C22

Infectious Uveitis: From Diagnosis to Specific Therapy

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

HAND-OUTS
Fuchs Uveitis
Laure Caspers 1, Lia Judice M Relvas 1,2, Christine Fardeau 3, and François Willermain 1,2

1. CHU St Pierre, Université Libre de Bruxelles, Brussels, Belgium
2. CHU Brugmann, Université Libre de Bruxelles, Brussels Belgium
3. Hôpital La Pitié-Salpêtrière, Paris, France

Fuchs heterochromic uveitis described in 1906 by Fuchs represents between 1.2 - 4.5% of 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 (Figure 1). 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 (Figure 2) 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 after postoperative inflammation of the anterior segment.10,11,12.

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.

Figure 1.
Right: KPs scattered over the whole cornea. Mix of fine, stellate, and larger KPs giving a granulomatous aspect in a patient with Fuchs uveitis (CWc + for rubella). The inflammation increased after cataract and glaucoma surgery. Left: KPs from a patient with Fuchs uveitis with a positive PCR for CMV. KPs are white, small and medium-sized dispersed throughout the endothelial surface.

Figure 2: Diagnostic signs are often difficult to identify in patients with brown eyes. Two eyes of a patient with unilateral Fuchs uveitis, brown eyes and no heterochromia. Top: normal iris, down: iris with Fuchs uveitis showing some velvet aspect with the loss of some iris crypts.
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. (Figure 3)

**Figure 3**: pigmented and atrophic chorioretinal lesion in a patient with Fuchs uveitis and PCR + for rubella virus

**Physiopathogeny:**

Many theories regarding the etiology and pathogenesis of Fuchs uveitis have been proposed. In the past, Fuchs uveitis related to toxoplasma *toxocariasis*, 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
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.

**Diagnosis:**

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.
### Diagnostic Signs of Fuchs Uveitis

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

**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


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

- HSV, VZV
- CMV
- HHV-8
- Presumed necrotizing herpetic retinitis
- Non necrotizing herpetic retinopathies
- Fuchs Uveitis Syndrome
- Posner-Schlossman

Viral associated uveitis

- HSV, VZV
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- Fuchs Uveitis Syndrome
- Posner-Schlossman
"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....

Nobel Prize in Medicine (1905)

Infectious diagnosis

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.

Diagnostic approach

SUSPECT/EXCLUDE INFECTIOUS ETIOLOGY!

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

Herpetic anterior Uveitis

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

Approx. 30% in Zoster Ophthalm.
(Non)-granulomatous uveitis
Variable course
More severe clinical course!
Hypopion + hyphema

Complications
- Iris atrophy (20%)
- Sec. glaucoma
- Cataract
- Phthisis bulbi

Herpetic anterior Uveitis

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

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

Signs

Herpetic anterior Uveitis

Signs
**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>25/37 (67%)</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 (75%)</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>45/51 (88%)</td>
<td>10/23 (43%)</td>
<td>1</td>
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</tbody>
</table>

*Based on Wensing et al., Ophthalmology 118: 1903-1904, 2011

**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><strong>Dosis per day</strong></td>
<td>3x5mg/kg/KG i.v.</td>
<td>5x800mg p.o.</td>
<td>2x90mg/kg/KG i.v.</td>
</tr>
<tr>
<td><strong>Long term dose</strong></td>
<td>2 - 3 x 500 - 600 mg oral</td>
<td>2 - 3 x 500 mg oral</td>
<td>2 - 3 x 500 mg oral</td>
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<tr>
<td><strong>Adverse effects</strong></td>
<td>Nausea, Renal, Blood count, Fever</td>
<td>Nausea, Renal, Blood count, Fever</td>
<td>Nausea, Renal, Blood count, Fever</td>
</tr>
</tbody>
</table>

**HSV**

**Prevention VZV: Zostavax®**

- Placebokontrollierte, doppelblinde Studie zur Zoster Prävention
- > 60 Jahre
- 1x ZOSTAVAX (n = 19,270)
- Placebo (n = 19,276)

**Endpunkt**

<table>
<thead>
<tr>
<th>Wirksamkeit des Impfstoffs*</th>
<th>95 % KI</th>
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<tbody>
<tr>
<td>Inzidenz von Zoster</td>
<td>51 %</td>
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<tr>
<td>Inzidenz Neuralgie</td>
<td>67 %</td>
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<tr>
<td>HZ Schmerz „Score“</td>
<td>61 %</td>
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</table>

**Aqueous humour analysis: Charité**

1/2004 - 6/2012
n=1883
**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
- Uveitis syndrome

**Posner-Schlossman-Syndrome**

- Aqueous humor analysis (n= 33)*
  - CMV 16 (52%)
  - HSV 8 (24%)
  - VZV 3 (9%)


**Posner-Schlossman-Syndrome**

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

  Posner Schlossman Syndrome

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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

Herpetic anterior Uveitis

Therapy: CMV

<table>
<thead>
<tr>
<th>Gender age</th>
<th>Diagnosis</th>
<th>Follow-up (months)</th>
<th>Duration (months)</th>
<th>Humovirone</th>
<th>Baseline VA</th>
<th>Final VA</th>
<th>Lines changed</th>
<th>Baseline IOP (mmHg)</th>
<th>Final IOP (mmHg)</th>
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<tr>
<td>M/60</td>
<td>Endotheliitis</td>
<td>30</td>
<td>36</td>
<td>Yes</td>
<td>20/70</td>
<td>20/1000</td>
<td>−12</td>
<td>21</td>
<td>14</td>
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<tr>
<td>M/60</td>
<td>Endotheliitis</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/50</td>
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<td>20/40</td>
<td>+4</td>
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<td>12</td>
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<td>20/30</td>
<td>20/29</td>
<td>+2</td>
<td>12</td>
<td>16</td>
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<tr>
<td>M/57</td>
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<td>24</td>
<td>2</td>
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<td>20/1000</td>
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<td>17</td>
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<tr>
<td>M/56</td>
<td>FUS</td>
<td>12</td>
<td>2</td>
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<td>20/35</td>
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<td>+1</td>
<td>27</td>
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<td>FUS</td>
<td>6</td>
<td>5</td>
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<td>20/25</td>
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<td>+1</td>
<td>8</td>
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<tr>
<td>M/41</td>
<td>FUS</td>
<td>5</td>
<td>2.5</td>
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<td>20/200</td>
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<td>+7</td>
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<tr>
<td>F/39</td>
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<td>+12</td>
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<td>20/800</td>
<td>−12</td>
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<tr>
<td>F/38</td>
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<td>Yes</td>
<td>20/20</td>
<td>20/18</td>
<td>+1</td>
<td>11</td>
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<tr>
<td>M/70</td>
<td>FSS</td>
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<td>27</td>
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<td>20/70</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

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)


Infectious etiology?
- Rubella virus
- Intracellular Antibody synthesis (> 90%)*
- Positive PCR-findings
- CMV Positive PCR-findings**

Quentin CD, 2004; deGroot-Mijnes, 2006; Ruokonen, 2008

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** Hwang YS et al., Graef`s Arch Clin Exp Ophthalmol, 249: 103-110, 2011


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Aqueous humour analysis: Charité

- HSV
- CMV
- Toxoplasma
- VZV

1/2005 - 6/2012
n=1983
**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: Viral anterior uveitis**
- Encompases broad spectrum of anterior uveits
- Significant morbidity
- Often late diagnosted
- Clinical findings may provide diagnostic hints
- Analysis of aqueous humor analysis is valuable
- Long term prevention necessary

**Summary**

- Clinical findings support suspected etiology

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

- Important role of aqueous humor analysis!

**Aqueous humor analysis**

- Encompases broad spectrum of anterior uveits
- Significant morbidity
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**Summary:**

- Encompases broad spectrum of anterior uveits
- Significant morbidity
- Often late diagnosted
- Clinical findings may provide diagnostic hints
- Analysis of aqueous humor analysis is valuable
- Long term prevention necessary
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.
Ocular Signs Predictive of Tubercular Uveitis

AMOD GUPTA, REEMA BANSAL, VISHALI GUPTA, AMAN SHARMA, AND PRADEEP RAMBERY

*PURPOSE:* To determine ocular signs predictive of tubercular uveitis.

*DESIGN:* Retrospective, nonrandomized, comparative interventional case study.

*METHODS:* Three hundred eighty-six patients with active uveitis were treated at a tertiary care single-center uveitis practice. Uveitis was presumed to be tubercular in patients who showed evidence of latent or manifest tuberculosis without any other known cause and who did not show recurrence of uveitis after 12 months of antitubercular therapy. One hundred eighty-two patients who thus obtained clinical diagnosis of presumed tubercular uveitis were enrolled in group A. Two hundred four patients with uveitis resulting from a nontubercular cause were enrolled in group B. Patients were monitored for the presence of types of keratic precipitates (mutton fat or fine), posterior synechiae (broad based or filiform), iris nodules, snowballs, snow banking, vasculitis (with or without choroiditis), serpiginous-like choroiditis, and other types of posterior uveitis (choroidal abscess, retinal neovascularization, or exudative retinal detachment) which were compared between the two groups. Statistical analysis was carried out at a 5% level of significance. The main outcome measures were clinical signs significantly associated with tubercular uveitis.

*RESULTS:* Broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis were seen significantly more commonly in patients with tubercular uveitis. Filiform posterior synechiae were more frequent in eyes with nontubercular uveitis.

*CONCLUSIONS:* Broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis in patients with latent or manifest tuberculosis in tuberculosis-endemic areas are suggestive of a tubercular cause of uveitis and merit specific treatment. (Am J Ophthalmol 2010;149:562-570. © 2010 by Elsevier Inc. All rights reserved.)

Intraocular tuberculosis (TB) produces a wide spectrum of clinical signs, including anterior granulomatous uveitis, chronic anterior uveitis, intermediate uveitis, choroidal, retinal vasculitis, serpiginous-like cho-

roditis, choroidal granuloma, and panuveitis.1 Because many of these entities also may be the result of nontubercular causes, diagnosing tubercular uveitis in TB-endemic areas poses a major challenge. In the absence of confirmatory investigations, the diagnosis of presumed tubercular uveitis is made in patients with supportive clinical findings and a positive clinical response to antitubercular therapy with no recurrence of inflammation thereafter.

Antitubercular therapy is highly effective in reducing the recurrences of uveitis in patients with latent or manifest TB.2-6 By June patients seek treatment for uveitis, most do not show evidence of manifest TB. The tuberculin skin test and the more recent QuantiFERON Gold test detect tubercular infection, and a positive test result may suggest a possible tubercular cause.2-5 Confirmatory test results, such as demonstration of acid-fast bacilli, culture of Mycobacterium tuberculosis, or histopathologic evidence, seldom are available from the ocular specimens. The conventional polymerase chain reaction technique to detect mycobacterial deoxyribonucleic acid from the ocular fluids, although highly specific, is an invasive procedure, besides having poor sensitivity.5 Determining specific clinical signs that predict a possible tubercular cause may enhance the diagnostic probability of a positive result from those investigations.

METHODS

We conducted a retrospective chart analysis of all consecutive uveitis patients attending the uveitis clinic of our institution between 1991 and 2005. Institutional ethics committee approval was obtained. We compared clinical signs between 2 groups of patients. Group A included patients with a diagnosis of presumed TB uveitis. Group B, which served as the control group, included patients with uveitis presumed to be of nontubercular origin. Patients with the following inclusion criteria were enrolled in group A: (i) complete clinical records of ophthalmic examinations including visual acuity, intracocular pressure, slit-lamp biomicroscopic findings including anterior as well as posterior segment details, laboratory investigations, and treatment records at the baseline and at all follow-up visits; (ii) all known causes of infectious uveitis except TB and known nontubercular uveitis syndrome ruled out; (iii) a documented positive tuberculin skin test (10 mm of induration or more) at 48 to 72 hours; (iv) received antitubercular therapy for a minimum of 12 months in addition to conventional corticosteroids; (v) a

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0002-9394/10/$ - see front matter. doi:10.1016/j.ajo.2009.11.020
Tuberculous Uveitis: 
Distribution of Mycobacterium tuberculosis 
in the Nontuberculous Uveitis

CLINICOPATHOLOGIC REPORTS, CASE REPORTS, AND SMALL CASE SERIES
SECTION EDITOR: W. RICHARD GREEN, MD

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 intranuclear tuberculous including retinal vasculitis and serpiginous choroiditis. The latter may manifest with multifocal lesions involving the inner choroid, which colocalize to 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 mycobacterium at 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 the selective distribution of acid-fast organisms in the RPE. These were confirmed to be Mycobacterium tuberculosis by macroinjection of the RPE, followed by real-time PCR. Report of a Case. The emaciated left eye of a 58-year-old woman was submitted to the Doheny Eye Pathology Laboratory with a brief clinical history, revealing a progressively worsening uveitis. The outer retinal changes were consistent with the diagnosis of tuberculosis.

Figure 1. Histologic examination of the globe. A, Normal retinal pigmented epithelium (RPE) and visual streak with a granulomatous infiltrate involving the choroid (hematoxylin-eosin stain, ×20). B, Marked retinal vasculitis involving the peripheral retina (hematoxylin-eosin stain, ×20). C, Normal retina containing a few RPE cells (hematoxylin-eosin stain, ×4). D, Normal retina with a few RPE cells (hematoxylin-eosin stain, ×40). E, Normal retina with a few RPE cells (hematoxylin-eosin stain, ×40).

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

Daniel Y. Yuen, MD, and J. Peter K. Kao, MD

Objective: To compare distinctive clinical features of presumed tuberculous serpiginouslike choroiditis (Tb-SLC) with classic serpiginous choroiditis (SC). 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 involved the macular high endothelial for tuberculosis and had been unsuccessfully treated with steroids/immunosuppressive agents. Results of serologic investigations were negative except for positive tuberculin skin test results. Patients received and tuberculostatic drugs, without recurrence (follow-up, 6-9 months). The involvement in Tb-SLC was mostly unilateral, with multiple irregular serpiginous lesions involving the posterior pole and periphery. No patient with SC presented with vitritis. Conclusion: In non-Tuberculous for tuberculosis, SC can be differentiated from Tb-SLC. Patients with Tb-SLC come from highly endemic countries and have 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 chorioretinal involvement with larger solitary lesions extending primarily from the juxtapapillary area and sparing the periphery.

SMAPSE, 2012/2013, 4:853-858

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.

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

Author Affiliation: Doheny Eye Institute and Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles (Drs Yuen and Kao); and Barnes Foster Institute, Department of Ophthalmology, Washington University, St Louis, Missouri (Drs Yuen and Kao).

A possible association between lesions resembling SC and tuberculosis was first considered in the middle of the 20th century. This issue was raised again in subsequent decades, but it was not until recently that tuberculostatic choroiditis simulating SC was recognized as a possibility. Distinct clinical entities and referred to as tuberculostatic serpiginous choroiditis (Tb-SLC). Differentiating this tuberculostatic entity from classic SC is critical because treatment of the former with immunosuppressive drugs has several potential adverse effects and each treatment course has devastating consequences due to worsening of concurrent tuberculosis infection. Conversely, antituberculostatic treatment may also be associated with significant adverse events, especially in patients with classic SC.

Establishing a diagnosis of intracocular tuberculosis remains challenging. The current approach involves the exclusion of other etiologies, together with a suggestive clinical history and signs; supportive systemic investigation, 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 the electrocardiogram. In the absence of supportive nucleic evidence, active systemic tuberculostatic agents are considered significant for the tuberculous tissue. Patients with SC were from areas endemic for tuberculosis, had negative serological results, and were successfully managed with antituberculostatic 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 centrifugally to the macula. No patient with SC presented with vitritis.
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 non-TB mycobacteria</td>
</tr>
<tr>
<td>Significant cross-reactivity between PPD and BCG vaccine</td>
</tr>
<tr>
<td>Limited sensitivity (75-90%)</td>
</tr>
<tr>
<td><strong>IGRAs</strong></td>
</tr>
<tr>
<td>ELImmunosorbentA / ELImmunospotA</td>
</tr>
<tr>
<td>More specific than TST</td>
</tr>
<tr>
<td>More sensitive than TST</td>
</tr>
<tr>
<td>Limitation: do not distinguish between latent and active TB</td>
</tr>
<tr>
<td>Increased posttest probability</td>
</tr>
<tr>
<td>Higher cost</td>
</tr>
<tr>
<td>Specialized lab</td>
</tr>
<tr>
<td>Result altered by a recent TST!</td>
</tr>
</tbody>
</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
<table>
<thead>
<tr>
<th></th>
<th>QuantiFERON-TB Gold Positive</th>
<th>QuantiFERON-TB Gold Negative</th>
<th>p^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 42</td>
<td>n = 54</td>
<td></td>
</tr>
<tr>
<td><strong>Epidemiology</strong></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><strong>Extraocular signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evocative of tuberculosis (%)^c</td>
<td>2 (5)</td>
<td>3 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Evocative of another etiology (%)^d</td>
<td>8 (19)</td>
<td>11 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Ancillary</strong></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) vs. Antituberculosis treatment

- Failure: 1.22 IU/ml [0.61 to 4.4] (n = 10)
- Success: 7.67 IU/ml [0.46 to 33.37] (n = 15)

p = 0.026
‘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-\(\gamma\) 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 Finkelstein\(^4\)

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

BrJ Ophthalml 2015
Treatment
Anti-TB drugs and Corticosteroids

- Isoniazid: 5 mg/kg/d
- Rifampicine: 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
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

Ingestion of water

Tissue Cyst Formation

Toxoplasma Gondii
- Obligatory intracellular
- Active penetration
- 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
- Retinitis, 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
- Tetracyclines
- Atovaquone
- Azithromycin
- Trovafloxacin

Another alternative

- Intravitreal Clindamycin 1mg/0.1ml