The eye in virology

This article outlines the ocular complications of viral infection. The emphasis is on the most common viruses encountered by the physician, and their clinical features and treatment are discussed while demonstrating the variation and often significant sequelae of ocular viral infection.

Viruses are small infectious agents that modify the intracellular environment of a host cell in order to enhance their replication. The high prevalence of viral infection worldwide can be explained by the efficacy of their modes of transmission and the development of complex host–virus interactions enabling lifelong infection. The ocular complications of viral infection are wide-ranging and affect all ophthalmic structures from the external orbit to the retina and optic nerve.

Adenoviral keratoconjunctivitis

Adenovirus infection is a common cause of acute conjunctivitis in adults and children, and can occur in epidemics. It presents as a red, painful eye, but is characterized by copious watery discharge, in contrast to bacterial conjunctivitis in which the discharge is typically sticky. Lymphoid follicles are also typically present on the inside of the lids, and there may be pseudomembranes and haemorrhages of the conjunctiva (*Figure 1*). The most common viral cause of conjunctivitis is adenovirus although it can be associated with the members of the herpes virus family.

Viral infection is usually self-limiting and requires only supportive measures such as cold compresses and topical lubricants. Antiviral treatment is not indicated, but antibiotic treatment may be required if secondary bacterial infection is suspected. Rarely, infection results in subepithelial keratitis. This presents as blurred vision and can lead to permanent corneal scarring, so referral to an ophthalmologist is recommended if visual acuity is significantly affected.

Figure 1. a. Adenoviral keratoconjunctivitis with a typical red eye appearance. b. On eversion of the upper lid, a typical appearance of lymphoid follicles can be seen.

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Herpetic eye disease

The herpes family comprises a large group of double-stranded DNA viruses of which eight are reported to infect humans: herpes simplex virus type 1, herpes simplex virus type 2, Epstein–Barr virus, varicella zoster virus, cytomegalovirus and human herpes viruses 6, 7 and 8 (Miyagawa and Yamanishi, 1999).

Herpes simplex virus

Herpes simplex virus is regarded as endemic in most populations worldwide, being present in the trigeminal ganglia of 18% of teenagers, increasing to 100% of elderly adults (Liedtke et al, 1993). Primary infection with herpes simplex virus results in latency in the sensory ganglia transported in the neuronal axons. Herpes simplex virus type 1 used to be thought to be responsible for oral and facial lesions, with herpes simplex virus type 2 being restricted to genital infection, but this division is now much less clear-cut and both types are responsible for significant amounts of ocular pathology.

Primary herpes simplex virus infection is characterized by oral or facial lesions requiring physical contact and therefore is more commonly transmitted in childhood or adolescence. The ophthalmic complications of primary herpes simplex virus infection occur as a result of droplet transmission or direct inoculation and most cases are mild or asymptomatic, involving self-limiting lesions of the lids and periorbital area or blepharoconjunctivitis, an inflammatory condition of the lid margin which causes redness and irritation. Reactivation of the virus can be triggered at a later date by a variety of events including physical and emotional stress, ultraviolet light, ionizing radiation and tissue damage (Whitley and Roizman, 2001). The site of reactivation may differ from the original site of primary infection. The non-ocular complications of herpes simplex virus consist of a spectrum of clinical entities, including recurrent infection of mucous membranes, encephalitis, neonatal and congenital and eczema herpeticum.

Keratouveitis

Herpes simplex virus causes two main types of ocular disease and is a major cause of cornea-related visual loss

worldwide. Corneal epithelial keratitis is caused by active viral replication in the cornea epithelium and commonly presents as a red eye with blurred vision, conjunctival injection, watering and discomfort. As virus replication occurs, infected epithelial cells swell, leading to destruction of the basement membrane (Edelhauser et al, 1969) and forming a dendritic ulcer. This takes the form of linear branching with characteristic terminal buds, and can be visualized by the application of fluorescein dye (*Figure 2*). Treatment is with topical aciclovir ointment, although direct debridement of the lesion may also be useful. A few patients are resistant to aciclovir, in which case 3-fluorothymidine drops can be used. The herpetic eye disease study has shown a benefit to patients with recurrent disease of taking prophylactic oral aciclovir for periods of up to a year (Barron et al, 1994).

Stromal keratitis occurs deeper in the cornea and is caused by an immune-mediated inflammatory response to viral antigen. Symptoms include gradual onset of blurred vision and haloes around lights. Clinically, stromal oedema presents as corneal haze and is often associated with anterior chamber cell activity (anterior uveitis) and raised intraocular pressure (Patterson et al, 1968). Necrosis and melting of the cornea may result with later opacification and scarring. Treatment is with topical steroids under antiviral cover to prevent reactivation of infective keratitis.

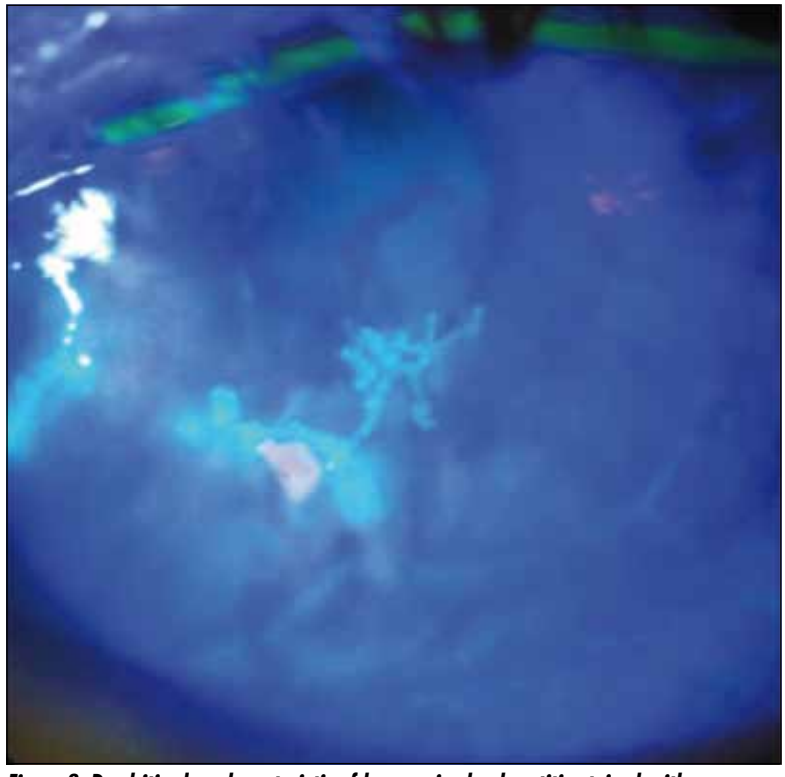
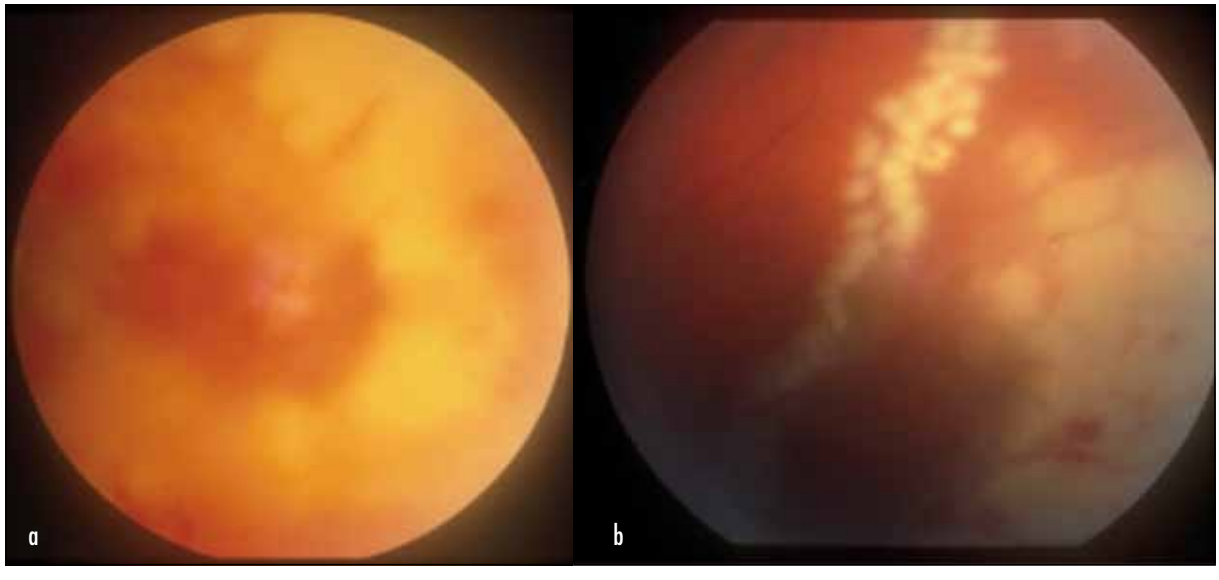


Figure 2. Dendritic ulcer characteristic of herpes simplex keratitis stained with fluorescein and illuminated under a cobalt blue light. Note the branching pattern of the epithelial lesion.

Acute retinal necrosis

Acute retinal necrosis is most commonly caused by herpes simplex virus, but can also be caused by varicella zoster virus or Epstein–Barr virus, and is a rare but potentially devastating vaso-occlusive necrotizing retinitis (*Figure 3*). Patients tend to be young and healthy and typically present with a unilateral loss of vision, with or without pain, although the symptoms are variable and may be absent until late on in the condition. Both anterior and posterior uveitis are typically present, with vitritis often obscuring the view of the retina with ophthalmoscopy, but careful peripheral examination usually reveals focal, well-demarcated white patches of retinitis.

Figure 3. a. Acute retinal necrosis. Note the hazy view as a result of marked vitritis and the underlying bright patches of retinitis and haemorrhage. b. A typical triple-row pattern of barrier argon laser retinal photocoagulation has been applied to the left of the patch of retinitis to reduce the risk of subsequent retinal detachment.



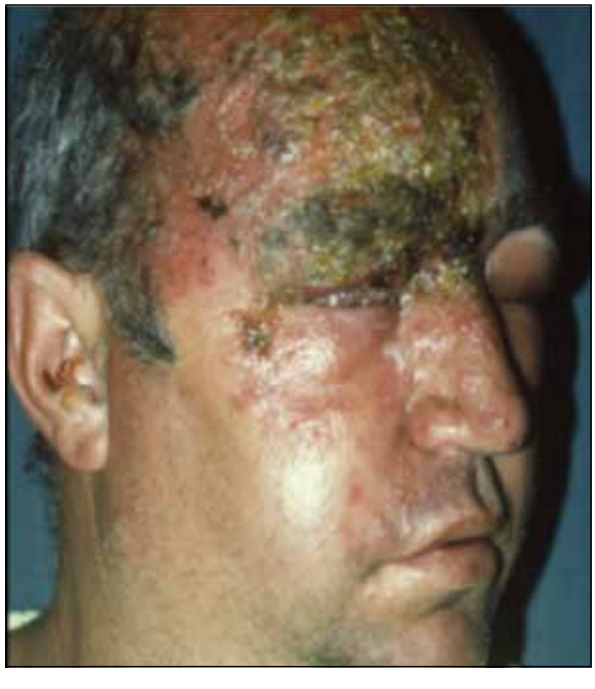
Treatment used to be as an inpatient with intravenous aciclovir, but oral valaciclovir has been shown to have similar ocular penetration and efficacy. Intravitreal therapy may be used in severe disease and can be given at the same time as a vitreous biopsy is taken to confirm the diagnosis by polymerase chain reaction testing. Treatment aims to control the retinitis in the affected eye and reduce the risk of second eye involvement. Barrier laser photocoagulation may be given to reduce the risk of retinal detachment (*Figure 3*), which is the major threat to vision in these patients. Bilateral acute retinal necrosis is occasionally seen in immunosuppressed patients.

Varicella zoster virus

Varicella zoster virus is another double-stranded DNA member of the herpes viruses. Primary infection with varicella zoster virus causes varicella (chickenpox), a benign and common illness of childhood characterized by contagious vesicular eruption of the skin often associated with fever and malaise. Transmission is by either inhalation of airborne droplets or by direct contact with vesicles. Viral spread to the dorsal root and cranial nerve sensory ganglia establishes latency. Ocular signs in varicella include lesions of the lids and eye and may include conjunctivitis and keratitis and anterior uveitis (Pavan-Langston, 2005). Uveitis may occur in up to 25% of children with vesicles of the lids (Jordan and Leon-Paul, 1984).

The secondary clinical manifestation of varicella zoster virus is herpes zoster (shingles), which occurs only in individuals who have had prior exposure to varicella zoster virus, either by infection or by vaccination (Liesegang, 1985). Clinical features include a prodrome of malaise, headache and fever with discomfort, itching or stinging in the distribution of the dermatome. Painful erythematous macular, papular and vesicular lesions then occur along the dermatome with pustules and later crusting (*Figure 4*). Post-herpetic neuralgia is a significant cause of morbidity persisting long after the rash has healed and patients with severe disease may require specialist pain management.

Figure 4. Herpes zoster ophthalmicus with a characteristic distribution and involvement of the tip of the nose (Hutchinson's sign), indicating that ocular involvement is more likely.



Herpes zoster ophthalmicus

Patients with herpes zoster involving the ophthalmic branch of the trigeminal nerve are classified as having herpes zoster ophthalmicus. The ophthalmic nerve divides into three branches along its course, the lacrimal, frontal and nasociliary branches, which is of clinical relevance as the nasociliary nerve supplies the uveal tract, cornea, sclera and skin of the upper and lower eyelids and the tip of the nose. Skin lesions at the tip of the nose are known as Hutchinson's sign and are a strong positive predictor of ocular involvement in herpes zoster (Hutchinson, 1865), with 76% of patients with this sign developing ocular complications (Harding et al, 1987).

Ophthalmic involvement in herpes zoster is regarded as its most serious complication (Edgerton, 1945). Epithelial keratitis and conjunctivitis may occur as a result of direct viral invasion and present with punctate corneal epithelial staining and microdendrites, which differ from those in herpes simplex as they lack terminal bulb and stain poorly with fluorescein. Secondary inflammation may result in uveitis, episcleritis and even scleritis, and damage to corneal nerves may lead to loss of corneal sensation and consequent neurotrophic keratitis characterized by corneal epithelial erosions and ulcers.

Less common causes of visual loss in herpes zoster ophthalmicus include optic neuritis and acute retinal necrosis, as described above, so it is recommended that patients with visual loss are referred for an ophthalmic

Figure 5. Progressive outer retinal necrosis in a patient immunocompromised following a allogenic bone marrow transplant. Note the clear view of the retinitis, indicative of a total lack of vitritis, and the scattered areas of multifocal infection surrounding the central lesion.

opinion. In the immunocompromised, both varicella zoster virus and herpes simplex virus are associated with progressive outer retinal necrosis (Walters and James, 2001), which is a rapidly progressive multifocal retinitis of the posterior pole (*Figure 5*). This most commonly occurs in patients with acquired immunodeficiency syndrome, but has also been reported following bone marrow transplantation (Khot et al, 2006).

The severity of herpes zoster ophthalmicus increases with age and with immunodeficiency. Treatment of the acute systemic disease is with oral aciclovir, but intravenous therapy (or high-dose oral valaciclovir) is required for acute retinal necrosis. Topical steroids under the care of an ophthalmologist may be required for ocular inflammation.

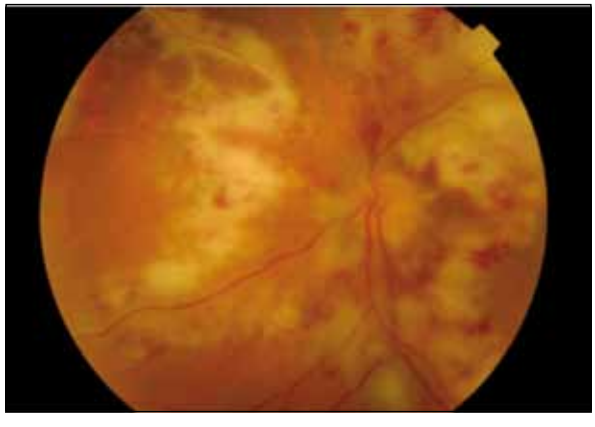
Cytomegalovirus

Cytomegalovirus forms part of the beta subgroup of the herpes viruses and is the most common cause of opportunistic infection in patients with acquired immunodeficiency syndrome, developing in up to 50% of patients before the advent of highly active antiretroviral therapy (Jabs, 1995). Primary cytomegalovirus infection is extremely common and causes a mild febrile illness, but can reactivate if immunity is compromised.

Cytomegalovirus retinitis may be asymptomatic, particularly because immunodeficient patients do not mount a vitritis in response to intraocular infection. The infection causes a necrotizing retinitis, but unlike herpetic retinitis, this tends to spread slowly at a rate of approximately 1.5 mm per week (*Figure 6*). Examination demonstrates patchy retinitis and haemorrhage that is said to resemble a 'pizza pie'. It is usually a clinical diagnosis, but polymerase chain reaction of a vitreous tap can provide useful confirmatory evidence.

Visual loss is variable depending on the location of the retinitis, but disease affecting the macula and optic disc causes irreversible visual loss. If more than a quarter of the retina is affected, there is a significant risk of retinal detachment, which may present with flashes and floaters followed by visual loss. Treatment is with either intravenous ganciclovir or oral valganciclovir, but intravitreal foscarnet may be used for severe disease to provide rapid control of infection. Where cytomegalovirus retinitis develops in patients with acquired immunodeficiency syndrome, immune restoration with highly active antiretroviral therapy is delayed by 2 weeks where possible, as there is otherwise a significant risk of developing immune recovery uveitis, a form of ocular inflammation that can be difficult to manage. This window allows the cytomegalovirus load to be decreased, thereby decreasing any subsequent inflammatory response when the immune system is restored.

Figure 6. Advanced cytomegalovirus retinitis, illustrating the 'pizza pie' clinical pictures of mixed retinitis and patches of haemorrhage. Both the macula and optic disc are involved, indicating that the disease has been present for some time, and compatible with irreversible visual loss.

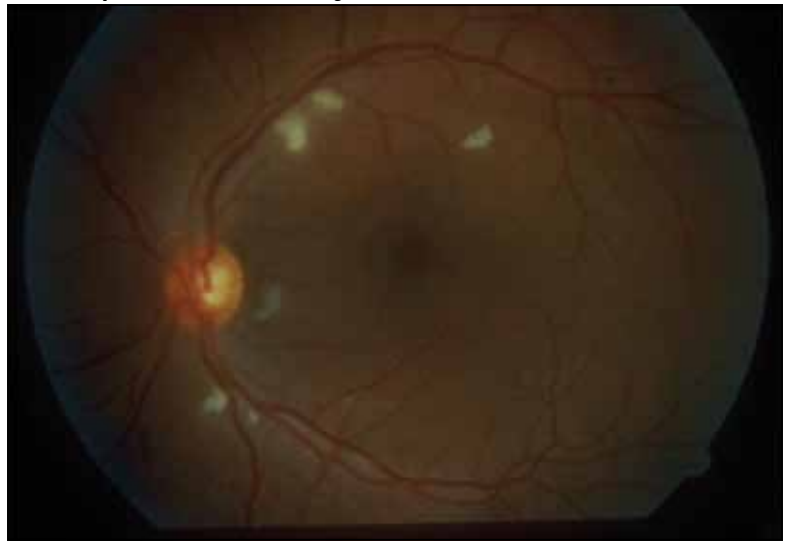


Human immunodeficiency virus

Infection with the human immunodeficiency virus is characterized by ocular involvement in several disease stages. Retinal microvasculopathy is the most commonly reported ocular manifestation and affects up to 50–70% of human immunodeficiency virus-positive patients (Pepose et al, 1985), its incidence rising as CD4+ count falls (*Figure 7*). It may be the presenting sign of acquired immunodeficiency syndrome: patients are usually asymptomatic, but retinal microaneurysms, cotton wool spots and scattered haemorrhages resembling diabetic retinopathy can be seen on fundoscopy. Its aetiology is thought to involve a combination of a hyperviscosity syndrome and direct endothelial cell infection. Large vessel disease can also occasionally be seen in patients infected with human immunodeficiency virus in the form of branch retinal artery and vein occlusions.

Increasing immunodeficiency also leads to an increased risk of opportunistic infection, and the eye can be affected by several different organisms, including *Toxoplasma*

Figure 7. Human immunodeficiency virus microvasculopathy in early human immunodeficiency virus infection demonstrated by scattered cotton wool spots. Often microaneurysms and small haemorrhages are visible on careful clinical examination.



gondii, cytomegalovirus and *Pneumocystis carinii*. Indeed, ocular examination can help with the underlying diagnosis as many of these conditions have characteristic appearances when they occur in conjunction with human immunodeficiency virus co-infection. The most common opportunistic infection is cytomegalovirus retinitis, and its development is highly suspicious for human immunodeficiency virus infection in patients with no other obvious reason for immunodeficiency.

Other viruses

Epstein–Barr virus is a double-stranded DNA virus that is transmitted through blood or saliva and is often contracted at a young age. In early life this is often asymptomatic but in adolescence it causes infectious mononucleosis, which may have ocular manifestations including conjunctivitis, keratitis and uveitis (Matoba, 1990). Epstein–Barr virus is also reported to be a cause of acute retinal necrosis, although the significance of the presence of Epstein–Barr virus in the vitreous on polymerase chain reaction testing is not yet clear.

Rubeola is a single-stranded RNA paramyxovirus that is the causative virus of measles. Infection acquired early in pregnancy may result in spontaneous abortion, fetal malformations and congenital disease (Wong et al, 1993). Congenital infection also leads to cataract and a pigmentary retinopathy (Greg, 1941). Retinopathy can also occur in acquired infection, as can optic disc swelling and attenuated vessels, but most disease is self-limiting and treatment is not indicated.

Rubella is a single-stranded RNA virus which causes congenital disease that can be described as a triad of ocular, hearing and cardiac defects (Mets and Chhabra, 2008). Its ocular manifestations are similar to those in measles and include cataract, microphthalmos and a 'salt and pepper' retinopathy. Acquired disease can rarely cause keratitis and conjunctivitis with a pigmentary retinopathy and exudative retinal detachments.

Conclusions

Viruses are a common cause of ophthalmic problems and can affect any part of the eye. Adenoviral conjunctivitis is usually self-limiting, but involvement of the cornea by this and other viruses can cause longer-lasting problems. Infection of the retina by herpes viruses is more serious and requires antiviral therapy if permanent visual loss is to be avoided – visual loss in viral infection is an indicator for early referral to an ophthalmologist. There are several ocular manifestations of human immunodeficiency virus, including early microvasculopathy and late opportunistic infection, whose identification can be useful in helping to diagnose underlying disease. **BJHM**

KEY POINTS

- Viral infection is a common cause of ocular symptoms and signs.
- Adenoviral conjunctivitis causes a watery, red eye and treatment is supportive, unless vision is compromised.
- Herpetic eye disease is a common causes of ocular morbidity and herpetic keratitis can be infectious or immune-mediated; ophthalmological input is required to distinguish these entities. Acute retinal necrosis is a rare complication that can cause severe visual loss.
- Human immunodeficiency virus infection causes a microvasculopathy early in the disease, but also predisposes to later opportunistic infection, characteristically cytomegalovirus retinitis.

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