HERPETIC RETINOPATHIES

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12th EURETINA Congress, Milan, 6-9 September, 2012
INTRODUCTION

- Herpetic viral agents
  - Herpes simplex (HSV) type 1 and type 2
  - Varicella-zoster virus (VZV)
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Others: Human herpes virus (HHV) 6, 7, and 8

- Herpes viruses: important infectious cause of ocular inflammation worldwide

- Primary infection, followed by persistence in a latent form

- Infection reactivation may occur in the form of keratitis, anterior uveitis, or retinitis (necrotizing +++, non-necrotizing)

- Role of the status of the host’s immune system in defining the pattern and outcome of ocular disease: immunocompetent vs immunocompromised

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Necrotizing herpetic retinopathies

1. “Normal” immune status

   Acute retinal necrosis (ARN) syndrome

2. Immunodepressed status

   Progressive outer retinal necrosis (PORN)
   CMV retinitis

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Herpetic Retinopathies

- Necrotizing
  - ARN
  - PORN
- Non necrotizing
  - CMV Retinitis
Herpetic Retinopathies

- "Normal" immune status
  - ARN
  - Non necrotizing
- Immunodepressed status
  - CMV Retinitis
  - PORN

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Acute retinal necrosis (ARN)

- Severe, sight-threatening disease, diagnostic and therapeutic emergency
- Unilateral, but involvement of the second eye in > 70% of untreated cases
- Both sexes equally affected
- Two-peak age distribution: 20 and 50 years
- Viruses: VZV (old patients), HSV types 1 and 2 (young patients), CMV (rarely), EBV (exceptionally)
- Risk factors: young age, history of neonatal herpes, preexisting chorioretinal scar, trauma or systemic corticosteroids
Acute retinal necrosis (ARN)
Clinical presentation

• Ocular symptoms:
  - Redness,
  - Photophobia,
  - Tearing,
  - Blurred vision,
  - Irritation,
  - Periorbital pain, and
  - Floaters
Acute retinal necrosis (ARN)

Clinical presentation

1. Anterior uveitis
2. Vitritis
3. Typical peripheral retinitis
4. Occlusive vasculitis (arteries)
5. Optic disc edema

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**Acute retinal necrosis (ARN)**

**Clinical presentation**

1. **Anterior uveitis**
   - Moderate or severe
   - Non-granulomatous or granulomatous (++)
   - Ocular hypertension

In any patient with anterior uveitis, a careful dilated fundus examination is mandatory not to miss the diagnosis of ARN syndrome

2. **Vitritis**
   - Moderate or severe, prominent feature of ARN (in contrast to CMV retinitis and PORN)
   - Worsens as the course of the disease progresses


**Standard diagnostic criteria for the acute retinal necrosis syndrome. Executive Committee of the American Uveitis Society.**

Holland GN.
3. Typical necrotizing retinitis

- Focal, well-demarcated areas of full-thickness retinal necrosis in the equatorial and pre-equatorial regions
- Sharp demarcation between whitened involved and normal retina
- Associated moderate hemorrhages
- Rapid progression: circumferentially as well as in posterior direction to form extensive retinitis, but macula is often spared
- Serous retinal detachment may occur
Acute retinal necrosis (ARN)

Clinical presentation

Particular anatomic forms of ARN syndrome:

1. ARN limited to 1 or 2 quadrants: milder form, better prognosis

2. ARN affecting the posterior pole: Worse visual prognosis and a higher rate of retinal detachment

Severity of ARN: according to surface of retina involved:

<table>
<thead>
<tr>
<th>Severity of ARN</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>Moderate</td>
<td>25 - 50%</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 50%</td>
</tr>
</tbody>
</table>

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Acute retinal necrosis (ARN)

Clinical presentation

4. Retinal vasculitis
   - Occlusive, involving the arterioles primarily, diagnosis and evaluation rely on clinical examination and fluorescein angiography
   - Involvement of either the entire retina or only areas affected by active retinitis
   - Sheathing and narrowing
   - Occlusion and non-perfusion, retinal vascular leakage

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5. **Optic disc involvement**

- Frequent and important component of ARN syndrome
- Mild to moderate hyperemia and optic disc staining without associated visual dysfunction
- True optic neuropathy: visual loss, relative afferent pupillary defect, optic disc edema without associated posterior retinal involvement
Acute retinal necrosis (ARN)  
Biological diagnosis

- Diagnosis of ARN: primarily based on typical clinical features

- Molecular diagnosis (Real time PCR+++ ) applied to intraocular fluid sample (aqueous humor, rarely vitreous) to confirm the diagnosis
  - Differentiation of ARN from other entities that may mimic ARN
  - Identification of the causative virus

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Acute retinal necrosis (ARN)
Complications

- Complications:
  - Severe, resulting in poor visual outcome
  - Early diagnosis and proper treatment are mandatory to reduce their frequency:
    - Extension of retinal necrosis,
    - Involvement of the second eye (70%),
    - Optic atrophy,
    - Retinal breaks, retinal detachment (> 75% of untreated eyes, complex, severe PVR, poor visual outcome)
    - Others: epiretinal membrane, CME, SRD, retinal/optic disc neovascularization, cataract, phthisis

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Uveitis entities that may mimic viral acute retinal necrosis mainly include:

- Toxoplasmosis
- Syphilis
- Fungal retinochoroiditis
- Primary intraocular lymphoma
- Sarcoidosis
- Behçet disease
- PORN
- CMV retinitis
Progressive Outer Retinal Necrosis (PORN)
Clinical presentation

- PORN is a necrotizing chorioretinitis that is found almost exclusively in people immunocompromised. PORN almost exclusively in AIDS patients with CD4+ count <100 cells/µL
  - Minimal nongranulomatous anterior uveitis without vitritis
  - Fulgurent necrotizing retinitis starting at the posterior pole and spread toward the peripheral retina
  - Bilateral

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Progressive Outer Retinal Necrosis (PORN)
Clinical presentation

- Characteristic macular lesion: (#ARN)
  - Parafoveal opacification with a “cherry-red spot”
  - Ø contiguous with peripheral lesions

- An afferent pupillary defect is present
- Optic nerve involvement can also masquerade as papillitis or neuroretinitis

- **Disease quiescence**
  - Dense white plaques: “cracked mud” appearance
  - Atrophic areas + holes

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CMV retinitis

- Immunocompromized patients: 75% to 85% of patients with AIDS, CD4+ counts <50 cells/µl
- Incidence in individuals with AIDS in the era of HAART: 0.36/100 person-years
- Patients on immunosuppressive therapy
  - Bilaterality: 52%
  - Mild signs of inflammation including fine keratic precipitates and anterior chamber cells
  - Minimal vitritis
CMV retinitis
Clinical presentation

- 3 patterns of active lesions have been described:
  - Hemorrhagic
  - Brush fire
  - Granular

Natural course:
- Regression
- Retinal detachment:
  - Serous
  - Rhegmatogenous: 13-29%
- Recurrence
- Use of HAART: lower incidences of visual field loss
Non-necrotizing herpetic retinopathies

- Entity reported recently
- PCR confirmed the presence of herpes virus DNA in patients presenting with different forms of chronic and atypical posterior uveitis:
  - Bilateral disease
  - Corticoresistance or corticodependance at a high level
  - Improvement of inflammation under antiviral therapy

Non-necrotizing Herpetic Retinopathies
Masquerading as Severe Posterior Uveitis

Non-necrotizing Herpetic Vasculitis

Wensing B, de Groot-Mijnes JD, Rothova A.
Necrotizing and nonnecrotizing variants of herpetic uveitis with posterior segment involvement.

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# Treatment of Acute Retinal Necrosis (ARN)

<table>
<thead>
<tr>
<th>Antiviral therapy</th>
<th>Induction dose</th>
<th>Maintenance dose</th>
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<tbody>
<tr>
<td>Acyclovir</td>
<td>5-10 mg/Kg/8h during 10-14 days</td>
<td>800mgx5/day</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1gx3/day</td>
<td>1gx3/day</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>IV: 5-10mg/Kg/12h during 14-21 days Intravitreal: 200-4000µg 2X/week during 2-3 weeks</td>
<td>IV: 5mg/Kg/day Intravitreal: 200-400 µg/week Implant:4,5 mg during 8 months</td>
</tr>
<tr>
<td>Valaganciclovir</td>
<td>Oral 900 mg every 12h during 3 weeks</td>
<td>Oral 900 mg/day</td>
</tr>
<tr>
<td>Foscavir</td>
<td>IV: 90 mg/Kg/8h during 14 days Intravitreal: 1200-2400 µg every 2-3 days</td>
<td>IV: 90-120mg/Kg/day Intravitreal: 1200-2400 µg/week</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 mgx3/day</td>
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Treatment of Acute Retinal Necrosis (ARN)

- **The standard treatment**: Intravenous acyclovir in three divided doses (10mg/kg x 3/day) over a period of 10 to 15 days, followed by oral treatment: acyclovir 4 g/day or valacyclovir 1 g x 3/day for an additional period of 1-3 months before regular tapering.
- Alternatively, oral treatment with valacyclovir alone (3 g/day)

- **Duration of antiviral therapy?** ≥ 14 weeks: significant role in preventing the involvement of the contralateral eye.
- Lesions must be stabilized after a mean period of 48 h (absence of new lesions), resolution (4th day), complete resolution (one month).
- Close monitoring of the retina is necessary in order to confirm the antiviral efficacy.

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ARN resistant to acyclovir, immunocompromised patients:

- Ganciclovir (5mg/kg/12h x 2 weeks; then 5mg/kg/day)
- Foscarnet (180mg/kg/day in 2 or 3 divided doses)
- Ganciclovir + foscarnet
- Intravitreal injections: optional
  - Ganciclovir: 200-4000 microg x 2 per week +++
  - Foscarnet: 1200 microg x 2 per week
Treatment of Acute Retinal Necrosis (ARN)

- Systemic corticosteroids: Necessary to control secondary inflammation (vitritis, retinal vasculitis, optic neuropathy) and subsequent retinal and optic disc damage
- Corticosteroids should not be administrated in the absence of antivirals
- Steroids must be initiated after stabilization of retinitis under antiviral treatment
- Initial dose: 0.5-1mg/kg of oral prednisone or prednisolone, progressive tapering over a period of 4-6 weeks, coverage with high doses of antiviral drug
- In some cases, intravenous pulses of methylprednisolone can be administrated during the first 3 days, followed by oral corticosteroids
- Steroids should be avoided in immunocompromised patients

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Treatment of Acute Retinal Necrosis (ARN)

- The effects of anticoagulants and aspirin on occlusive vasculitis remain controversial.
- Retinal detachment prophylaxis with laser (four rows of 500 micron spots placed posterior to the advancing border of retinitis): controversial efficacy.
- Retinal detachment surgery: vitrectomy, laser, silicone oil tamponade according to the severity of anatomical lesions.
Treatment of Progressive Outer Retinal Necrosis (PORN)

- More aggressive antiviral therapy should be initiated based on intravenous foscarnet or ganciclovir.

- Intravitreal ganciclovir injection (200 μg/0.05 ml) and intravenous foscarnet (1200 μg/0.05 ml, administered every other day, for four doses especially in immunocompromised patients but no protection for fellow eye.

- Long-term therapy is the only possible way to avoid further relapses, especially in patients with monophthalmus status effects.
# Treatment of CMV retinitis

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<td>IV: 5 mg/kg QD Implant: 4.5 mg q5–8 months</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>IV: 60 mg/kg TiD for 2–3 weeks</td>
<td>IV: 30–40 mg/kg TiD</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>IV: 5 mg/kg qwk for 2 wk</td>
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Treatment of non-necrotizing herpetic retinopathies

- Systemic antiviral drugs according to results of PCR
- Duration of antiviral therapy?
- Low dose oral prednisone
- Interferon alpha in severe cases

Nonnecrotizing Herpetic Retinopathies
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CONCLUSIONS

• Herpetic eye disease is very common in our clinical practice
• Diagnosis of herpetic anterior uveitis and necrotizing retinitis is primarily based on typical clinical features
• Laboratory tests on ocular fluids (PCR+++ ) are useful in atypical clinical presentations
• Treatment is complex and requires careful monitoring to provide the appropriate balance of antiviral medication and corticosteroids

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