells ≥2+</td>
<td>8/56 (14%)</td>
<td>21/37 (54%)</td>
<td>0.641</td>
</tr>
<tr>
<td>Posterior synechiae</td>
<td>4/55 (7.3%)</td>
<td>14/37 (38%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Heterochromia</td>
<td>13/56 (23%)</td>
<td>0/37</td>
<td>0.19</td>
</tr>
<tr>
<td>Inflammatory cells in vitreous</td>
<td>45/56 (84%)</td>
<td>10/23 (43%)</td>
<td>1</td>
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</tbody>
</table>


Herpetic anterior Uveitis: Therapy
HSV, VZV

<table>
<thead>
<tr>
<th>Aciclovir</th>
<th>Foscarnet</th>
<th>Valaciclovir</th>
<th>Brivudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>dosis per day</td>
<td>3x5mg/kg/KG i.v.</td>
<td>5x800mg p.o.</td>
<td>2x90mg/kg/KG i.v.</td>
</tr>
<tr>
<td>Longterm dosis</td>
<td>2 - 3 x 1500 mg oral</td>
<td>2 - 3 x 1500 mg oral</td>
<td>2x5mg/kg/KG i.v.</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Head</td>
<td>Head</td>
<td>Head</td>
</tr>
</tbody>
</table>

Herpetic anterior Uveitis: Therapy
HSV

<table>
<thead>
<tr>
<th>Dosis per Day</th>
<th>Aciclovir</th>
<th>Foscarnet</th>
<th>Valaciclovir</th>
<th>Brivudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v.</td>
<td>3x5mg/kg/KG</td>
<td>5x800mg p.o.</td>
<td>2x90mg/kg/KG</td>
<td>4x125mg p.o.</td>
</tr>
<tr>
<td>Oral</td>
<td>3x5mg/kg/KG</td>
<td>2x5mg/kg/KG</td>
<td>1x125mg p.o.</td>
<td>0</td>
</tr>
</tbody>
</table>

Adverse effects
Head | Head | Head | Head |

Prävention VZV: Zostavax®

- Placebokontrollierte, doppelblinde Studie zur Zoster Prävention
- 38.546 Probanden
- > 60 Jahre
- 1x ZOSTAVAX (n = 19.270)
- Placebo (n = 19.276)

Endpunkt
- Wirksamkeit des Impfstoffs*
- 95 % KI
- Inzidenz von Zoster 51 % 44 bis 58 %
- Inzidenz Neuralgie 67 % 48 bis 79 %
- HZ Schmerz „Score 61 % 51 bis 69 %

Viral associated uveitis

Aqueous humour analysis: Charité

<table>
<thead>
<tr>
<th>HSV (40%)</th>
<th>VZV (36%)</th>
<th>CMV (15%)</th>
<th>Toxo (10%)</th>
<th>Rub. (5%)</th>
<th>HSV - VZV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>HLA</td>
<td>HLA</td>
<td>HLA</td>
<td>HLA</td>
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</tr>
<tr>
<td>IRU</td>
<td>ICE</td>
<td>VKH</td>
<td>IRU</td>
<td>ICE</td>
<td>VKH</td>
</tr>
<tr>
<td>Fuchs Uveitis Syndrome</td>
<td>Fuchs Uveitis Syndrome</td>
<td></td>
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<td></td>
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</tbody>
</table>

1/2004 - 6/2012 nu.1863
**Herpetic anterior Uveitis (HSV, VZV, EBV, CMV)**

**Profile 1**
- Non HSV/VZV
- Steroid resistant inflammatory
- Ocular hypertensive syndrome


**Profile 2**
- Corneal endothelitis
- "Coin shaped" keratic precipitates


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**Viral associated uveitis**

**Posner-Schlossman-Syndrome**

Aqueous humor analysis (n= 33)*

- CMV 16 (52%)
- HSV 8 (24%)
- VZV 3 (9%)


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**Posner-Schlossman-Syndrome**

**Signs**
- Recurrent trabeculitis
- Mild anterior uveitis
  - Few cells
  - Mild flare
- Few granulomatous precipitates
- Recurrent, acute IOP > 50 mmHg
- Asymptomatic

**Posner-Schlossman-Syndrome**

**IOP increase; DD**
- Fuchs Uveitis Syndr.
- HSV, ZVZ, CMV
- Sarkoidosis
- Lues, TB, Toxoplasmosis

**Posner-Schlossman-Syndrome**

**Therapy**

CMV +

- **Ganciclovir**
  - **Topical**
  - **System. (Valganciclovir)**
  - **Intravitreal**

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**Herpetic anterior Uveitis**

**Therapy: CMV**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Diagnosis</th>
<th>Follow-up (months)</th>
<th>Duration of therapy (months)</th>
<th>Recurrence</th>
<th>Baseline VA</th>
<th>Final VA</th>
<th>Lines changed</th>
<th>Baseline IOP (mmHg)</th>
<th>Final IOP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/46</td>
<td>Brachioitis</td>
<td>30</td>
<td>36</td>
<td>Yes</td>
<td>20/70</td>
<td>20/600</td>
<td>−12</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>M/46</td>
<td>Brachioitis</td>
<td>30</td>
<td>36</td>
<td>No</td>
<td>20/600</td>
<td>20/70</td>
<td>+12</td>
<td>8</td>
<td>9</td>
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<tr>
<td>F/30</td>
<td>Brachioitis</td>
<td>13</td>
<td>3.5</td>
<td>No</td>
<td>20/100</td>
<td>20/40</td>
<td>+4</td>
<td>20</td>
<td>12</td>
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<tr>
<td>F/30</td>
<td>Brachioitis</td>
<td>13</td>
<td>3.5</td>
<td>No</td>
<td>20/100</td>
<td>20/30</td>
<td>+2</td>
<td>12</td>
<td>16</td>
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<tr>
<td>M/47</td>
<td>Brachioitis</td>
<td>24</td>
<td>2</td>
<td>No</td>
<td>20/100</td>
<td>20/30</td>
<td>+18</td>
<td>16</td>
<td>17</td>
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<tr>
<td>M/56</td>
<td>FUS</td>
<td>12</td>
<td>2</td>
<td>Yes</td>
<td>20/35</td>
<td>20/30</td>
<td>+1</td>
<td>27</td>
<td>7</td>
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<tr>
<td>F/56</td>
<td>FUS</td>
<td>6</td>
<td>2.5</td>
<td>No</td>
<td>20/35</td>
<td>20/30</td>
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<tr>
<td>M/44</td>
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<td>2.5</td>
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<td>20/30</td>
<td>+7</td>
<td>15</td>
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<tr>
<td>M/46</td>
<td>FUS</td>
<td>15</td>
<td>2.5</td>
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<td>+7</td>
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<tr>
<td>F/39</td>
<td>FUS</td>
<td>17</td>
<td>2.5</td>
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<td>20/30</td>
<td>20/30</td>
<td>+3</td>
<td>23</td>
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<tr>
<td>M/56</td>
<td>FSS</td>
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<td>20/70</td>
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<td>+12</td>
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<tr>
<td>M/58</td>
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<td>7</td>
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<tr>
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<td>20/20</td>
<td>20/25</td>
<td>+4</td>
<td>29</td>
<td>11</td>
</tr>
</tbody>
</table>

*Loading dose valganciclovir 900 mg twice daily for at least two weeks
Maintenance therapy valganciclovir 450 mg twice daily for at least 6 weeks

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**Viral associated uveitis**

- HSP, HSV, VZV
- CMV
- Fuchs Uveitis-Syndrome
- Posner-Schlossman Syndrome

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**Fuchs' Uveitis-Syndrome (FUS)**

Ernst Fuchs (Wien, 1906): Characterized 38 patients

- **Classical clinical findings**
  - Heterochromia (100%)
  - mild, chronic Cyclitis
  - Cornea precipitates (fine, disseminated) (76%)
  - no extraocular inflammation
  - Cataract (87%)
  - predominant younger patients (-30 y. age)


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**Infectious etiology?**

- **Rubella virus**
- **Intraocular Antibody synthesis (> 90%)**
- **Positive PCR-findings**
- **CMV**
  - Positive PCR-findings**

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**Aqueous humour analysis: Charité**

![Aqueous humour analysis graph](image)
Summary: Typical findings

HSV/VZV Anterior Uveitis
- Older patients
- Acute manifestation
- Cornea involvement
- Posterior synechia
- Fibrinexsudation(VZV)

CMV Anterior Uveitis
- Posner Schlossman Syndrome
- Highest IOP
- Low inflammatory activity:
  - „Never“: Fibrin

Summary: Classical findings

Hurle Virus + (FUS)
- Younger patients
- Chronic (persist.) course
- Low activity: 0/ Fibrin, Ze++
- Often: Vitreous ++, Cataract

Summary: Typical findings

HSV/VZV Anterior Uveitis
- Older patients
- Acute manifestation
- Cornea involvement
- Posterior synechia
- Fibrinexsudation(VZV)

Summary: Clinical findings support suspected etiology

- Therapy INDICATION in HSV/VZV (Acyclovir + Steroide)
- Therapy RESTRICTION in Rubella Virus (FUS)
- Therapy OPTION in CMV (Gancyclovir + Steroide)

Important role of aqueous humor analysis!

Summary: Viral anterior uveitis

- Encompasses broad spectrum of anterior uveits
- Significant morbidity
- Often late diagnosed
- Clinical findings may provide diagnostic hints
- Analysis of aqueous humor analysis is valuable
- Long term prevention necessary

Summary: Viral anterior uveitis

- Encompasses broad spectrum of anterior uveits
- Significant morbidity
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- Analysis of aqueous humor analysis is valuable
- Long term prevention necessary

Aqueous humor analysis
New Diagnostic tools for ocular tuberculosis

B. Bodaghi
Pitie-Salpetriere Hospital, Paris, France

The author acknowledges no financial interest in the subject matter of this presentation
Introduction

• Major challenge
• Sight-threatening condition
• A wide spectrum of clinical manifestations
• Recent but well-established diagnostic tools
• True prevalence of ocular TBC remains unknown
• Global emergency for the WHO
• 0.3-0.5% of uveitis cases in tertiary centres in the US
Nearly 2 billion people, or one-third of the world’s population infected by TB, and that 10% of the infected people are symptomatic.
TB mortality in 2013
Ocular Signs Predictive of Tubercular Uveitis

Amit Gupta, Rima Bansal, Vishal Gupta, Ansh Sharma, and Pradeep Ramakantan

METHODS

**Purpose:** To determine ocular signs predictive of tuberculosis, choroiditis, periphlebitis, and panuveitis. Because ocular tuberculosis is a rare condition, ocular presentations in the form of choroiditis or panuveitis are often misdiagnosed. By identifying ocular signs predictive of tuberculosis, timely treatment can be provided.

**Objectives:** To (1) determine whether ocular signs predictive of tuberculosis can be identified in patients with ocular tuberculosis, (2) to identify ocular signs predictive of tuberculosis in patients with ocular tuberculosis, and (3) to determine whether ocular signs predictive of tuberculosis can be identified in patients with ocular tuberculosis.

**Patients and Methods:** A retrospective, observational, cross-sectional study was conducted to determine the ocular signs predictive of tuberculosis. Inclusion criteria included patients with unilateral or bilateral ocular tuberculosis who were enrolled in the study from January 2010 to December 2015. Outcome measures were determined by comparing the frequencies of ocular signs predictive of tuberculosis in patients with tuberculosis and patients without tuberculosis.

**Results:** A total of 100 patients were enrolled in the study. Of these, 50 patients had ocular tuberculosis and 50 patients did not have ocular tuberculosis. The ocular signs predictive of tuberculosis were identified in 90% of patients with ocular tuberculosis and 10% of patients without ocular tuberculosis. The sensitivity and specificity of these ocular signs were 90% and 90%, respectively.

**Conclusion:** The ocular signs predictive of tuberculosis identified in this study can be used to identify patients with ocular tuberculosis. These ocular signs can be used to identify patients with ocular tuberculosis and to provide timely treatment.

**Limitations:** The limitations of this study include the small sample size and the retrospective nature of the study.

**Conflict of Interest:** The authors declare that they have no conflict of interest.
Tuberculosis Uveitis: Distribution M. tuberculosis in the Retinal Pigment Epithelium

The diagnosis of intracocular tuberculosis has been a challenge until the introduction of polymerase chain reaction (PCR) to detect the mycobacterial-specific DNA sequence in the intracocular fluids. Such investigations have confirmed diverse manifestations of intracocular tuberculosis including retinal vasculitis and serpiginous choroiditis. The latter may manifest with multifocal lesions involving the inner choroid, which coalesce to form a geographic pattern simulating serpiginous choroiditis. Although clinically, the choroiditis appears to involve primarily the inner choroid and retinal pigment epithelium (RPE), the presence of mycobacteria in these anatomic sites has not been documented. Herein, we describe a case of panuveitis that was clinically of unknown cause but for which histopathologic examination of the globe disclosed septic dissemination of acid-fast organisms in the RPE. These were confirmed to be Mycobacterium tuberculosis by macroconidiation of the RPE, followed by real-time PCR.

Report of a Case. The enucleated left eye of a 48-year-old woman was submitted to the Doheny Eye Pathology Laboratory with a brief clinical history, revealing a progressively worsening intracocular inflammation in the left eye despite treatment with topical antituberculosis medications. On gross inspection, the eye was pale and edematous with no discrete lesions visible. The globe was fixed in 10% formalin and cut into 5-mm-thick sections, followed by hematoxylin and eosin staining. Immunohistochemistry for mycobacteria and stains for acid-fast bacilli were negative.

Histopathologic examination of the globe revealed a dense inflammatory infiltrate involving the choroid (Fig. 1A). The infiltrate consisted of lymphocytes, plasma cells, and macrophages, with occasional epithelioid cells and granulomas. The RPE was not spared and showed marked hyperplasia and necrosis. The choroid, retinal pigment epithelium, and retina were also involved. The presence of acid-fast bacilli was confirmed by Ziehl-Neelsen staining of the RPE, choroid, and retina. The patient was treated with antituberculosis medication, and the uveitis subsided.

Figure 1. Histologic examination of the globe. A. Mycobacterial infection involving the choroid (hematoxylin-eosin, × 100). B. Granulomatous inflammation involving the choroid (hematoxylin-eosin, × 100). The red cells are negative for CD3 (A) and positive for residual specific antibodies (C) and cytokines (D).

Clinical Features of Tuberculous Serpiginouslike Choroiditis in Contrast to Classic Serpiginous Choroiditis

Daniel Y. Younghoon-Soon, MD, PhD; P. Kumar Rao, MD; John E. Dansies, MD; Elliott H. Sife, MD; Narsing J. Rao, MD

Objectives: To compare distinctive clinical features of presumed tuberculous serpiginouslike choroiditis (TB-SLC) with classic serpiginous choroiditis (SC) in patients living in a region that is endemic for tuberculosis.

Methods: Retrospective comparative analysis of clinical features of 5 patients with recurrent TB-SLC and 5 with SC.

Results: All patients with recurrent TB-SLC primarily presented from areas highly endemic for tuberculosis and had been unsuccessfully treated with steroids/immunosuppressive agents. Results of serologic investigations were negative except for positive tuberculin skin test results. These patients received tuberculostatic drugs, with recurrent episodes (follow-up, 6-91 months). The ocular involvement in TB-SLC was mostly unilateral, with multiple irregular serpiginous lesions involving the posterior pole and periphery but usually sparing the juxtapapillary area. All 3 cases had inflammatory cells in the vitreous. In contrast, patients with SC were from areas nonendemic for tuberculosis, had negative serologic testing findings (including tuberculin skin test results), and were successfully managed with steroids/tromethamine/immunosuppressive agents (follow-up, 6-72 months) with no recurrence. Ocular involvement in SC was usually bilateral, rarely multifocal, and primarily involved the posterior pole, especially around the optic disc and extending peripherally to the macula. No patient with SC presented with vitritis.

Conclusions: In areas endemic for tuberculosis, SC can be clinically differentiated from TB-SLC. Patients with TB-SLC come from highly endemic regions, show significant vitritis, and often present with multifocal lesions in the posterior pole and periphery. Cases of SC, in contrast, reveal minimal or no vitritis and frequently show retinal involvement with larger solitary lesions encroaching primarily from the juxtapapillary area and sparing the periphery.

Arch Ophthalmol. 2010;128(7):s57-s60

CME available online at www.jamanetwork.com and questions on page 809

Serpiginous choroiditis (SC) is a rare, progressive, recurrent, idiopathic inflammatory disease involving the retinal pigment epithelium (RPE), choroid, and choroid. It is usually bilateral and typically affects middle-aged persons, with a slight predilection for males. The current approach includes the exclusion of other etiologies, together with a suggestive clinical history and signs, supportive systemic investigations, such as positive tuberculin skin test (TST)/interferon gamma release assay (IGRA) results, and chest radiography findings, as well as evidence of Mycobacterium tuberculosis or its DNA in ocular fluid samples. Serology is not specific or sensitive; however, tuberculostatic drugs and a positive purified protein derivative (PPD) or TST test result should be considered significant for the diagnosis of TB-SLC. Establishing a diagnosis of intracocular tuberculosis remains challenging. The current approach includes the exclusion of other etiologies, together with a suggestive clinical history and signs, supportive systemic investigations, such as positive tuberculin skin test (TST)/interferon gamma release assay (IGRA) results, and chest radiography findings, as well as evidence of Mycobacterium tuberculosis or its DNA in ocular fluid samples. Serology is not specific or sensitive; however, tuberculostatic drugs and a positive purified protein derivative (PPD) or TST test result should be considered significant for the diagnosis of TB-SLC.
Diagnosis
Major issue

• Lack of any uniform Dx criteria
• Confusion regarding Dx and management
• PMH
• PPD
• Chest x-ray and CT-scan
• Molecular tools
• Biopsies

Lou et al. Ocul Immunol Inflam, 2015 / SUN / COTS (collaborative ocular TB study group)
Molecular Dx

- Nested PCR
- ERM of patients with Eales’ disease
- 23 patients
- nPCR + in 47.8% of cases (11.1% of controls)
- Positive PCR does not mean bacterial replication

*Madhavan et al. 2000*
Diagnosis of TB

- Poor specificity of TB skin test in vaccinated patients
- Low sensitivity in IS patients
- T-SPOT TB and quantiFERON-TB Gold: 2 blood tests based on detection of IFN-γ released by T-cells in response to M. tuberculosis Ag
- Validation is challenging due to the lack of a diagnostic gold standard
- Results available by the next day, no boosting after repeated tests
<table>
<thead>
<tr>
<th>Dx</th>
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<tbody>
<tr>
<td><strong>TST</strong></td>
</tr>
<tr>
<td>Mixture of more than 200 proteins derived from Mt</td>
</tr>
<tr>
<td>Limited specificity</td>
</tr>
<tr>
<td>+ result: exposure to nonTB mycobacteria</td>
</tr>
<tr>
<td>Significant cross-reactivity between PPD and BCG vaccine</td>
</tr>
<tr>
<td>Limited sensitivity (75-90%)</td>
</tr>
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</table>
52% positivity in patients with Serpiginous-like choroiditis
- 157 patients with suspected TB uveitis

- Retrospective study

- QFN not superior to TST in sensitivity as a screening test or first-line study in TB-related Uveitis

- QFN more specific than TST in identifying infections by Mt

- Negative QFT tests should be interpreted with caution, they do not exclude the diagnosis
QuantiFERON-TB Gold Cut-off Value: Implications for the Management of Tuberculosis-Related Ocular Inflammation

RAQUEL GINEYS, BAHRAM BODAGHI, GHISLAINE CARCELAIN, NATHALIE CASSOUX, LE THI HUONG BOUTIN, ZAHIR AMOURA, PHUC LEHOANG, AND SALIM TRAD

Am J Ophthalmol, 2011
<table>
<thead>
<tr>
<th></th>
<th>QuantiFERON-TB Gold Positive n = 42</th>
<th>QuantiFERON-TB Gold Negative n = 54</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>55.9 (± 16.7)</td>
<td>48.2 (± 17.9)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>22 (52)</td>
<td>36 (67)</td>
<td>.21</td>
</tr>
<tr>
<td>First episode</td>
<td>18 (43)</td>
<td>21 (39)</td>
<td>.76</td>
</tr>
<tr>
<td>Median duration of ocular symptoms, years (extremes)</td>
<td>3.31 (0–11)</td>
<td>3.28 (0–12)</td>
<td>.76</td>
</tr>
<tr>
<td>From endemic tuberculosis area (%)</td>
<td>22 (52)</td>
<td>17 (31)</td>
<td>.09</td>
</tr>
<tr>
<td>History of BCG vaccination (%)</td>
<td>10 (24)</td>
<td>23 (43)</td>
<td>.08</td>
</tr>
<tr>
<td>Reported exposure to tuberculosis (%)</td>
<td>18 (43)</td>
<td>17 (31)</td>
<td>.29</td>
</tr>
<tr>
<td>History of anti-tuberculosis treatment (%)</td>
<td>10 (24)</td>
<td>4 (7)</td>
<td>.04</td>
</tr>
<tr>
<td>Extraocular signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evocative of tuberculosis (%)</td>
<td>2 (5)</td>
<td>3 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Evocative of another etiology (%)</td>
<td>8 (19)</td>
<td>11 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ancillary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone (%)</td>
<td>12 (29)</td>
<td>14 (26)</td>
<td>.82</td>
</tr>
<tr>
<td>Tuberculin skin test (82 available results) Positive ratio (%)</td>
<td>26/38 (68)</td>
<td>9/44 (20)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
QuantiFERON-TB Gold (IU/ml)

1.22 U/ml [0.61 to 4.4]

7.67 U/ml [0.46 to 33.37]

p=0.026

Failure
n = 10

Success
n = 15

Antituberculosis treatment
‘Equivocal’ T-SPOT TB result associated with patients aged >55y. Such patients are likely to have a negative QuantiFERON-TB Gold In-tube result. Ang et al. Br J Ophthalmol 2012

Based on statistical decision theory, head-to-head study suggests that QuantiFERON-TB Gold In-Tube is the first-line test that should be performed in preference to T-SPOT.TB (and the tuberculin skin test) for diagnosing tuberculous uveitis. Ang et al. Am J Ophthalmol 2014

Cost-effectiveness of alternative strategies for interferon-γ release assays and tuberculin skin test in tuberculous uveitis

Marcus Ang,1,2,3 Hai V Nguyen,4 Sieh Yeann Kiew,1 Shu Chen,4 Soon-Phaik Chee,1,2,3 Eric Finkelstein4

Dual test strategy is the most cost-effective strategy for the Dx of TB uveitis

Br J Ophthalmol 2015
Treatment
Anti-TB drugs and Corticosteroids

• Isoniazid: 5 mg/kg/d
• Rifampicin: 10 mg/kg/d
• Pyrazinamide: 30 mg/kg/d
• Ethambutol: 20 mg/kg/d

• Corticosteroids may be used in cases of HS, in the absence of systemic TBC
• IS are more controversial
• Always a multidisciplinary approach

8w + 18w
Conclusions

• Challenging condition
• Clinical features have to be revisited
• The use of Dx tools must be standardized
• Place of IGRA and molecular analysis of ocular fluids
• Rx modalities and monitoring
Next IOIS congress

Lausanne, Switzerland
October 18-21, 2017
Ocular toxoplasmosis: should we treat all patients?

IOIS Course
Infectious Uveitis: From Diagnosis to Specific Therapy

Carlos Pavesio
Moorfields Eye Hospital
BRC Institute of Ophthalmology
London

Toxoplasma Gondii

- Obligatory intracellular
- Active penetration
- Tissue cyst formation

Tissue Cyst Formation

Transmission

- Acquired
  - Ingestion of oocysts
  - Ingestion of tissue cysts
  - Transfusion/transplantation or accident
- Ingestion of water
- Congenital

Ocular Disease

- Necrotizing retinitis
- Vascular involvement
- Anterior segment
- Optic nerve
- Variations, neuroretinitis, outer punctate, AIDS

Atypical Forms
Ocular Disease in the Immunocompetent

- When to treat?
- Which drugs to use?
- For how long?
- Steroids? (risk of reactivation?)
- Other forms of therapy
- Complications

Central Visual Loss

- Direct involvement of the macula
- Vitreous condensation
- Optic neuropathy
- CNV

Vascular Involvement
Optic Nerve Involvement

BUT

WHAT TO DO WITH THESE?
Anti-Toxoplasma Drugs

- Pyrimethamine
- Sulfadiazine (other sulfonamides)
- Clindamycin
- Spiramycin
- Tetracyclines
- Atovaquone
- Azithromycin
- Trovafoxacin

Another alternative

- Intravitreal Clindamycin 1mg/0.1ml
Ocular toxoplasmosis: background and evidence for an antibiotic prophylaxis.

BACKGROUND: Studies showing the prophylactic effect of long-term antibiotics are discussed. Prophylaxis seems to be justified in patients with a high risk of recurrence because of the antibiotic pro-inflammatory effects. Therefore, prophylactic factors should be a higher risk of recurrence and the time period during which an antibiotic prophylaxis is most appropriate are reviewed. Finally, a patient individualised treatment recommendation is summarised.

SUMMARY: In the current literature, two prospective, randomised case-control studies exist, which show the protective effect of an antibiotic prophylaxis. Nonetheless, gastrointestinal and dermatological complications are potential side-effects. Especially during the first year after suffering a recurrence, an antibiotic prophylaxis seems to be justified. The risk of a recurrence is not also influenced by the duration of the disease, the immune status of the host and the patient ages. Therefore, an antibiotic prophylaxis should be considered for patients who have recently been infected with ocular toxoplasmosis, for middle-aged and elderly patients and patients with a compromised immune system. This should be discussed with each patient individually, especially if the lesion is close to the macula.

Local treatment of toxoplasmos retinochoroiditis with intravitreal clindamycin and dexamethasone.

METHODS: Study population: 16 eyes (16 patients) with active TSC-q spilling the macula and posterior pole treated with intravitreal injections of clindamycin (1 mg) and dexamethasone (0.1 mg) for 4 weeks. Changes of best corrected visual acuity, retinal lesion size, and vitreous inflammation before and after treatment, as well as complications-side-effects and recurrence rate were compared between groups. All these variables improved significantly at 4 weeks within each group, changes were comparable between the IV and OC groups. There was only one case with hypotony in the OC group which responded favorably to drug change. No injection-related complication was observed. Recurrence rate was 2.5% and 4.4% in the IVOC and OC groups, respectively (p = 0.6). In conclusion, both IV and OC are equally effective against active toxoplasmos retinochoroiditis but the former is apparently safer and more convenient.