**HERPETIC RETINOPATHIES**

Moncef Khairallah, MD, Rim Kahloun, MD

Department of Ophthalmology,
Fattouma Bourguiba University Hospital
Faculty of Medicine, University of Monastir, Monastir, TUNISIA

---

**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 causes 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

---

**Necrotizing herpetic retinopathies**

1. “Normal” immune status
   - Acute retinal necrosis (ARN) syndrome
   - Non-necrotizing herpetic retinopathies

2. Immunodepressed status
   - Progressive outer retinal necrosis (PORN)
   - CMV retinitis
• 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
• Moderate associations with HLA-DQw7 (phenotype Bw62) and DR4 antigens in Caucasian patients in the USA and HLA-Aw33, -B44 and -DRw6 in Japan

Viruses: VZV (old patients > 50 years), HSV types 1 and 2 (young patients), CMV (rarely), EBV (exceptionally)

Risk factors for HSV-2 ARN: young age, history of neonatal herpes, neurosurgery, preexisting chorioretinal scar, pericocular trauma, high-dose systemic corticosteroids

In patients with concomitant encephalitis or meningitis, the most likely pathogenic agents are HSV-1 and HSV-2, respectively

• Delay in diagnosis: ARN overlooked or misdiagnosed as another uveitic entity
  - Inappropriate analysis of clinical features
  - Lack of use of molecular diagnosis

• Mistakes in management:
  - Corticosteroids without antivirals
  - Inappropriate use of antivirals: too late, too low, too short, failure to recognize resistance to antiviral therapy

• Consequences: progression, complications, bilateralization, blindness
Acute retinal necrosis (ARN) Clinical presentation

- Various, non-specific ocular symptoms:
  - Redness
  - Photophobia
  - Irritation
  - Tearing
  - Blurred vision
  - Periorbital pain
  - Floaters

Acute retinal necrosis (ARN) Clinical presentation

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

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, may make retinal lesions difficult to see
Acute retinal necrosis (ARN) Clinical presentation

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

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

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></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</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>
Acute retinal necrosis (ARN)
Clinical presentation

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)
Clinical Diagnosis

- Diagnosis of ARN: initially strictly clinically, based on AUS criteria (1994)
- A clinical diagnosis of ARN may be difficult:
  - Wide variation in clinical presentations and course
  - Cloudy media
  - Atypical clinical findings
  - Other entities may mimic ARN
- Delay in diagnosis and treatment: progression, complications, bilateralization, blindness
- Specific and sensitive laboratory tests needed to confirm the diagnosis
Acute retinal necrosis (ARN)

**Laboratory diagnosis**

- Molecular diagnosis (Real time PCR) applied to intraocular fluid sample (aqueous humor, rarely vitreous):
  - Gold standard for the definitive diagnosis of ARN
  - Highly sensitive and specific (>90%)
  - Differentiation of ARN from other entities that may mimic ARN
  - Identification of the causative virus
  - Can be used in monitoring response to treatment

**Natural course and Complications**

- Severe, resulting in poor visual outcome: VA < 20/200 in over 2/3 of patients
  - Extension of retinal necrosis
  - Involvement of the second eye (70%, greatest in the first 14 weeks)
  - Optic atrophy
  - Retinal breaks, retinal detachment (> 75% of untreated eyes, complex, severe PVR, poor visual outcome)
  - Others: epiretinal membrane, CME, SRD, central retinal artery occlusion, retinal/optic disc neovascularization, cataract, phthisis

*Early diagnosis and proper management are mandatory to reduce the ocular morbidity of ARN syndrome*

**Differential diagnosis**

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

- Toxoplasmosis
- Syphilis
- Fungal retinochoroiditis
- Primary intraocular lymphoma
- Sarcoidosis
- Behçet disease
- PORN
- CMV retinitis
Patients with or without diabetes, without local immunosuppression or following intravitreal triamcinolone acetonide, or corticosteroid implants

- High doses of regional corticosteroid may exhibit a localized effect by lowering the overall (CD4+ and CD8+) lymphocyte count.

Clinical features:
- Necrotizing retinitis + occlusive arteriolitis
- Unilateral cotton wool spots
- White chorioretinal spots

---

**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

---

**Treatment of Acute Retinal Necrosis (ARN)**

<table>
<thead>
<tr>
<th>Antiviral Therapy</th>
<th>Induction dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>10-15 mg/kg/8h during 10-14 days</td>
<td>800mg/6h/day</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1-3g/3day</td>
<td>1g/3day</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>IV:5-10mg/kg/12h during 14-21 days, intravitreal: 100-600 µg/2x/week during 2-3 weeks</td>
<td>IV:5mg/kg/day intravitreal: 200-600 µg/week or 2 mg/ml 3x weekly or 4 mg/ml 1x weekly intravitreal 4 mg during 8 weeks</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>Oral 600 mg every 12h during 3 weeks</td>
<td>Oral 600 mg twice daily</td>
</tr>
<tr>
<td>Foscavir</td>
<td>IT: 80 mg/kg/8h during 14 days or IV: CMV 60 mg/kg/24h for 2-3 weeks, HSV: 68 mg/kg/12h for 3 days, intravitreal: 1200-2400 µg every 2-3 days or 2.4 mg/0.1 ml injection, weekly</td>
<td>IV: 90-120mg/kg/day intravitreal: 1200-2400 µg/week 2.4 mg/0.1 ml</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 mgx3/day</td>
<td>500 mgx3/day</td>
</tr>
</tbody>
</table>
Treatment of Acute Retinal Necrosis (ARN)

- The standard treatment: Intravenous acyclovir in three divided doses (10-15mg/kg x 3/day) for at least 7 days, followed by oral treatment: acyclovir 4 g/day or valacyclovir 1 g x 3/day for an additional period of 3-4 months
  Alternatively, oral treatment with valacyclovir alone (3g/day, higher doses, up to 6g or more per day)
  As effective as IV + Oral treatment

- Duration of antiviral therapy: controversial: at least 3-4 months
  Prolonged antiviral therapy reduces the risk of the fellow eye involvement: from more than 70% to less than 15%
  Close monitoring for haematopoetic and renal toxicity

Treatment of Acute Retinal Necrosis (ARN)

- If retinitis threatens or involves the optic nerve or macula, or
- Presence of severe occlusive vasculitis, or
- Serous detachment involving the posterior pole
  In addition of systemic antiviral treatment, intravitreal injection of either foscarnet 2.4 mg/0.1 ml or ganciclovir 2–5 mg/0.1 ml

Treatment of Acute Retinal Necrosis (ARN)

- Close monitoring of the retina to confirm the antiviral efficacy: Clinical examination, sequential fundus photographs:
  - Stabilization (No new lesions after a mean period of 48 h)
  - Resolution (4th day)
  - Complete resolution (one month)
Treatment of Acute Retinal Necrosis (ARN)

- **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 µg x 2 per week
    - Foscarnet: 1200 µg x 2 per week

- **Systemic corticosteroids:** necessary to control secondary inflammation (vitritis, retinal vasculitis, optic neuropathy) and subsequent retinal and optic disc damage
- Steroid therapy initiated after stabilization of retinitis under antiviral treatment: initial dose: 0.5-1 mg/kg of oral prednisone or prednisolone, followed by gradual tapering
- Intravenous pulses of methylprednisolone followed by oral corticosteroids in selected cases
- Steroids should be avoided in immunocompromised patients

- **The effects of anticoagulants and aspirin on occlusive vasculitis remain controversial**
- Retinal detachment prophylaxis with laser (four rows of 500 µ spots placed posterior to the advancing border of retinitis): seems to reduce the risk of RD?
- Retinal detachment surgery: vitrectomy, laser, silicone oil tamponade according to the severity of anatomical lesions
Treatment of CMV retinitis in immunocompetent

- Induction and maintenance therapy with intravenous ganciclovir, intravenous foscarnet, intravenous cidoflovir, or oral valganciclovir is efficacious in inducing remission of cytomegalovirus retinitis.
- Intravitreal ganciclovir 2000 µg weekly, or twice weekly
- Intravitreal Foscarnet: 1200 µg x 2 per week
- Implant of ganciclovir: effective for 8 months

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

Conclusion

- Herpetic eye disease is common in our clinical practice
- Diagnosis of herpetic retinopathies is primarily based on typical clinical features
- Confirmation of diagnosis relies on PCR applied to ocular fluid
- Prompt initiation and prolonged systemic antiviral therapy, well as a good balance of antiviral medication and corticosteroids: essential to reduce the risk of progression, complications, and subsequent loss of vision