

Herpetic Retinitis

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KEY WORDS

z *HERPESVIRUS RETINITIS* z *ACUTE RETINAL NECROSIS*
z *PROGRESSIVE OUTER RETINAL NECROSIS*
z *CYTOMEGALOVIRUS RETINITIS* z *EPSTEIN-BARR VIRUS RETINITIS*

SUMMARY

This paper provides an appreciation of the various forms and consequences of retinal inflammation caused by human herpesviruses. Herpes simplex virus types 1 and 2, varicella zoster virus, cytomegalovirus and Epstein-Barr virus are known to cause retinitis. The prognosis of herpetic retinitis remains poor because it is associated with a high incidence of complications, both during and after the acute disease phase. On diagnosis of retinal necrosis, antiviral treatment must be started promptly to limit disease progression; following this, prophylactic maintenance therapy may be required.

Introduction

VIRUSES ARE AMONG the most common causes of infections involving the posterior segment of the eye. Such infections may be either congenital or acquired, and may primarily affect the retina or the choroid. Herpesviruses, which are widely disseminated in nature, are the main pathogenic microbes that cause chorioretinitis. The human herpesviruses known to cause retinitis are: herpes simplex virus (HSV) types 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Although there is nothing in the literature to confirm how prevalent such infections might be, clinical forms of retinitis have been described and differentiated according to appearance. When retinitis is suspected on clinical examination, antiviral treatment must be introduced promptly, after obtaining ocular diagnostic specimens (if possible). The prognosis of herpetic retinitis remains dismal because of the high incidence of ocular complications during and after the acute disease phase, such as retinal detachment or macular necrosis. The authors have witnessed the life-altering effects of herpes retinitis on patients and have written this article to provide the readership of *Herpes* with a general appreciation of the various forms and consequences of this condition.

Retinitis Associated with HSV and VZV

Globally, HSV-1 and 2 are widespread pathogens; both affect the general population¹ and are transmitted through close personal contact. Primary HSV infections, which can be asymptomatic, usually involve the mucosa. HSV establishes latency in sensory ganglia and may be reactivated by various stimuli throughout life.

Primary infection with VZV causes chickenpox, but ophthalmic involvement usually happens as a reactivation from latency (namely, herpes zoster) and may lead to the formation of vesicles on the eyelids, conjunctiva and cornea. Anterior uveitis occurs in up to

25% of patients with herpes zoster ophthalmicus; posterior segment involvement is unusual.²

Sight-threatening acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN)³⁻⁵ are two ends of the spectrum of herpetic retinitis that can occur, depending on the host's immune status. ARN is commonly seen in those with normal to mildly depressed immune states,⁶ whereas PORN is found in people with moderate or severe immunosuppression, such as those with AIDS. There have, however, also been reports of progression from ARN to PORN in the same person at different times, depending on his or her immune status.⁷

Acute Retinal Necrosis

First described in 1971,⁸ ARN is characterized by focal, well-demarcated areas of peripheral retinal necrosis (full-thickness retinitis) with rapid circumferential progression, occlusive retinal arteritis, and anterior uveitis and vitritis from inflammation. These criteria were published in 1994 by the American Uveitis Society.^{9,10} VZV, HSV-1, HSV-2, CMV and EBV have all been implicated in the aetiology of ARN.

There is no known association between gender, race or age and the incidence of ARN.¹⁰ Typically, HSV-2 causes ARN in people aged <25 years, whereas VZV and HSV-1 cause this form of retinitis in those aged >25 years.¹¹ In people with a history of encephalitis, ARN is most likely to be caused by HSV-1, whereas HSV-2 is implicated in people with a history of meningitis. HSV-2 ARN may be a consequence of viral reactivation rather than primary infection.¹¹

Unlike PORN, ARN usually occurs in apparently immunocompetent patients, leading to severe ocular morbidity and permanent visual impairment.¹² Bilateral acute retinal necrosis (BARN) occurs in 33% of patients with herpetic retinitis,¹³ but may not present until many years after the initial diagnosis (the longest reported interval described is 34 years).¹⁴ In the absence of vitritis and anterior chamber inflammation, other forms of retinitis (such as CMV retinitis and PORN) should be considered. VZV is reported to be the most common cause of both PORN and ARN; it may be two times more common than HSV as a cause of ARN.^{10,15}

Why this devastating infection occurs in individuals who purportedly have a functioning immune system is open to conjecture. Interferon (IFN)- γ levels in the vitreous have a positive correlation with final visual acuity in people with ARN,¹⁶ although subjects with the most severe presentations of VZV-associated ARN in this study had absent delayed-type hypersensitivity (DTH) responses against VZV antigens, with low IFN- γ levels.¹⁶ The explanation offered for these findings is as follows: IFN- γ induces major histocompatibility complex (MHC) class II expression on the cell surface, facilitating antigen presentation and the induction of

an immune response. Low IFN- γ levels reduce MHC class II expression, leading to the persistence of infection, allowing easy viral replication, causing continued damage and (in the case of ocular involvement) reduced visual acuity. Conversely, high IFN- γ levels reflect an immune response and the influx of T-helper cells. A high level of immune response against VZV presumably results in infection clearance and abrogation of inflammation in the anterior chamber and vitreous, both resulting in a return to the pre-infective 'normal' state of high visual acuity. The severity of other viral diseases, such as respiratory syncytial virus and HIV, has also been shown to inversely correlate with IFN- γ levels.^{17,18} Rochat *et al.* found that, along with impaired cellular immunity and absent delayed-type hypersensitivity-type responses, the number of B-lymphocytes in the peripheral blood of ARN patients (by flow cytometry analysis) also increased, prompting them to hypothesize an imbalance between the cellular and humoral immune responses in patients with ARN.¹⁹ Other authors have also reported the curious finding that patients with VZV-associated ARN have high antibody titres against VZV, and that these titres correlate inversely with the intensity of VZV-DTH responses.

Though HSV-related ARN is typically seen in healthy and non-debilitated people, the immunocompromised may also be affected. It is probably unsurprising that immunocompromised patients frequently have bilateral involvement, are more predisposed to retinal detachments, have more recurrences and fare worse despite antiviral therapy.²⁰

CLINICAL PRESENTATION

Initially, people with ARN experience symptomatic small declines in vision. Symptoms include blurred vision, pain and photophobia; occasionally, retinal haemorrhages may be present. Severe central visual loss is an atypical presentation, since retinal detachment typically occurs later in the disease course. On clinical examination, signs include varying degrees of anterior segment inflammation (such as white blood cells in the anterior chamber and/or in the vitreous cavity seen by slit-lamp biomicroscopy). The posterior pole is generally spared, while peripheral retinal lesions (retinal inflammation and obliterative arteritis, Figure 1) rapidly progress circumferentially and posteriorly, and can form a confluent creamy retinitis (Figure 2). Optic-nerve involvement may cause visual field defects, colour aberrations and an afferent pupillary defect. Complications include rhegmatogenous retinal

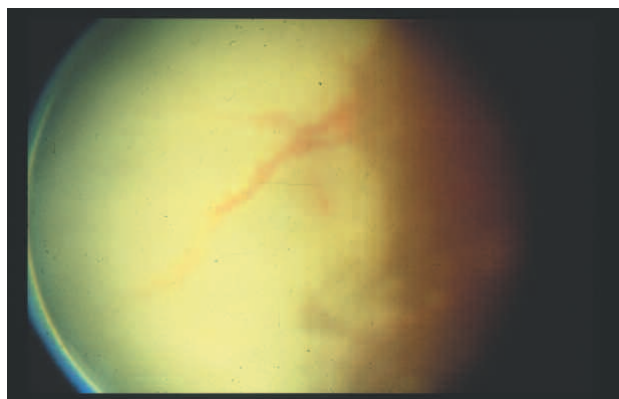


Figure 1: Slit-lamp biomicroscopy of peripheral retinal lesions in acute retinal necrosis, showing peripheral retinal necrosis, +++ vitritis (vitreous inflammation) and retinal arteritis (inflammation of the retinal arteries).

detachment (in up to 75% of cases)²¹ secondary to an atrophic and thinned retina with development of a retinal tear.

In children with leukaemia and other haematological malignancies, posterior segment involvement may mimic leukaemic infiltration, causing a diagnostic dilemma.^{2,22} Leukaemic involvement may cause retinal vessel changes, haemorrhages or optic nerve involvement.

Progressive Outer Retinal Necrosis

First reported in 1990 by Forster,²³ PORN is a necrotizing chorioretinitis that is found almost exclusively in people with advanced stages of AIDS, in whom it is the second most common cause of blindness.²⁴ PORN cases have also been reported in patients otherwise immunocompromised (either from systemic disease or iatrogenically from treatment of their disease) such as those with idiopathic thrombocytopenic purpura, cutaneous non-Hodgkin's lymphoma, renal transplantation and allogeneic stem-cell transplantation.²⁵

CLINICAL PRESENTATION

The incidence of PORN is far less than that of ARN; the typical clinical symptoms of PORN are decreased vision (20/20 to no light perception), 'floaters' (which represent shadows cast on the retina by vitreal inflammatory cells/debris) and loss of peripheral vision. Rarely, an afferent pupillary defect is present. Optic nerve involvement can also masquerade as papillitis or neuroretinitis. Slit-lamp biomicroscopy shows that inflammatory cells are usually present in the vitreous, but there is minimal vasculitis; cotton-wool spots and multifocal areas of retinal whitening with confluent necrosis are found, but intraretinal haemorrhages are rare (Figure 3). The multifocal, peripheral lesions coalesce and rapidly progress, despite treatment, and PORN generally advances rapidly, leading to bilateral and complete visual loss despite treatment with antiviral agents.

Most people with PORN have generalized herpes zoster infection prior to, or coincident with, its development.²⁴ Haematogenous VZV dissemination has been suggested as a risk factor for PORN, as has aciclovir-resistant VZV (which occurs as a result of mutations in VZV thymidine kinase genes).²⁶ Complications include rhegmatogenous retinal detachment, secondary to an atrophic and thinned retina with multiple holes.

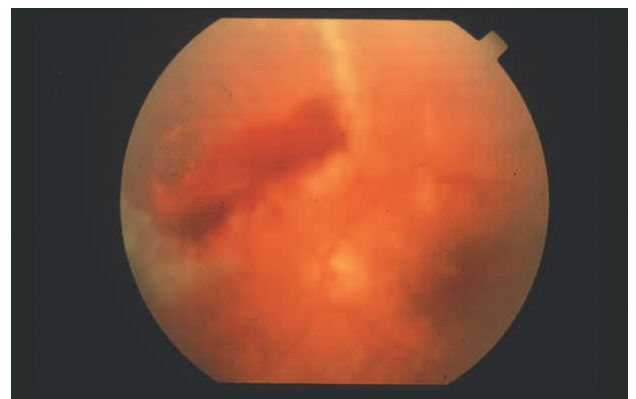


Figure 2: Slit-lamp biomicroscopy of confluent creamy retinitis (top left of photo) in acute retinal necrosis, with ++ vitritis.

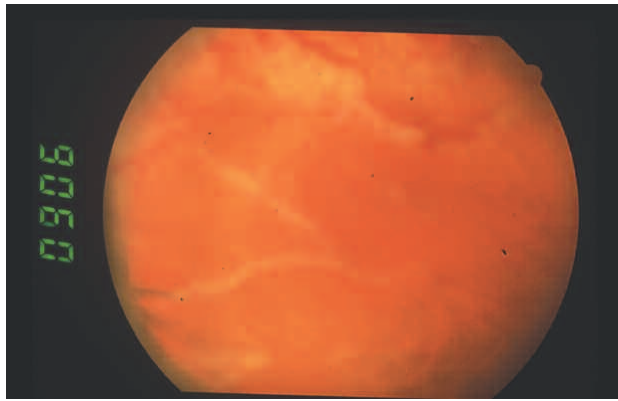


Figure 3: Slit-lamp biomicroscopy showing cotton-wool spots and multifocal areas of retinal whitening with confluent necrosis (top) in progressive outer retinal necrosis. Note that the vessels are still somewhat normal in calibre and can be distinguished, but have perivascular exudates (retinal sheathing) around them, compared with the abnormal vessels seen in Figure 1.

Diagnosing Retinal Necrosis

The diagnosis of viral retinitis (both ARN and PORN) is generally based on clinical examination, but overlapping fundus findings early in the disease course make a diagnosis of CMV, VZV or HSV retinitis difficult. Knox and associates found a strong correlation between the development of HSV retinitis and a previous history of encephalitis or a neurosurgical procedure.²⁷ Herpesvirus-related retinitis may also be difficult to distinguish from that caused by other micro-organisms such as *Treponema pallidum* or *Toxoplasma gondii*.^{28,29} The differential diagnosis of ARN includes Behçet's disease, CMV retinitis, primary intraocular lymphoma, sarcoidosis, syphilis, toxoplasmosis and VZV-induced retinitis.

Diagnostic evaluation of the intraocular fluid can be useful, using methods such as electron microscopy, immunocytochemistry, fluorescent antibody testing and viral isolation in cell cultures, together with serological analysis of serum/intraocular fluid for immunoglobulin (Ig)G. However, these techniques all have low thresholds for detection and low sensitivities, and therefore are not currently recommended as diagnostic tests. The development of the polymerase chain reaction (PCR), which is a rapid, sensitive and specific diagnostic test with small sample requirements, has been a major diagnostic advance. The sensitivity and specificity for diagnosing CMV retinitis using PCR are reported to be 95 and 99%, respectively, and for VZV retinitis are reported to be 100 and 97%, respectively.²⁷ The current gold standard for diagnosis is PCR of aqueous or vitreous samples to detect viral DNA,³⁰ although this technique may also be performed on serum samples.² Attempts to standardize a multiplex PCR (mPCR) have been successful, reducing time and cost with the same sensitivity and specificity levels, therefore being more efficient. Abe and associates³¹ found that PCR was more sensitive and specific for detecting the aetiological agents when they compared PCR and local antibody production for ARN diagnosis. Others who have compared PCR with viral culture³² and *in situ* hybridization³³ have found PCR to be superior to all of these alternatives. Samples obtained by anterior chamber paracentesis are preferable to those obtained by pars plana vitrectomy (PPV): they are easier and more convenient to obtain, especially in an emergency,

and the potential side-effects (hyphema, cataract formation) are relatively rare. Several studies using PCR found no important complications.^{31,32} Conversely, and considering the weakness of the affected retina, PPV seems to have a higher rate of potential risks, especially retinal detachment.

Treating Retinal Necrosis

Intravenous (i.v.) aciclovir (1500 mg/m²/day in three divided doses, over 10–14 days) is the standard care for ARN patients;³⁴ oral aciclovir is then employed for variably prolonged periods. Retinal lesions typically dissipate 4–5 days after therapy initiation, thereby decreasing the risk of subsequent development of BARN.³⁴ Palay *et al.* showed that only 13% of aciclovir-treated patients developed BARN, compared with 70% of untreated patients.³⁵ Thankfully, most immunocompetent patients with necrotizing herpetic retinopathy respond to i.v. aciclovir.

Following 24–48 h of antiviral treatment, oral corticosteroids at dosages of 40–60 mg/day may be introduced to limit the amount of inflammatory response, in cases of HSV retinitis. However, some patients may be infected with HSV strains resistant to conventional therapy; intravitreal antiviral therapy may be introduced to improve visual prognosis in these patients.³⁶ Some patients benefit from intravitreal ganciclovir injection (200 µg/0.05 ml) and i.v. foscarnet (1200 µg/0.05 ml, administered every other day, for four doses).^{2,37} In cases of ARN caused by VZV, brivudine and valganciclovir have shown good results.³⁸ Valganciclovir is a valyl ester prodrug of ganciclovir, with proven efficacy comparable to that of intravenous ganciclovir.³⁹ Famciclovir has also been used.

Argon laser photocoagulation posterior to the edge of necrosis may be performed as prophylaxis against retinal detachment, which is the major cause of visual loss after acute manifestations have resolved. Recommendations include three or four rows of 500 micron spots placed posterior to the advancing border of retinitis. The chorioretinal scars produced by the laser burns act as 'spot welds', which may hold the retina in place in the event that retinal tears develop in the area of retinal necrosis, with subsequent retinal detachment in that area.

CMV Retinitis

Cytomegalovirus seldom causes clinically apparent disease in immunocompetent people. Neonates and immunocompromised patients with leukaemia, lymphoma, conditions requiring immunosuppressive therapy, and especially AIDS, are the main groups at risk for CMV retinitis (CMVR).⁴⁰ The mode of transmission is not totally clear, but probably requires close contact with body fluids containing the virus. Most CMVR cases result from a reactivation of previously acquired infection, which is usually subclinical.⁴¹ CMVR occurring after intravitreal injection of steroids has also been described.⁴²

Congenital CMV disease affects approximately 10% of the neonates born to pregnant women with primary CMV infection.¹ CMVR affecting neonates is frequently associated with other systemic signs and symptoms, such as fever, thrombocytopenia, hepatosplenomegaly or anaemia.⁴³ The posterior segment examination normally shows multifocal areas of brushfire retinitis, which is sometimes difficult to appreciate because of cataract formation. The resolution is usually accompanied by a mixture of pigmented and atrophic lesions.

Acquired CMVR was quite rare before the AIDS era. In the mid-1990s, prior to the introduction of highly active antiretroviral therapy (HAART), about 30% of people with AIDS developed CMVR during their lifetime.⁴⁴ However, HAART has resulted in a 75% reduction in the incidence of CMVR.⁴⁵

Finally, we should not forget that CMV is a possible cause of ARN (Table 1). The features of CMV-associated ARN are very similar to those of ARN caused by other herpesviruses, described previously in this paper.

CLINICAL PRESENTATION

Cytomegalovirus retinitis is a slowly expanding lesion, usually beginning as a small, white, retinal infiltrate. The rather slow rate of viral replication is important to differentiate this from the more aggressive HSV retinitis.⁴⁷ Initially, CMVR may be difficult to diagnose because it can simulate a cotton-wool spot, which is commonly present in HIV retinopathy. The clinical features representing distinct manifestations of the same entity (or different disease stages, depending on host-defence mechanisms and rapidity of dissemination) are mainly as follows:

- Granular, white, multifocal satellite lesions of patchy retinitis (which may represent infection of a terminal vessel) with limited or no retinal haemorrhage. This variant often shows a central atrophic zone;
- An arc-shaped, solitary, expanding patch of retinitis, usually concurrent with multiple retinal haemorrhages and no atrophic zone in the lesion's centre (Figure 4). This variant is normally referred to as fulminant retinitis and is probably caused by infection of the major vascular arcades;

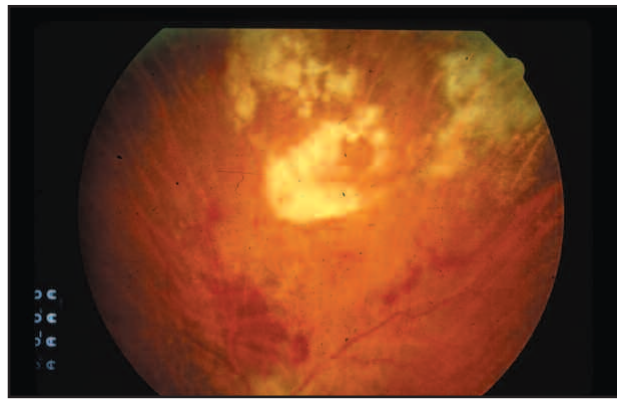


Figure 4: Clinical appearance of CMV retinitis in an AIDS patient: Full-thickness white retinal opacification associated with hard exudates and haemorrhages. Note the minimal amount of overlying vitreous inflammation because of severe immunosuppression in AIDS.

- Sometimes in CMVR, perivasculitis may be predominant with some retinal necrosis. This variant is called frosted-branch angiitis. The degree of vitritis in these patients is typically low because of extreme immunosuppression.

DIAGNOSING CMVR

The diagnosis of CMVR is principally based on clinical criteria, i.e. the appearance of retinal lesions with 'classic' or typical features in immunocompromised patients, in whom this disease is discovered at autopsy or chorioretinal biopsy.⁴⁰ Serum antibodies (especially IgG), which can be detected in the majority of people,

Table 1: Summary of human herpesviruses that may cause chorioretinitis

Herpesviruses	Type of retinitis caused	Special features
Herpes simplex virus type 1	ARN	Typically in patients aged >25 years More common with history of encephalitis ⁵
	PORN	Immunocompromised
Herpes simplex virus type 2	ARN	Typically in patients aged <25 years More common with history of meningitis
	PORN	Immunocompromised ⁶
Varicella zoster virus	ARN ¹⁶	Typically in patients aged >25 years Most common cause
	PORN	Immunocompromised ³⁶ Most common cause
Epstein-Barr virus	ARN ⁴⁶	Immunocompromised (few cases described)
Cytomegalovirus	CMVR	Immunocompromised ⁴⁰ Immunocompetent ⁴¹ (much less frequent)
	Granular, patchy retinitis	
	Fulminant retinitis	
	Frosted-branch angiitis	
	Congenital CMVR	Neonates from pregnant women with primary infection ¹
	ARN	

ARN, acute retinal necrosis; PORN, progressive outer retinal necrosis; CMVR, cytomegalovirus retinitis.

merely show evidence of previous exposure to CMV and therefore have limited diagnostic value.

Detection of antibody levels from vitreous and/or aqueous humour (and comparison with serum levels using the Goldman–Witmer coefficient) can be helpful in selected cases, particularly if combined with PCR analysis.⁴⁸ PCR from ocular tissue, if other malignant entities are suspected,⁴⁹ or fluid (aqueous or vitreous humour) can demonstrate the existence of viral DNA, but it is important to remember that this does not directly give the diagnosis of CMVR because CMV can persist in tissue without causing disease.⁴³ When retinal biopsy is performed, histopathological study of the specimen will demonstrate giant or cytomegalic cell formation; electron microscopy and immunohistochemical studies will also assist the diagnosis. Finally, the CMV load may have utility as a screening tool to exclude resistance and is useful in monitoring treatment.⁵⁰

Entities, besides herpes simplex retinitis, that should be considered in the differential diagnosis of CMVR are: tuberculosis, cat-scratch disease, *Candida* endophthalmitis, and all those included in the differential diagnosis of ARN, previously mentioned.⁴⁷

TREATING CMVR

Treatment for CMVR is complex, requiring collaboration between the ophthalmologist and the treating specialist. Anti-CMV drugs are virostatic and cannot eliminate the pathogen, which is why – in an immunocompromised state – the possibilities of relapse or progression are important.⁴⁰ The first step is to improve the patient's immune status, if possible. In some patients (but not people with AIDS), the discontinuation or reduction of immunosuppressive therapy may be sufficient to result in a cure. However, some will show active vitritis coinciding with the revitalization of their immune system. This has been described as immune recovery uveitis, and should not be interpreted as a relapse.⁵¹

AIDS

Systemic and local anti-CMV drugs are needed in almost all AIDS patients, with ganciclovir, foscarnet and cidofovir being the most commonly used agents. Ganciclovir is usually administered intravenously, the initial high-dose induction therapy (5 mg/kg twice daily for 2 weeks) is followed by long-term maintenance therapy (5 mg/kg once daily). If there is a good response to induction therapy, oral maintenance therapy can be used. Foscarnet is administered intravenously and requires high-dose induction therapy (60 mg/kg every 8 h for 2 or 3 weeks) followed by long-term maintenance therapy (90–120 mg/kg/day 5 or 7 days a week). Others approved are fomivirsen and valganciclovir.⁴³ These drugs are usually administered systemically (i.v. and/or orally), but in patients who cannot tolerate them, or those who show progression despite high dose of therapy, intravitreal (injections or implants) of ganciclovir or foscarnet can be considered.^{43,52} Under topical anaesthesia, an intravitreal injection of 2.0 mg in 0.1 ml of ganciclovir (or 2.4 mg in 0.1 ml of foscarnet) is given once a week. Lesion size is the main indicator of therapeutic response, but in chronically immunocompromised patients, anti-CMV therapy will need to be maintained indefinitely. Despite the remarkable initial treatment responses that have been described with the drugs listed above, active retinitis may recur. The duration of drug treatment is a controversial issue and probably should be maintained until the patient's immune reconstitution is achieved (CD4+ T-cell counts of >200/μl in the case of AIDS patients).⁵³ Nevertheless, regular ophthalmological examinations are

required to detect new events. Prognosis in terms of retinitis progression, fellow eye involvement and survival time has improved considerably among AIDS patients since the introduction of HAART.^{45,53,54}

Epstein–Barr Virus

The role of EBV in ocular diseases is not completely understood because approximately 90% of the adult population is EBV-seropositive and few, to our knowledge, suffer from ocular disease.^{1,54} EBV may affect the eye in many different ways, usually as conjunctivitis or uveitis.

Retinitis associated with EBV infection is an uncommon complication that has been described in people with infectious mononucleosis,⁵⁵ X-linked lymphoproliferative disorder,⁴⁶ AIDS⁵⁶ or even those who are otherwise healthy.¹ The clinical features of EBV-associated retinitis are similar to those described in ARN caused by the other herpesviruses: intense vitreous inflammatory reaction, pale-yellow infiltration of the retina with retinal haemorrhages and occlusive vasculitis.⁴⁶ It is a severe condition in which the patient typically develops extensive chorioretinal scarring, located in the areas of previously necrotic retina.

The diagnosis, as with other causes of ARN, is primarily based on clinical findings, but it is very difficult to establish EBV as the aetiological agent. PCR is reported as useful for confirming the diagnosis; co-infection with EBV and CMV in an AIDS patient has been demonstrated using tissue microdissection and PCR.⁵⁷

Serum antibody titres against EBV may be helpful, especially if initially high levels are followed by decreases that coincide with the resolution of the acute phase.⁵⁸ Retinal biopsy shows haemorrhagic and necrotic retina interspersed with atypical lymphocytes (which are characteristic of EBV infections). *In situ* hybridization of the specimen shows a positive response for EBV-DNA in lymphocytes (and negative response for CMV, HSV and VZV), but not in retinal cells.⁵⁵ The pathogenesis of these findings remains controversial, and two possible mechanisms explaining the extensive retinal necrosis in the absence of EBV positivity in the retinal cells have been postulated:

- Bystander-killing activity that results from cytotoxic T-cells: in people with X-linked lymphoproliferative disorder, fulminant hepatitis and necrotizing skin lesions occur, for example, in the absence of direct infection of parenchymal cells;
- Lymphocytic vasculitis, based on the presence of lymphocytic infiltrates, thrombosed blood vessels, and extensive haemorrhagic retinal necrosis, commonly seen in the retinal biopsy samples of EBV-associated retinitis patients.

The differential diagnosis of EBV-associated retinitis would be the same as in other types of ARN. Treatment decisions are, however, controversial. The first appropriate step may be to begin with the same therapy regimen described for ARN.

Conclusions

A summary of the herpesviruses that can cause chorioretinitis is given in Table 1. Despite great advances in diagnostic techniques and antiherpetic pharmacopoeia, the prognosis of herpetic retinopathies remains poor, due to a high incidence of ocular complications. Early

i.v. treatment, in addition to the available laboratory tests to determine disease aetiology, seems to limit the progression of retinal necrosis. Initial treatment often needs to be followed by prophylactic maintenance in order to improve long-term prognosis.

Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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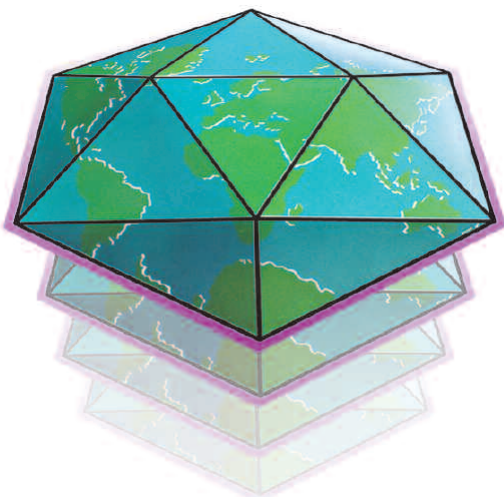
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