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Viral posterior uveitis

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Abstract

The causes of posterior uveitis can be divided into infectious, autoimmune, or masquerade syndromes. Viral infections, a significant cause of sight-threatening ocular diseases in the posterior segment, include human herpesviruses, measles, rubella, and arboviruses such as dengue, West Nile, and chikungunya virus. Viral posterior uveitis may occur as an isolated ocular disease in congenital or acquired infections or as part of a systemic viral illness. Many viruses remain latent in the infected host with a risk of reactivation that depends on various factors, including virulence and host immunity, age, and comorbidities. Although some viral illnesses are self-limiting and have a good visual prognosis, others, such as cytomegalovirus retinitis or acute retinal necrosis, may result in serious complications and profound vision loss. Since some of these infections may respond well to antiviral therapy, it is important to work up all cases of posterior uveitis to rule out an infectious etiology. We review the clinical features, diagnostic tools, treatment regimens, and long-term outcomes for each of these viral posterior uveitides.

Keywords

viruses; posterior uveitis; viral posterior uveitis; CMV retinitis; herpetic retinitis; polymerase chain reaction

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1. Introduction

Posterior uveitis is an inflammation of the posterior uveal tract (retina and choroid). According to the International Uveitis Study Group[24] and Standardization of Uveitis Nomenclature working group[106] classification, posterior uveitis includes focal, multifocal or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, and neuroretinitis.

The incidence of uveitis has been estimated between 17 and 52 cases per 100,000 population per year, with a prevalence of 38–714 cases per 100,000 population.[242] Uveitis generally has an equal gender distribution,[242] with a slight female predominance in some studies.[55,131,150,153] Uveitis can occur at any age, but the mean age of incidence is between 30 to 40 years in most studies.[12,55,131,150,153,188,248] About 60%–80% of uveitis occurs between the ages of 20 to 50 years.[242] In terms of anatomic classification, anterior uveitis is the most common form of uveitis, followed by panuveitis, posterior uveitis, and intermediate uveitis. The prevalence of anterior uveitis, panuveitis, posterior uveitis, and intermediate uveitis is reported to be 24.5%–52.3%, 11.8%–52.9%, 7.1%–46.0%, and 6.3%–19.3%, respectively, in several studies.[12,55,131, 150,153,188,248] The causes of posterior uveitis can be infectious (bacterial, viral, fungal, and parasitic), noninfectious (autoimmune or associated with a systemic disease), or part of a masquerade syndrome.[53] A significant proportion of the cases of posterior uveitis are infectious (Table 1).[12,55,131,150,153,188,248]

The pathophysiology of infectious uveitis is almost always hematogenous spread of infection from another part of the body to the highly vascular uvea, with a breach in the blood-eye barrier.[178] Viral etiologies of infective posterior uveitis include human herpesviruses (HHVs), HIV, measles, rubella, arboviruses (dengue, chikungunya, Rift Valley virus, and West Nile virus [WNV]), and other rare causes such as influenza, Ebola, and Zika virus (ZIKV). Viral posterior uveitis may occur as an isolated ocular disease or as part of a systemic viral illness.

2. Viral posterior uveitis

2.1. Risk factors

The most important risk factor associated with viral posterior uveitis is an immunocompromised state, particularly in patients with HIV infection and AIDS. Opportunistic ocular infections are common among AIDS patients, with cytomegalovirus (CMV) retinitis and herpetic progressive outer retinal necrosis (PORN) being the 2 main types of viral posterior uveitis.[141] Patients with multiple medical comorbidities that suppress the immune system are also predisposed to developing viral retinitis.[218]

Nonetheless, viral posterior uveitis may also occur in apparently immunocompetent individuals. In 2 studies by Rochat and colleagues[201] and Guex-Crosier and colleagues[80] that evaluated the effects of an individual's immune status on the presentation of necrotizing herpetic retinopathies, however, immune dysfunction was found in all apparently immunocompetent and HIV-negative patients diagnosed with herpetic retinitis. All patients may have abnormalities in one or more immunologic parameters, including diminished lymphocytic proliferative response, diminished cutaneous anergy, and relative or absolute

increase in B-lymphocytes.[80,201] This suggests that most, if not all, patients with herpetic retinitis have an underlying immunodeficiency that predisposes them to infection, even when they appear to be immunocompetent.[79,200] Although the pathogenesis in these individuals has yet to be established, further studies to determine the effect of virulence and host susceptibility in immunocompetent individuals in whom viral posterior uveitis is developed will be valuable in understanding the disease pathology.

In recent years, viral retinitis has appeared as a complication of intraocular injections. Several reports have shown that viral retinitis develops later in patients who received intraocular corticosteroid injections, including CMV, herpes simplex virus (HSV), and varicella zoster virus (VZV) retinitis.[51,208,218,232,237] Since the first case of CMV retinitis following a sub-Tenon injection of triamcinolone acetonide was reported in 2002 by D'Alessandro and colleagues,[51] several other studies have appeared (Table 2).[51,66,208,232,237,252]

2.2. Clinical features

Viral posterior uveitis may present with symptoms of decreased visual acuity, visual field defects, floaters, photopsia, photophobia, and occasionally pain.[270] Typical signs on examination include subconjunctival hemorrhage, mild anterior segment inflammation with or without conjunctival injection with diffuse fine keratic precipitates. There may be retrolental cells, ocular hypertension, or glaucoma.[270] Fundus examination may reveal inflammatory infiltrates on the retina either retinitis or retinal vascular sheathing, macular edema in acute cases, scarring, retinal pigment epithelium (RPE) hyperplasia, and peripheral retinal neovascularization in long-standing cases.[270]

2.3. Diagnosis

The diagnosis of viral posterior uveitis is usually clinical. Characteristic features on the slit lamp and dilated fundus examination are used to diagnose viral posterior uveitis. Retinal imaging, including fundus photography, fundus fluorescein angiography (FFA), wide field retinal imaging, and optical coherence tomography (OCT), is useful in establishing the diagnosis and monitoring response to treatment.[81] Other ancillary investigations, including laboratory tests for viral serology and imaging, can be used to confirm the diagnosis.[270]

Polymerase chain reaction (PCR) analyses of intraocular fluid samples are an effective aid for diagnosis[50,70,135,229,239,267] and subsequent management[84,204] of viral posterior uveitis caused by HSV, VZV, and CMV. The tetraplex PCR analysis of intraocular fluids for HSV, VZV, and CMV is effective in confirming the etiological pathogen involved in 59–100% of cases,[28,84,204,211] with PCR having a sensitivity of 80.9%–84.0% and a specificity of 97.4%–100.0%.[50,84,135,211] Serial PCR analysis may be useful in monitoring viral activity and response to treatment.[45,269] Negative PCR is useful in ruling out the disease in challenging cases. The Goldmann-Witmer coefficient analysis of intraocular antibody titers can also be used to identify the virus involved[204]; however, the tetraplex PCR has a greater sensitivity and specificity than the Goldmann-Witmer coefficient analysis in the diagnosis of herpes viruses (HSV, VZV, and CMV) involved in posterior uveitis.[204] Chorioretinal biopsy is another diagnostic tool that may be useful in confirming the diagnosis and guiding

subsequent management in selected cases where both the PCR and Goldmann-Witmer coefficient analyses are negative, and there is still a high index of suspicion.[163,207]

2.4. Treatment

The treatment of viral posterior uveitis[263,270] includes systemic antivirals given orally or intravenously, intravitreal antivirals or intraocular antiviral implants, and topical and systemic corticosteroids.[40] Management of complications is also important to ensure a favorable prognosis. Measures include photocoagulation for neovascularization, vitrectomy for vitreous hemorrhage or retinal detachment,[10,245] and intravitreal injection of antivascular endothelial growth factor agent for choroidal neovascularization or macular edema.

2.5. Outcomes

Early diagnosis and management may improve the visual prognosis of viral posterior uveitis. If diagnosis or treatment is delayed serious complications can develop, including cataracts, band keratopathy, uveitic glaucoma, cystoid macula edema (CME), and retinal detachment.[270] All these can lead to permanent vision loss. Ultimately, the long-term outcomes depend on the type of viral posterior uveitis, severity, duration, responsiveness to treatment, associated conditions or medical comorbidities, and immune status of the patient.

2.6. Human herpesviruses

The most frequent causes of viral posterior uveitis come from the HHV family, with CMV being the most common, followed by HSV and VZV.[131,153,188,248] The family of HHV includes HSV-1, HSV-2, VZV, Epstein-Barr virus (EBV), and CMV. HHV is an important infectious cause of ocular inflammation. Primary infection of the virus is followed by persistence in the latent form. Reactivation of the virus in the eye may occur in the form of keratitis, anterior uveitis, or retinitis (necrotizing and nonnecrotizing). The severity and outcome of ocular disease is influenced by a multitude of factors, including the host immune response, human leukocyte antigen (HLA) differences, virulence, and possibly intraocular viral load.

2.7. Etiologic viruses

2.7.1. Herpes simplex virus—HSV-1 and HSV-2, also known as human herpes virus 1 and 2, respectively, are double-stranded DNA viruses that belong to the Herpesviridae family. Both HSV-1 and HSV-2 cause orofacial infections (cold sores), genital herpes, and encephalitis and can be vertically transmitted from infected mothers to neonates.[261] As a neuroinvasive and neurotoxic virus, HSV persists in the latent state in the dorsal root ganglia after the initial primary infection and occasionally reactivates.[261] HSV infection is usually asymptomatic, but symptoms of infection include fever and painful blisters in the skin and mucous membranes of the mouth and genitals.[261] There are 2 forms of HSV retinitis–necrotizing and nonnecrotizing. Necrotizing herpetic retinitis caused by both HSV-1 and HSV-2 may be found in patients with concomitant HSV encephalitis or HSV meningitis.[39,67,130,228] Acute retinal necrosis (ARN) with HSV encephalitis is more commonly associated with HSV-1, whereas HSV meningitis is more often caused by

HSV-2.[67] HSV-1 retinitis is more common in older patients, whereas HSV-2 retinitis is more likely to occur in younger patients.[71,130,240]

HSV posterior uveitis typically presents with features of ARN or nonnecrotizing herpetic retinitis (NNHR). In children, HSV-2 retinitis may be due to a delayed reactivation of asymptomatic neonatal HSV infection.[76] HSV posterior uveitis generally has a good prognosis if there is no evidence of ARN. Often the lesions can be treated with systemic acyclovir and corticosteroids with complete resolution of inflammation.[77,199]

2.7.2. Varicella zoster virus—VZV is a double-stranded DNA virus belonging to the herpesviridae family.[227] VZV causes 2 disease entities–a primary infection known as chickenpox that usually occurs during childhood and a secondary herpes zoster, also known as shingles, a result of its neurotropic properties that allow viral latency in ganglia and subsequent reactivation later in life.[227,257,270] Transmission of VZV is by direct contact, droplets, or airborne particles.[257] Symptoms of VZV infection include fever, malaise, and diffuse rash and vesicles in chickenpox and headache, malaise, and painful vesicles in a unilateral dermatomal distribution in shingles, with the thoracic, cranial, and cervical dermatomes being most commonly affected.[257] VZV posterior uveitis typically presents with features of PORN, ARN, or NNHR.

VZV is the most common virus found in atypical necrotizing retinitis.[70] VZV accounts for approximately half of ARN cases in non-HIV patients, more than one-third of ARN cases in HIV patients, and more than 70% of PORN cases.[264] VZV retinitis may occur during concomitant chickenpox infection in adults, and is rare in children. It is more common in older patients[67] and may precede shingles, especially in immunocompromised patients.[162]

VZV retinitis lesions may occasionally spontaneously regress[270] or may be complicated by retinal tears or detachment and optic neuropathy.[149] Visual prognosis is poor if there is ARN or PORN.

2.7.3. Epstein-Barr virus—EBV, also known as HHV-4, is a B lymphotropic, double-stranded DNA virus in the Herpesviridae family. The seropositive prevalence of EBV is more than 90% of the population worldwide.[9] EBV is spread by direct contact via saliva, airborne, or blood. EBV infection is lifelong but usually clinically silent in immunocompetent hosts.[9] Similar to other HHV, EBV may be latent. Reactivation of EBV causes diseases usually of a lymphocytic nature−including infectious mononucleosis, lymphoproliferative disorders−or epithelial, such as nasopharyngeal carcinoma and undifferentiated gastric carcinoma.[9]

Known ocular complications of EBV include conjunctivitis, episcleritis, keratitis, iritis, optic neuritis, ARN, and retinal vasculitis.[90,167,192,258] There have been a few reports of EBV infection associated with posterior uveitis.[89,90, 118,133,146,192,213,258] Posterior uveitis associated with EBV typically presents as chorioretinitis. It can occur at any age, and there is usually a preceding history of EBV infection.[89,118,133,192,213,258] The demographics and clinical features of EBV posterior uveitis are found in Table 3.[89,118,133,192,213,258]

The role of EBV as a pathogen in the eye is unclear, as up to 20% of normal cadaver eyes have intraocular evidence of EBV by PCR.[38] Most cases of ARN in which EBV is positive on PCR are also simultaneously positive for VZV.[90,146] There are a few case reports of ARN that were only positive for EBV on PCR and histopathologic evidence in the retinal biopsy specimen.[89,133,213]

In general, EBV posterior uveitis appears to be as self-limited as infectious mononucleosis.[192,258,270] Treatment of EBV posterior uveitis is supportive and may include corticosteroids for intraocular inflammation[118] and antivirals such as oral valacyclovir 1 g 3 times daily,[133] acyclovir 400 mg 5 times daily,[258] or famciclovir,[213] and monitoring for resolution. The visual prognosis in EBV posterior uveitis is generally good. Vision usually improves and intraocular inflammatory signs resolve rapidly, with near complete recovery in the majority of the cases.[118,133,192]

2.7.4. Cytomegalovirus—CMV, or HHV-5, is a double-stranded DNA virus that belongs to the Herpesviridae family. Primary CMV infection is transmitted perinatally, by close contact, including sexual contact, or parenterally.[270] The seropositive prevalence worldwide is between 60% and 100%.[197] It is usually asymptomatic in immunocompetent hosts.[270] An infectious mononucleosis-like syndrome develops in some patients, whereas more severe diseases may manifest in immunocompromised patients in the form of encephalitis, pneumonitis, hepatitis, colitis, and uveitis.[197,270] The virus remains latent in mononuclear lymphocytes in immunocompetent hosts and only reactivates when immunity is suppressed.[197,270]

The most frequent ocular manifestation of CMV is CMV retinitis.[108] Rarely, CMV may cause ARN[42,172] and optic neuritis.[161]

2.8. Acute retinal necrosis

2.8.1. Background—ARN, a severe, sight-threatening ocular emergency, was initially described in 1971 by Urayama and colleagues[246] in healthy young Japanese adults as an acute unilateral panuveitis with retinal periarteritis progressing to diffuse necrotizing retinitis with retinal detachment. ARN is rare, with an incidence of 1 of 2 million individuals per year in the UK.[42,179] There is a 2-peak age distribution−20 and 50 years old, and both genders are equally affected.[270] The demographics and clinical features of ARN are found in Table 4.[42,90,146,172,179,205,240]

ARN is usually found in immunocompetent individuals,[73] but the risk factors for ARN include a younger age, history of previous herpes infections such as chickenpox, shingles and HSV encephalitis, preexisting chorioretinal scar, trauma, systemic corticosteroids, and genetics.[42,96,146,172,179,205,240] ARN can present without a viral prodrome many years after the initial primary herpes infection or following herpetic encephalitis.[42,130,205]

2.8.2. Causative viruses—VZV is the leading cause of ARN.[146] Patients with ARN caused by VZV and HSV-1 tend to be older, whereas HSV-2 is found in younger patients.[42,130] Rarely, ARN may be caused by CMV and EBV.[42,90,137,146,172,210]

2.8.3. Clinical features—Symptoms of ARN include redness, blurring of vision, photophobia, floaters, ocular pain, and flu-like symptoms or recent history of herpes infection.[146,179,205,270] Bilateral involvement occurs in approximately one-third of patients, but some cases start off as a unilateral disease with subsequent involvement of the second eye.[172,205]

Characteristic features on examination include prominent anterior chamber inflammation and vitritis, peripheral necrotizing retinitis with focal areas of full thickness necrotic lesions, circumferential extension of necrotic foci, and occlusive vasculitis with arteriolar narrowing.[93]

ARN often occurs in 2 phases, the acute herpetic phase consisting of anterior uveitis and vitritis, peripheral confluent necrotizing retinitis with well-demarcated areas of full thickness yellow necrotic lesions, hemorrhages, occlusive vasculopathy, and rapid progression circumferentially toward the posterior pole. The late cicatricial phase consists of secondary retinal atrophy, proliferative vitreoretinopathy, and serous or rhegmatogenous retinal detachment.[42,56,90,146,172,179,205,240]

The severity of the disease is classified according to the amount of surface area affected–mild (less than 25%), moderate (25%–50%), and severe (more than 50%).[172] The severity of retinitis at presentation may be predictive of retinal detachment risk and final visual outcome. There is a correlation between mean initial and subsequent visual acuities with the severity of retinitis.[172,205]

2.8.4. Diagnosis—Diagnosis of HHV posterior uveitis can be made clinically based on history and signs seen on complete ophthalmologic examination and supported with laboratory testing of viral serology. Viral antibodies may be detected with complement fixation test, immunofluorescence, or enzyme-linked immunosorbent assay (ELISA) techniques.[270] PCR analysis of intra-ocular fluids is particularly useful and commonly done to confirm the etiological viruses involved in cases of ARN.[42,90,146,172,179,205,240] Specifically, the diagnosis of ARN can be summarized by the diagnostic criteria established by the executive committee of the American Uveitis Society[93] (Table 5).

Ocular imaging may be used to determine the extent of disease. FFA may show dye leakage from retinal vessels, choroid, RPE, or optic disk and is useful for confirming the diagnosis of co-existing pathologies such as CME, vascular occlusion, and retinal or choroidal neovascularization.[81,255] OCT scan is useful for establishing the extent and depth of lesions and monitoring response to therapy. OCT scans may demonstrate full thickness tissue loss in necrotizing herpetic retinitis and demarcate the extent, depth, and thickness of macular edema or retinal detachment.[23,81]

In the acute phase of ARN, OCT shows inner retina hyperreflectivity with disorganization of the retinal structure, corresponding to areas of retinal necrosis. There may be subretinal exudates and macular edema.[183,230] With resolution, there is marked inner and outer retina thinning within areas of retinal necrosis and resolution of the hyperreflectivity consistent with retinal tissue loss and scar formation, even when funduscopy is normal.[183,230] This

suggests that regression of necrotic lesions does not mean normalization of the retinal structure, and retinal breaks may still occur.[230] Thus, OCT is useful to monitor for early signs of retinal detachment.[183] The necrotizing lesions extending into the macula are associated with irreversible damage and may lead to poor central vision.[183] These findings are similar to those observed in central retinal artery occlusion as the necrotic lesions likely reflect ischemic changes caused by obstructive retinal vasculitis.[230]

2.8.5. Treatment—The goals of treatment in necrotizing herpetic retinitis are to eliminate active viral infection in the eye, stop progression of retinal necrosis to avoid complications such as retinal detachment and optic atrophy, prevent fellow eye involvement, and mitigate ocular damage from the host immune response. Treatment should begin immediately after a clinical diagnosis is made without waiting for the laboratory results. Details of the various pharmacologic treatment modalities for HHV posterior uveitis are found in Table 6.

Antivirals are the mainstay of treatment for ARN. The standard of care used to be inpatient hospitalization and induction with intravenous (IV) acyclovir 10 mg/kg every 8 hours or 1500 mg/m^2 per day for 5 to 10 days, followed by maintenance with oral acyclovir 800 mg 5 times daily for an additional 6 weeks.[6,26,56] Acyclovir is a synthetic acyclic purine-nucleoside analogue that is viral static and stops viral replication by inhibiting DNA polymerase.[26] There has, however, been a shift in recent years toward outpatient management of HSV- and VZV-associated posterior uveitis with the newer oral and intravitreal antivirals. Newer oral antivirals such as valacyclovir (a prodrug of acyclovir) and famciclovir have greater bioavailability and systemic concentrations similar to that of IV acyclovir.[6,15,60,102] Thus, they may be used as induction agents. A few studies reported that all patients treated with either oral valacyclovir 1 g 3 times daily or oral famciclovir 500 mg 3 times daily had complete resolution of retinitis without the need for IV acyclovir therapy.[6,15,60] To achieve a similar area under the curve as IV acyclovir, oral agents must be used in high doses. There are only data for valacyclovir in this regard. Higher oral doses of valacyclovir 2 g 4 times daily are well tolerated and produce a daily area under the curve similar to that of IV acyclovir 10 mg/kg every 8 hours.[2,79] Antiviral agents can also be delivered via intravitreal injections in cases of severe retinitis or that refractory to systemic antiviral therapy. This may be done immediately after diagnostic sampling of intraocular fluid is taken. Intravitreal foscarnet 2.4 mg/0.1 mL has been used successfully to treat ARN caused by HSV and VZV.[265] Intravitreal ganciclovir 4 mg/0.1 mL may be effective in treating necrotizing herpetic retinitis in immunocompetent patients.[134,155]

Besides antivirals, systemic corticosteroids such as oral prednisone 40–80 mg daily, topical, or intravitreal corticosteroids can be added to the treatment regime in cases with significant inflammation, such as severe vitritis, serous retinal detachment, and retinitis or vasculitis involving the macula.[40,258] This, however, should only be done after initiation of antiviral therapy, as the corticosteroids may promote viral replication.[258]

Surgery is performed for complications of ARN. Retinal detachment occurs in up to 3 quarters of ARN cases.[25,41,146] Pars plana vitrectomy, lensectomy, air-fluid exchange, endolaser, gas, or silicone oil tamponade is performed for reattachment and recovery of vision.[5,25,90,170] Other than treatment of retinal detachment that has already occurred, early

prophylaxis can also be considered in severe cases, as it has been found to lower the risk of retinal detachment in eyes where necrotic lesions do not extend beyond the mid-periphery.[103] The role of prophylactic panretinal photocoagulation or prophylactic vitrectomy in patients with ARN is controversial. There is ongoing debate about whether or not prophylactic panretinal photocoagulation provides any protection. The issue is that there may be a selection bias. Milder cases of ARN may get laser because the media is clear and detach less frequently due to milder disease not prophylactic prophylactic panretinal photocoagulation. Conversely, prophylactic vitrectomy may select for more severe cases of ARN. Park and colleagues[187] critically reviewed the role of laser photocoagulation in patients with ARN. Laser treatment does not prevent the progression of retinitis but forms a barrier posterior to the involved retina to form a stronger chorioretinal adhesion posterior to the retinal breaks, hence preventing potential retinal detachment. Though there are a number of studies showing the benefit of prophylactic laser versus no laser, there are no randomized control trials, and all are retrospective studies.[187]

Although there are several aspects of management of ARN, the long-term outcomes depend on the severity, duration, and comorbidities of the patient. Final visual acuity may be poor despite optimal treatment, especially in cases where the optic disk or macula is involved.[5,25,90,170]

2.8.6. Outcomes—ARN is a severe, blinding disease with poor visual outcomes. Two-third of eyes has a final best corrected visual acuity of 6/60 or worse.[205,240,270] Complications include extension of retinal necrosis, involvement of the second eye in more than one-third of untreated cases, retinal detachment (up to 75% of untreated eyes), optic atrophy, CME, neovascularization, secondary vitreous hemorrhage, epiretinal membrane, cataracts, and phthisis or hypotony.[41,42,56,58,90,146,172,179,184,205,239] Early diagnosis and proper treatment are critical to reduce the impact of these complications.

2.9. Progressive outer retinal necrosis

2.9.1. Background—PORN is a highly destructive and rapidly progressive variant of ARN found almost exclusively in immunocompromised individuals such as AIDS patients with low CD4+ T-lymphocytes count[75,94,191,241] or posttransplant recipients.[114,128,244] The demographic factors and clinical characteristics of PORN are found in Table 7.[75,114,128,191,241,244] PORN occurs in people between the ages of 20 to 50 years, has a male predominance, and is usually bilateral.[75,114,128,191,241,244]

2.9.2. Causative viruses—PORN is almost exclusively caused by VZV[16,75,114,128,191,241,244] and may be associated with a previous or concurrent history of herpetic disease such as herpes zoster.[75,114,128,191,241,244]

2.9.3. Clinical features—PORN may present with acute or progressive blurring of vision, scotoma, and other visual field defects, but there is no pain or photophobia unlike in ARN.[75,104,114,128,191,241,244] There is minimal nongranulomatous anterior uveitis and vitritis.[191,241] Extensive multifocal necrotizing chorioretinitis begins at the posterior pole and spreads toward the peripheral retina. There are peripheral confluent satellite lesions that

coalesce rapidly.[114,175,191,241,244] The characteristic macular lesion is a white, necrotic parafoveal opacification with a central cherry red spot.[175,191] There is RPE mottling, but absence of vascular inflammation and minimal hemorrhage.[128] Optic disk involvement can masquerade as papillitis or neuroretinitis with the presence of relative afferent pupillary defect.[191]

2.9.4. Diagnosis—Diagnosis of PORN is based on the diagnostic criteria described by Engstrom and colleagues[57] which includes clinical history and fundoscopic findings of well-demarcated, multifocal, coalescing, and deep or full thickness areas of predominantly posterior retinal necrosis in immunocompromised patients, supported with laboratory testing of VZV and HIV serology, and PCR analysis of intraocular fluids for VZV.

In PORN, although it may appear clinically as an outer retinal necrosis, OCT shows widespread full thickness neurosensory retina loss, particularly as the disease progresses.[23,241] Similarly to ARN, OCT findings in acute PORN are similar to those in central retinal artery occlusion. At presentation, there is extensive perifoveal retinal thickening with hyperreflectivity corresponding to the retinal edema and posterior shadowing.[11] At resolution, however, there is total loss of identifiable retina layers corresponding to areas of retinal necrosis unlike a diffuse retinal thinning seen in central retinal artery occlusion.[11]

2.9.5. Treatment—As PORN tends to progress rapidly, early initiation of aggressive systemic and intravitreal antiviral therapy (a combination of ganciclovir, acyclovir, cidofovir, and foscarnet) is important to arrest the progression of retinitis, induce remission, prevent involvement of the fellow eye, and maintain useful vision.[114,191,241]

Similarly to ARN, antivirals are the mainstay of treatment. Acyclovir, ganciclovir, foscarnet, and cidofovir block the replication of VZV by selectively inhibiting viral DNA polymerase.[244] Systemic antiviral therapy includes IV foscarnet 24 mg/mL 3 times daily,[114] IV ganciclovir 5 mg/kg/24 h,[128,241,244] IV cidofovir[128] or IV acyclovir.[191] PORN may have a poor response to IV acyclovir therapy alone.[241] A combination therapy of IV ganciclovir and foscarnet, intravitreal ganciclovir combined with IV acyclovir or foscarnet, or intravitreal ganciclovir with foscarnet results in better visual outcomes.[241] Intravitreal ganciclovir 4 mg/0.1 mL[171,193,241,244] or intravitreal foscarnet 1.2 mg/0.05 mL[114,128] has been effective in treating PORN in immunosuppressed patients. When response to treatment is observed, patients may also be given maintenance of oral valacyclovir 1 g 3 times daily,[128] valganciclovir, or famciclovir.[241] Oral prednisolone 40 mg/day[128] may be given to reduce intraocular inflammation such as vitritis.

Surgery may be performed for complications of PORN. Panretinal photocoagulation can be performed for extensive full thickness necrosis,[114,241] although prophylactic photocoagulation in preventing retinal detachment is not useful in most patients.[241] Retinal detachment may be treated by vitrectomy with silicon oil tamponade.[244]

In AIDS patients, highly active antiretroviral therapy (HAART) may benefit by lowering the HIV viral load and maintaining high CD4+ T-cell counts.[241] Maintenance therapy is necessary despite immune recovery after HAART.[241]

2.9.6. Outcomes—PORN has a poor visual prognosis with rapid and profound vision loss. Two-thirds of eyes progress to no light perception.[57,75,128,191,241,244] PORN tends to have a worse prognosis than ARN because PORN does not respond as well to antiviral therapy. Complications of PORN include retinal detachment in 70% of cases, optic disk edema or atrophy, vitreous hemorrhage, macular edema, and involvement of the fellow eye.[73,75,114,128,191,241,244]

2.10. Cytomegalovirus retinitis

2.10.1. Background—CMV retinitis is a form of opportunistic viral posterior uveitis that occurs mostly in severely immunocompromised AIDS patients[195] or, rarely, in those on immunosuppressive therapy after organ transplantation or who are on systemic corticosteroids.[4,100,105,108,139,140,189,214] 75%–85% of AIDS patients with CD4+ counts less than 50 cells/μL have CMV retinitis.[97,100,105,195,254] CMV retinitis is the most frequent manifestation of CMV disease among AIDS patients and accounts for 75%–85% of all CMV end-organ disease.[108] Rarely, CMV retinitis may occur in immunocompetent individuals, although these patients usually have some degree of immune dysfunction, such as advanced age, diabetes mellitus, corticosteroid, and noncytotoxic immunosuppressive medication use.[214]

CMV retinitis can occur at almost any age, but is most common between the ages of 30 and 60. Most patients are males.[4,100,105,108,140,189,214] CMV retinitis usually begins as a unilateral disease, but progresses to involve the contralateral eye within 6 months in about 20% of cases, presumably from hematogenous spread.[119,140] The disease follows a chronic clinical course.[214] The demographics and clinical characteristics of CMV retinitis can be found in Table 8.[4,100,105,108,140,189,214]

2.10.2. Clinical features—CMV retinitis is asymptomatic in 50% of cases, and symptoms include blurred vision, floaters, scotomata, and ocular discomfort.[4,100,105,108,140,189,214,270] Acute complaints such as pain, redness, and photophobia are typically absent.[214]

CMV retinitis presents with mild anterior segment inflammation, including keratic precipitates, anterior chamber cells, and minimal vitritis.[189] The distinguishing feature is a single focus of full thickness yellow-white necrotizing granular retinitis in the peripheral retina with a perivascular distribution that expands centrifugally.[100,214,270] There may be vitritis, retinal hemorrhage, and vasculitis, usually in the form of retinal arteritis,[4,100,105,108,140,189,214] which have been described as a “pizza pie retinopathy.”[189] CMV posterior uveitis may also present as an optic neuritis.[161]

There are 2 stages in CMV retinitis. The first stage is an active retinitis. Three patterns of active retinal lesions have been described: fulminant/edematous, indolent/granular, and exudative.[254] The fulminant/edematous form consists of large areas of retinal hemorrhage in

a background of confluent retinal necrosis.[254] The indolent/granular pattern consists of granular satellite lesions with little or no hemorrhage.[254] The exudative pattern, also known as frosted branch angiitis, has extensive vascular sheathing.[154,189] The second stage is widespread necrosis and retinal tears. In quiescent disease, there is retinal atrophy with fibrosis, calcification, and sclerotic vessels.[270]

2.10.3. Diagnosis—CMV retinitis is diagnosed clinically on indirect ophthalmos-copy with concurrent documentation on digital fundal photography, as described by Newman and colleagues,[181] and supported by clinical history, systemic review, laboratory, and ancillary tests. PCR analysis of CMV DNA in intraocular fluid samples aids with the diagnosis, subsequent management, and monitoring of treatment response.[84,135,229]

2.10.4. Treatment—The mainstay of treatment in CMV retinitis is the reversal of immunodeficiency. In the setting of HIV/AIDS, initiation of HAART, or checking for antiviral resistance if CD4+ counts is low despite HAART, is an aspect of management. In iatrogenically immunosuppressed patients, immunosuppression should be minimized as much as possible. Since CMV retinitis is found mostly in AIDS patients (and recently in immunocompetent individuals as well[66,252]), the use of HAART to treat the coexisting HIV infection lowers the progression of CMV retinitis and incidence of subsequent visual loss.[100,108,120,260] Anti-CMV therapy may be discontinued in patients with sustained immune recovery to CD4+ counts ≥100 cells/μL.[105,260]

Antivirals such as ganciclovir, valganciclovir, cidofovir, and foscarnet are used in the treatment of CMV retinitis because these antivirals competitively inhibit CMV DNA po-lymerase.[95,100,166,254,270] Ganciclovir was also available as a surgically implanted delivery device, Vitrasert (Bausch & Lomb, Rochester, NY, USA), that released a sustained concentration of the drug into the vitreous cavity and had a low risk of complications.[115,164] This device was used for patients who could not tolerate systemic ganciclovir or foscarnet[270]; however, because of lack of demand, the ganciclovir implant is no longer available.

Since CMV retinitis is a manifestation of a systemic disease, antiviral therapy has to be given systemically. Studies from the Studies of Ocular Complications of AIDS have demonstrated that mortality is significantly increased in HIV/AIDS patients with CMV retinitis, if the CMV retinitis is treated locally alone by intravitreal injections or ganciclovir implant.[1]

2.10.5. Outcomes—The natural course of CMV retinitis includes regression, complications like retinal detachment, or recurrence. Most studies demonstrate improvement or stabilization of vision and ophthalmic findings in majority of patients, with many achieving complete remission.[270]

Complications of CMV retinitis are severe and may result in profound vision loss and blindness.[120] Complications[4,97,100,105,108,140,189,214] include extension of retinitis (although less rapidly than in HSV or VZV retinitis), involvement of second eye, epiretinal membrane, CME, retinal neo-vascularization, posterior subcapsular cataracts, phthisis, optic atrophy,

and rhegmatogenous retinal detachment in up to one-third of eyes.[100,209] The strongest predictor for retinitis progression, involvement of the contralateral eye, and risk of retinal detachment is low CD4+ T-cell counts less than 50 cells/μL.[108] CMV necrotizing retinitis can be differentiated from ARN by increased rates of neovascular complications and decreased rates of retinal detachment.[214]

Immune recovery uveitis is a HAART-dependent, noninfectious inflammatory response that occurs in up to 63% of patients with treated CMV retinitis and increased CD4+ counts.[100,121,254] Complications include epiretinal membrane, CME, neovascularization, cataracts, and severe proliferative vitreoretinopathy.[100,121,254] The risk of immune recovery uveitis increases with the severity of CMV retinitis and use of cidofovir during treatment.[225] This risk is reduced by delaying HAART therapy until induction of CMV antiviral therapy begins.

2.11. Nonnecrotizing herpetic retinitis

2.11.1. Background—NNHR is a relatively new disease entity first reported in 2003 by Bodaghi and colleagues.[27] Five of 37 patients included in the initial report had PCR-confirmed herpetic infections masquerading as atypical posterior uveitis.[27] A viral etiology must be excluded in cases of sight-threatening and atypical posterior uveitis that is unresponsive to conventional corticosteroid treatment.[27] The demographics and clinical features of NNHR are found in Table 9.[7,27,259,262] NNHR can occur in any age group, with slightly more males affected than females. Most cases tend to be unilateral and chronic.

2.11.2. Causative viruses—VZV accounts for up to three-quarter of NNHR cases, followed by HSV in the remaining cases.[7,27,259,262]

2.11.3. Clinical features—Patients may present with symptoms of blurred vision or ocular pain.[262] There is mild anterior chamber inflammation with vitritis. Fundus examination may reveal peripheral retinitis, diffuse occlusive retinal vasculitis, peripheral neo-vascularization, intraretinal or vitreous hemorrhage, retinal edema, and papillitis but no signs of retinal necrosis.[7,27,259,262] In patients with atypical ARN or NNHR, the retinal lesions tend to progress slowly and generally do not completely destroy the involved retina.[259]

2.11.4. Diagnosis—Diagnosis of NNHR is made based on the clinical features described by Bodaghi and colleagues,[27] in patients with atypical posterior uveitis that is PCR positive for HSV or VZV in the intraocular fluids and remain unresponsive to conventional therapy with systemic corticosteroids and immunomodulatory therapy.[7] Viral serologies are measured by ELISA.[27] Tetraplex PCR analysis is done using aqueous or vitreous samples to identify the herpes virus involved.[7,27,259,262]

2.11.5. Treatment—NNHR does not respond to conventional therapy with systemic corticosteroids or immunosuppressive therapy, but a favorable response may be achieved with systemic antivirals.[7,27]

Antivirals should be started immediately after identification of the virus. The use of antivirals stabilizes intraocular inflammation, allows eventual tapering of corticosteroids and discontinuation of immunosuppressive therapy.[27] Systemic antivirals include oral acyclovir 800 mg 5 times daily or oral valacyclovir 2–3 g/day (depending on the creatinine clearance), tapered and maintained for 7–8 months.[7,27,259,262] Relapses may be treated with oral acyclovir until resolution of the retinitis.[7] Long-standing preventive antiviral therapy may be considered for patients who present with recurrent intra-ocular inflammation.[7]

Most patients may be treated with corticosteroids before diagnosis and identification of a viral etiology. Oral steroids should not be stopped but progressively tapered to avoid recurrences.[27] Oral prednisone 10–20 mg/day or topical corti-costeroids[7,259,262] and immunosuppressive treatment (such as cyclosporine A)[7,27] are progressively tapered over a few months.[27,262] Laser photocoagulation of the ischemic zones[7,259] or pars plana vitrectomy can be performed for retinal detachment or diagnostic purposes.[259]

2.11.6. Outcomes—NNHR has a good visual prognosis, and a majority of cases show improvement in visual acuity and stabilization or resolution of uveitis.[7,27,259,262] There was severe visual loss in one patient from multiple complications.[7] Wensing and colleagues[259] noted that the presence of occlusive vasculitis was associated with a worse visual acuity at follow-up. Complications of NNHR include multiple recurrences of anterior uveitis or retinal vasculitis, CME, retinal detachment, retinal atrophy, band keratopathy, and cataracts.[7,27,259,262]

2.12. Other herpetic posterior segment manifestations

The most frequent findings in congenital HSV retinitis are multifocal, confluent patches of white retinal opacification, at times presenting as ARN.[76] In acquired infections, typical features include vascular sheathing, arteriolar attenuation, hemorrhage, retinal and optic disc edema, multifocal chorioretinitis, and yellowish exudative plaques in the macula and posterior pole.[39,77,228,270]

In congenital VZV infections, posterior segment findings include discrete white chorioretinal scars.[34] In acquired infections there may be focal, yellow-gray chorioretinitis, perivasculitis, or ARN features of diffuse necrotizing retinitis with macular extension, hemorrhage, retinal tears, edema, and vascular sheathing.[107,117] A hemorrhagic variant of VZV retinitis was reported, with dense vitreous hemorrhage, per-ipapillary edema and hemorrhage, and intraretinal whitening.[149]

Features of EBV posterior uveitis include relative afferent pupillary defect, mild anterior chamber inflammation, vitritis, chorioretinitis, yellow-white fluffy retinal opacifications, multifocal choroiditis, localized choroidal effusions, hemorrhage, vasculitis, and optic neuritis.[89,116,118,133,185,192,213,226,258] Other reported findings associated with EBV infection include subretinal fibrosis and uveitis syndrome and punctate outer retinitis with retinal pigment epithelial clumping and depigmentation.[185,198]

2.13. Human immunodeficiency virus

2.13.1. Background—HIV is a single-stranded RNA retrovirus that causes AIDS. HIV is spread by sexual contact, blood, or vertical transmission from mother to child. AIDS is a multisystemic disease associated with progressive failure of the immune system that can cause opportunistic infections and viral-induced cancers.[222]

Ocular disease occurs in up to 70% of AIDS patients throughout the natural history of HIV infection.[36,47] HIV itself is an extremely rare infectious cause of posterior uveitis. There have been few reports of posterior uveitis occurring in AIDS patients in the absence of other viral etiologies.[148] AIDS patients are at risk of other opportunistic ocular infections secondary to their immunosuppressed state. The 2 most common viral posterior uveitis in AIDS patients are CMV retinitis and PORN, and rarely, HSV-related ARN.[47–49,141,145,254] HIV-related uveitis can also be the result of drug toxicity or Immune recovery uveitis.[47]

2.13.2. Clinical features—HIV retinitis may present with symptoms of blurred vision, floaters, photophobia, tearing, and foreign body sensation. Levinson and colleagues[148] reported in 1998 that several patients infected with HIV were found to have slowly progressive mid-peripheral multifocal retinal infiltrates, diffuse or located in clusters, with irregular faint yellow-white or translucent discrete foci, lacy inflammation in between, minimal anterior chamber inflammation, vitritis or vasculitis, and no retinal hemorrhage or necrosis. There was no evidence of opportunistic infections. The median CD4+ count at presentation was 272 cells/μL.[148] Vrabec and colleagues[254] also describe HIV retinitis as a peripheral multifocal retinitis with low-grade vitritis, retinal vasculitis, and no hemorrhage. Besides HIV retinitis, AIDS patients commonly present with features of CMV retinitis, PORN, or ARN.[49,141,145,254]

Retinal vascular changes, including cotton wool spots, intraretinal hemorrhages, and microaneurysms, are the most common manifestations of HIV retinopathy. These are caused by noninfectious microvasculopathy of HIV disease that may result in ischemic maculopathy.[46] Visual symptoms are usually bilateral and abrupt in onset. On examination, there is juxtafoveal opacification of the superficial retina, cherry red spot, and intraretinal hemorrhages. Patients were diagnosed with ischemic maculopathy based on FFA changes, which show enlargement of the foveal avascular zone and mild staining of the juxtafoveal vessels.[46]

2.13.3. Diagnosis—Diagnosis of HIV retinitis is made based on positive HIV serology by ELISA for antibodies to the p24 antigen, signs on fundus examination, and exclusion of other etiologies.[270]

The CD4+ T-lymphocyte count has been used to predict the onset of certain ocular infections.[49,243] Studies have found that a CD4+ count of less than 50 cells/μL is associated with CMV retinitis and PORN.[97,100,105,191,195,254]

2.13.4. Treatment—HIV retinitis responds to antiretroviral therapy such as zidovudine, saquinavir, and nelfinavir mesylate, but not to other antivirals such as ganciclovir or acyclovir commonly used to treat other types of viral retinitis.[148,254]

HAART, a combination of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors, is a therapy used in AIDS patients to lower the plasma levels of HIV RNA and increase CD4+ T-lymphocyte counts, thereby improving the overall immune function of the patient[43,83] and salvage the vision of AIDS patients by stopping the progression of ophthalmic opportunistic infections.[99]

Any infection or intraocular lymphoma should be treated with specific antimicrobial or antineoplastic therapy. Inflammatory complications such as severe vitritis, CME, or posterior synechiae should be treated with corticosteroids, in conjunction with a cycloplegic agent.[47]

2.13.5. Outcomes—The prognosis of HIV retinitis depends upon the location of the lesions and the CD4+ counts. The few complications reported include epiretinal membrane formation and CME, but there were no cases of retinal detachment, neovascularization, vascular occlusion, or optic nerve involvement.[148]

2.14. Measles

2.14.1. Background—Measles is a single-stranded, enveloped (nonsegmented) RNA *Morbillivirus* from the Paramyxoviridae family.[98] Measles is an airborne disease that spreads via direct contact with secretions. It usually presents with fever, cough, coryza, and Koplik spots before the onset of rash.[194]

Posterior uveitis associated with measles can occur in both congenital and acquired infections, although it is more common in the latter.[270] It may occur concomitantly with measles encephalitis, also known as subacute sclerosing pan-encephalitis (SSPE).[17,18,216,238,268,270,271] Ocular involvement occurs in up to 50% of SSPE cases.[18,216,268] SSPE is a condition that mainly affects children and young adults.[17,216,238,268,271] SSPE is characterized by a history of primary measles infection, several asymptomatic years, followed by a gradual, progressive psychoneurological deterioration consisting of behavioral changes, myoclonic seizures, ocular abnormalities, and coma.[17,194,268] The prevalence has declined since the introduction of the measles vaccine.[21,30]

The demographics and clinical characteristics of measles retinopathy are found in Table 10.[17,18,182,212,216,238,268,271] Measles retinopathy mainly affects younger patients and males. It is usually bilateral, and patients are often immunocompetent.[17,18,182,212,216,238,268,271]

2.14.2. Clinical features—Measles posterior uveitis may present with symptoms of painless visual loss. Fundus findings include optic disk swelling, arteriolar attenuation, diffuse retinal edema, scattered hemorrhages, and exudative stellate macular lesions.[212,270] Upon resolution, there is optic disk pallor, peripapillary vascular sheathing, and secondary pigmentary retinopathy with a “salt and pepper” appearance.[212]

In SSPE, visual symptoms and retinopathy precede the onset of neurological findings by weeks to years. The most characteristic fundus lesion in SSPE is focal necrotizing retinitis or chorioretinitis that starts in the macula and progresses toward peripheral retina. It preferentially affects the retina with secondary involvement of the RPE and

choroid.[17,18,182,216,238,268,271] Ground-glass whitening of the retina with ill-defined margins and RPE mottling occur. Other findings include optic nerve involvement, such as papilledema and optic atrophy, and retinal changes such as retinal folds, edema, hemorrhage, serous detachments, and occlusive vasculitis.[17,18,271] There is minimal vitreous inflammation.[17] The lesions usually resolve rapidly with varying degrees of scarring and depigmentation.[238,268,271]

2.14.3. Diagnosis—Diagnosis of measles posterior uveitis is clinical and confirmed by positive measles serology with complement fixation, enzyme immunoassay, immunofluorescent and hemagglutination inhibition tests, or positive measles antibodies in the cerebral spinal fluid in cases of SSPE.[270] FFA may show early hypofluorescence which changes into hyperfluorescence at later stages, compatible with chorioretinal inflammation, diffuse leakage secondary to widespread retinal edema, and zones of atrophy, RPE mottling, or occlusive vasculitis.[18,212,268] OCT shows signs of necrotizing retinitis with focal areas of moth-eaten disorganization in the macula.[18]

2.14.4. Treatment—There is no definitive treatment for measles retinopathy or SSPE.[182,216] SSPE can be managed with medications if treatment is started early; however, no cure for SSPE exists, and the condition is often fatal. Various treatment regimens have been tried with little success, including IV IgG, plasma exchange, cytarabine, amantadine, and interferons. The most promising results to date use a combination of isoprinosine (inosiplex), an antiviral agent, and intraventricular, intra-thecal, or intracameral interferon alpha as an immunomodulator, with stabilization or improvement in some cases.[17,18,147,182,216,238] The role of corticosteroids in the management of measles posterior uveitis is controversial, and there is lack of any evidence or published literature about administering corticosteroids to prevent vision loss.

2.14.5. Outcomes—In measles retinopathy, permanent ocular damage due to complications of retinitis pigmentosa, macular scarring, and RPE mottling is developed in some patients.[18,212,216] Even with return of useful vision, the visual fields usually remain constricted to less than 15 degrees.[212,270]

2.15. Rubella

2.15.1. Background—Rubella, also known as German measles or 3-day measles, is a single-stranded RNA *Rubivirus* from the Togaviridae family. Rubella virus is spread via airborne inhalation of aerosols or vertical transmission from mother to child.[20] Rubella usually presents with fever, coryza, Forchheimer spots, cervical lymphadenopathy and a scarlatiniform rash that fades after 3 days.[20]

Retinopathy caused by rubella is usually associated with congenital rubella syndrome, characterized by a triad of auditory, ocular (cataracts, microphthalmos and pigmentary retinopathy) and cardiac defects.[20] Pigmentary retinopathy secondary to rubella was first observed by Mitchell in 1941 as a pale fundus with scattered irregular spots of pigment.[74] Pigmentary retinopathy is developed in about 20%–60% of children with congenital rubella syndrome.[44,138,186] Like measles, the prevalence of congenital rubella syndrome and

rubella-related posterior uveitis has decreased since the introduction of the rubella vaccine.[144]

Rubella retinopathy is a bilateral disease that usually occurs in immunocompetent children or young adults with a history of congenital rubella syndrome. The demographics and clinical characteristics of rubella retinopathy can be found in Table 11.[44,52,86,92,129,138,186,256]

2.15.2. Clinical features—Congenital rubella causes a progressive pigmentary retinopathy that is characterized by a “salt and pepper” fundus. It often occurs in the posterior pole and macula, consisting of black, irregular pigmentary lesions, areas of depigmentation and hyperpigmentation, waxy disk, coarse macular mottling, and hemorrhage.[44,92,129,138,186,256,270] Morlet described 3 types of fundus features–gross and generalized pigmentary changes, peripheral pepper-like pigmentary changes, and diffuse strange, moth-eaten areas with a waxy disk.[129,138]

Rubella retinitis, a rare feature of acquired rubella infection in adults,[86] may present as a diffuse chorioretinitis with dark gray atrophic lesions at the posterior pole and diffuse retinal detachment, normal retinal vessels and optic disk, and absence of hemorrhage.[86] There has also been a report of rubella neuroretinitis, characterized by diffuse retinal edema, macular star, vasculitis, and papillitis.[52]

2.15.3. Diagnosis—Diagnosis of rubella retinopathy is difficult because of a lack pathognomonic signs. Serological diagnosis is based on the presence of rubella IgM antibodies or detection of an IgG increase of fourfold or more, with hemagglutination inhibition, complement fixation, ELISA, or immunofluorescent[44,52,86,138,270] in the absence of other possible causes. Fundus autofluorescence imaging is a sensitive and noninvasive method that supports the diagnosis of rubella retinopathy when stippled fluorescence is highlighted in the fundus.[72] In some cases, FFA shows transmission and blockage of choroid fluorescence with subretinal neovascularization and multifocal leakage into the subretinal space.[86,270] There is no published literature to support the role of PCR in the diagnosis of rubella posterior uveitis.

2.15.4. Treatment—There is no definite treatment for rubella retinopathy. Rubella retinopathy is usually just monitored as the retinopathy is generally benign and does not affect vision unless choroidal neovascularization develops in the macula.[129,256] Systemic corticosteroids may be beneficial in instances where there is severe inflammation.[52] Photodynamic therapy may be effective for choroidal neovascularization secondary to rubella retinopathy, with a resulting improvement of visual acuity.[256]

2.15.5. Outcomes—The long-term prognosis of rubella retinopathy is excellent.[44,92,138] Rubella retinopathy is usually benign, nonprogressive, and does not interfere with vision.[129] Rare complications include subretinal or choroidal neo-vascularization, macular hemorrhage, and disciform scarring, which may lead to a significant reduction in visual acuity.[92,186,256]

2.16. Vector borne diseases

Vector borne diseases contribute to some of the most serious epidemics in the world and are of great public health importance. Disease transmission by hematophagous arthropods was first reported by Manson in 1877. Since the discovery of filariasis being spread by *Culex* mosquitoes in 1877, other diseases such as malaria (1898), yellow fever (1900), and dengue (1903) have been shown to have similar transmission modes.[78] Although malaria is the most important vector borne disease because of its global distribution and numerous deaths, arboviruses are the most abundant.[78]

There is insufficient evidence to suggest if the associated retinitis, choroiditis, or optic nerve involvement in these vector borne diseases are related to live viruses or a secondary immunologic process.

2.17. Dengue virus

2.17.1. Background—Dengue fever is caused by 4 closely related, but antigenically distinct, *Flavivirus* serotypes, and transmitted by the mosquito, *Aedes aegypti*. Dengue is endemic in Southeast Asia, Central America, and South America. Globally, approximately 50–100 million cases of dengue fever and 500,000 cases of dengue hemorrhagic fever occur each year, although the public health impact of dengue is likely to be greatly underestimated.[78]

Dengue infection produces a clinical spectrum of disease, ranging from a nonspecific viral illness to severe and fatal dengue hemorrhagic fever or dengue shock syndrome. Dengue fever is usually characterized by fever, arthralgia, headache, and rash.[82,136,151,234]

The first case of dengue fever-related posterior uveitis was described by Deutman and colleagues[54] in 1979 among tourists who returned from dengue endemic countries. Since 2000, more cases have been reported, especially in the Southeast Asian countries.[37,68,82,111,136,151,223,231,234] Dengue-related posterior uveitis is acute, bilateral in 75% of cases, and occurs in immunocompetent individuals.[37,82,111,136,151,223,231,234] The demographics and clinical features of dengue posterior uveitis are found in Table 12.[37,82,111,136,151,223,231,234]

2.17.2. Clinical features—Symptoms of dengue-related posterior uveitis include blurring of vision, paracentral scotoma, metamorphopsia, floaters, red eyes, and systemic symptoms of dengue fever such as fever, petechial rash, and myalgia. There is no pain, photophobia, or tearing. Ocular symptoms frequently occur 1 week after the onset of dengue fever.[37,82,111,136,151,223,231,234]

Dengue-related posterior uveitis may present as chorioretinitis or a hemorrhagic retinopathy. On examination, there is minimal anterior chamber inflammation and vitritis. In dengue chorioretinitis, the characteristic feature is a chorioretinitis with maculopathy. The macular region is often involved. There may be focal chorioretinitis or choroiditis, retinal edema, vascular sheathing, retinal hemorrhages, foveolitis, cotton wool spots, and neuroretinitis.[68,111,136,151,223,231,234] Foveolitis is a newly described manifestation specific

for dengue fever and is described as a discrete, round yellow-orange lesion localized to the fovea.[111]

Hemorrhagic retinopathy associated with dengue hemorrhagic fever is related to the induced thrombocytopenia.[37,82] The onset of visual symptoms is usually observed within 1 day from the resolution of fever and at the nadir of the thrombocytopenia. Fundoscopic examination shows multiple dot and blot hemorrhages within the vascular arcades and macula.[37,82]

2.17.3. Ocular imaging findings—On FFA, there may be extensive retinal vasculitis, choroidal hyperfluorescence, blocked fluorescence, or capillary non-perfusion.[136,151] Similarly, on indocyanine green angiography, there may be early diffuse choroidal hypercyanescence with late silhouetting of the larger choroidal vessels[151] or hypo-fluorescent spots corresponding to yellow subretinal lesions seen clinically and additional spots in areas without clinically evident dots.[123] On OCT scan, there are 3 patterns of maculopathy–diffuse retinal thickening, CME, and foveolitis.[32,234,235] In diffuse retinal thickening, there is increased central or paracentral fovea thickness associated with loss of foveal dimple.[235] CME is characterized by large intraretinal ovoid areas of hyporeflectivity with reflective septa separating the cystoid cavities.[235] Foveolitis is characterized by an area of thickening and high reflectivity at the subfoveal outer retina layer. There may be a tented elevation and separation of the highly reflective layer with accumulation of subretinal fluid (area of low reflectivity) within cystic.[235] Serial OCT imaging demonstrates spontaneous rapid resolution of edema, but patients may complain of persistent central or paracentral scotoma after resolution of the disease.[234]

2.17.4. Diagnosis—Dengue fever can be confirmed with serological tests such as serum PCR and dengue antibodies using ELISA, antibody capture, monoclonal antibody, or hemagglutination.[190] There is also thrombocytopenia in the full blood count.[64] Thrombocytopenia has been found to have a predictive value for spontaneous ocular bleeds.[190] Dengue posterior uveitis is diagnosed based on clinical history, signs, and positive dengue serology.

2.17.5. Treatment—Treatment of dengue fever and dengue retinitis is mainly supportive, with fluid correction for electrolyte imbalance and hypotension, and management of complications. There is no specific antiviral available for dengue, but systemic corticosteroids such as IV methylprednisolone or oral prednisone may be used to control the inflammation.[82,136,151,234] In dengue hemorrhagic retinopathy, other than supportive care, platelet transfusion may be given to correct severe thrombocytopenia.[37]

2.17.6. Outcomes—Dengue posterior uveitis is a self-limiting condition with spontaneous recovery or recovery after treatment within 6 months.[136] It has a good visual prognosis. Ocular complications associated with dengue fever are rare but may result in permanent visual impairment. Complications include neo-vascularization, vitreous hemorrhage, nummular scars, persistent scotoma, and optic neuropathy with impaired color vision.[136,151,223,231,234]

2.18. Chikungunya virus

2.18.1. Background—Chikungunya virus is a single-stranded RNA *Alphavirus* from the Togaviridae family that is transmitted by *Aedes* mosquitoes. Chikungunya is relatively uncommon and poorly documented, but is endemic in India, Asia, and Africa. More than 266,000 people were infected during the 2007 outbreak in Réunion and 1,400,000 cases were reported in India in 2006.[196]

Chikungunya fever is a self-limiting condition that presents with fever, skin rash, and myalgia. The characteristic feature of chikungunya is a debilitating and prolonged arthralgia that primarily affects the peripheral small joints.[196]

Ocular manifestations of chikungunya virus range from conjunctivitis to retinitis and optic neuritis.[143,157] Chikungunya posterior uveitis is an acute disease that affects immunocompetent individuals.[33,143,158,159,174,177,180,203] The demographics and clinical features of Chikungunya posterior uveitis are found in Table 13.[33,143,158,159,174,177,180,203]

2.18.2. Clinical features—Chikungunya posterior uveitis usually presents with fever, headache, arthralgia, and skin rash a few weeks before the onset of visual symptoms (blurring of vision, diplopia, scotomata, redness, and retro-orbital pain).[33,143,158,159,174,177,180,203] On examination, there may be mild vitritis, areas of retinitis with or without macular star, retinal hemorrhages, retinal edema, multifocal choroiditis, neuroretinitis, and optic neuritis.[33,143,158,159,174,177,180,203] It may morphologically mimic herpetic viral retinitis, but the clinical history (symptoms of fever, joint pain, and rash) can be used to distinguish between the 2.[158] It may also resemble WNV retinitis; however, peripheral fundus lesions and linear chorioretinal streaks seen in WNV retinitis are not present in chikungunya retinitis.[31]

2.18.3. Ocular imaging findings—FFA may show early hypofluorescence with late hyperfluorescence with disk leakage and capillary nonperfusion corresponding to the areas of retinitis.[33,158,159,177] On OCT scan, areas of retinitis are seen as hyperreflective with after shadowing, whereas serous retinal detachment is seen as a hyporeflective area.[158,177]

2.18.4. Diagnosis—The gold standard of diagnosis of chikungunya is a viral culture inoculation of mosquito cell cultures or mammalian cell cultures[196]; however, this is not normally done, and nearly all studies reporting ocular manifestations of chikungunya fever used reverse transcriptase PCR assay or chikungunya ELISA IgM antibodies instead.[33,143,158,159,174,177,180,203]

2.18.5. Treatment—There is no established treatment for ocular manifestations of chikungunya fever. Antipyretics such as acetaminophen, nonsteroidal antiinflammatory drugs, chloroquine, and hydration are given for supportive management.[158] Systemic corticosteroids have been used to treat inflammation and optic neuritis caused by chikungunya virus infection.[33,143,158,159,174,177,180,203] It is important to institute early therapy once there is onset of optic disk involvement, as a delay in treatment could result in poor visual outcomes.[174] There is no specific antiviral available for chikungunya virus.

Some patients have been empirically treated with acyclovir, although its efficacy is doubtful.[158,177,180]

2.18.6. Outcomes—Majority of patients with chikungunya posterior uveitis recover well with good visual outcome. Complications include retinal detachment, central retinal artery occlusion, and optic nerve involvement (papillitis, neuroretinitis optic atrophy, or edema), which may result in severe vision loss in the minority.[33,143,158,159,174,177,180,203]

2.19. Rift Valley fever

2.19.1. Background—Rift Valley fever (RVF) virus is a single-stranded RNA *Phlebovirus* belonging to the Bunyaviridae family. Since the first report of a RVF outbreak in Kenya in 1930, several epidemics have occurred in Africa, including the largest outbreak in Egypt in 1977 involving 18,000 cases and 598 fatalities, and others in Kenya and Somalia from 1997 to 1998, as well as Saudi Arabia in 2000.[8]

RVF is an arboviral disease that affects livestock as well as humans.[219] In humans, it is usually asymptomatic or causes an acute, self-limiting, influenza-like febrile disease. In 1%–3% of cases, however, it can cause serious morbidity and mortality from severe manifestations such as meningoencephalitis or hemorrhagic fever.[8,219]

Ocular complications of RVF range from blurred vision to macular exudates, retinitis, and vasculitis. Most cases are unilateral and affect males, although there are no updated reports in the literature after 2005. The demographics and clinical characteristics of Rift Valley retinitis are found in Table 14.[8,62,215,220,221]

2.19.2. Clinical features—Systemic symptoms of RVF include pyrexia of unknown origin, headache, joint pain, and myalgia that occur 1 week before the onset of ocular symptoms such as blurring of vision, scotoma, floaters and retro-orbital pain.[8,62,215,219–221] The most common fundus findings are progressive macular or paramacular necrotizing retinitis consisting of white exudate-like lesions, accompanied by retinal edema, hemorrhages, occlusive vasculitis, optic disk edema, and vitreous haze.[8,62,215,220,221] Nongranulomatous anterior uveitis was always accompanied by posterior uveitis (panuveitis).[8]

2.19.3. Ocular imaging findings—In the acute phase, FFA shows obscuration of background fluorescence, delayed peripapillary choroidal filling corresponding to the area of lesion, widespread vascular occlusion with extensive leakage, and late staining of retinal lesions. After resolution, there may be a window defect at areas of scarring, residual delay in peripapillary choroidal filling, and residual sheathed vessels.[8,221]

2.19.4. Diagnosis—Diagnosis of RVF posterior uveitis is made based on the presenting history, ocular signs, and positive serology of RVF antibodies in ELISA, hemagglutination inhibition or complement fixation tests that show a 4-fold or higher rise in paired acute and convalescent samples.[8,219–221]

2.19.5. Treatment—There is no established treatment for RVF infection, and management is mainly supportive with IV fluids, antimicrobials, blood transfusion, hemodialysis, or mechanical ventilation.[8]

2.19.6. Outcomes—The visual prognosis of RVF posterior uveitis is poor, with 40%–50% of cases having a permanent loss of visual acuity after resolution of retinitis.[8,219,221] Most active retinal lesions spontaneously resolve within 12 weeks. The most common complications of RVF retinitis include chorioretinal (macular or paramacular) scarring in about half of cases, vascular occlusion and optic atrophy, leading to a persistent central scotoma and permanent vision loss.[8,62,215,220,221] Up to 70% of patients remain legally blind.[8]

2.20. West Nile virus

2.20.1. Background—WNV is a single-stranded RNA *Flavivirus* from the Flaviviridae family that is transmitted by infected mosquitoes. WNV can be found in North America, Europe, Africa, Asia, and Australia. Since the spread of WNV in the Western Hemisphere after a 1999 outbreak in New York, there have been more than 16,000 cases and 660 deaths in North America.[87]

Majority of WNV infections are asymptomatic or present with a mild, self-limited febrile illness with fever, headache, myalgia, vomiting, and chills. Neurologic disease, including meningitis, encephalitis, and a poliomyelitis-like syndrome, develops in an estimated 1% of cases.[87] WNV posterior uveitis is associated with WNV meningo-encephalitis.[14,85]

WNV chorioretinitis tends to occur in older patients, those with coexisting diabetes mellitus, with higher likelihood of presenting with encephalitis.[85] Diabetes mellitus has been reported as a potential risk factor for multifocal chorioretinitis in WNV infection.[88,122,126,127] The demographic factors and clinical characteristics of WNV chorioretinitis are found in Table 15.[13,14,19,69,88,122,126,127,218,224]

2.20.2. Clinical features—WNV posterior uveitis may present with symptoms of blurring of vision, visual field defect, floaters, diplopia, eye redness, or pain about 1 to 2 weeks after the onset of fever, headache, myalgia, and nausea.[19,87] The most common ocular manifestation of WNV infection is bilateral multifocal chorioretinitis, found in more than 80% of patients The characteristic feature of WNV chorioretinitis is a curvilinear clustering of whitish yellow chorioretinal scars with a “target-like” appearance, following the course of the retinal nerve fibers.[19,126] Other features include occlusive retinal vasculitis, optic neuritis or edema, retinal hemorrhages, and no or minimal anterior and vitreous inflammation.[13,14,19,69,85,88,122,126,127,217]

2.20.3. Ocular imaging findings—Affected eyes are classified as active chorioretinitis or inactive chorioretinitis with or without residual active lesions, based on ophthalmoscopic and FFA findings.[122] Active chorioretinal lesions appear as circular, deep, creamy lesions on ophthalmoscopy with early hypofluorescence and late staining on FFA. Inactive chorioretinal lesions appear partially atrophic and partially pigmented with central hypofluorescence and peripheral ring-like hyperfluorescence.[13,19,69,89,122,127,217,224]

Indocyanine green angiography shows well-delineated hypo-fluorescent choroidal lesions, more numerous than those appreciated by FFA or clinically.[125,126,218,224] On OCT scan there may be inner retinal edema in active inflammation and retinal atrophy in the late stage.[218,224]

2.20.4. Diagnosis—WNV posterior uveitis is diagnosed based on clinical history, signs, and positive serology. The most common method used for detecting WNV is detection of WNV IgM ELISA antibodies, which has a sensitivity approaching 100% at titres greater than 1:30.[13,14,19,69,88,122,125–127,224]

2.20.5. Treatment—Currently, there is no proven treatment for WNV infection. Management of WNV infection and chorioretinitis is mainly supportive. Topical prednisolone may be given to reduce the inflammation. Khairallah and colleagues[122] treated all of their hospitalized patients with ribavirin, according to its proven *in vitro* activity against WNV infection, although its efficacy has not been established. Complications of WNV may be managed with panretinal photocoagulation for neovascularization, vitrectomy for vitreous hemorrhage or retinal detachment, and intravitreal injection of antivascular endothelial growth factor agent for macular edema.[3,13,14,19,69,88,122,126,127,217]

2.20.6. Outcomes—WNV chorioretinitis is a self-limiting disease and usually has good visual prognosis. Visual acuity returns to the baseline in most patients, with up to half of patients having a final best corrected visual acuity of 6/12 or better.[13,14,19,69,88,122,126,127,217] Visual prognosis tends to be better in patients with focal retinitis and worse in patients with occlusive vasculitis.[224] Complications of WNV chorioretinitis include significant visual field loss, chorioretinal scarring, optic atrophy, retinal detachment, vitreous hemorrhage, choroidal neovascularization, and severe ischemic maculopathy.[3,13,14,19,31,69,88,122,126,127,217,224]

2.21. Zika virus

2.21.1. Background—Zika virus (ZIKV), a neurotropic mosquito-borne *Flavivirus* related to the dengue, yellow fever, and WNVs, was first identified in monkeys in 1947 and further isolated in humans in 1952. ZIKV is mostly transmitted by *Aedes* mosquitoes. Direct interhuman transmission by sexual intercourse, vertical, perinatal, and breast milk transmission has also been reported.[63,249,251] Since the ZIKV emergence in Brazil in April, 2015, it is estimated that more than one million Brazilians were infected. Nearly, 80% of patients with ZIKV infection are asymptomatic or oligosymptomatic.[63,249,251]

Six months following the onset of the ZIKV outbreak, a 20-fold annual increase of microcephaly cases was observed, with a prevalence of 99.7 per 10,0000 live births, leading the Brazilian Ministry of Health to confirm a relation between ZIKV and microcephaly. Up to 34.5% of infants born with presumed ZIKV-associated microcephaly have sight-threatening ocular lesions. Majority of the children affected were female, and bilateral findings were present in 70% of cases.[63,249,251]

2.21.2. Clinical features—Several infants with microcephaly were found to have mild to gross macular pigment mottling, foveal reflex loss, well-demarcated circular areas of

neuroretinal or chorioretinal atrophy with a predilection for the posterior pole and macula, posterior pole pigmentary clumping, and optic nerve hypoplasia with a double-ring sign, pallor, and increased cup-to-disk ratio.[63,109,169,249–251] In addition, there may also be pigmentary and hemorrhagic retinopathy, extensive vascular tortuosity, vascular absence, early abnormal vascular termination, and torpedo maculopathy.[173] Other ocular abnormalities that have been reported include lens subluxation and iris coloboma, but no infants had vasculitis or active uveitis.[169] These ocular findings can contribute to the diagnosis of ZIKV congenital infection in children with microcephaly.[63,109,169,249–251]

It remains unclear, however, whether the ocular lesions are a direct result of ZIKV or caused by microcephaly (secondary to ZIKV), but there could be a dual-mechanism involved. Ongoing registry studies are under way to confirm the causative association between ZIKV and microcephaly.[109,176]

Although posterior uveitis in acquired ZIKV infection has not been reported, uveitis may be a potential manifestation of acquired ZIKV infection. At least one case of ZIKV anterior uveitis has been reported, in which the anterior chamber paracentesis PCR tested positive for ZIKV RNA, with signs of conjunctival hyperemia, punctate keratitis, non-granulomatous keratic precipitates, and anterior chamber cells.[65]

2.21.3. Diagnosis—Although ZIKV infection in infants could not be tested by reverse transcriptase PCR, small head circumference and cerebral calcifications or lissencephaly were characteristic findings on computed tomography. In addition, the affected mothers had dengue-like symptoms in the first or second trimester of pregnancy, and both the mothers and infants had negative serology for toxoplasmosis, rubella, CMV, and HIV, thus fulfilling the Brazilian Ministry of Health's clinical criteria for ZIKV-related microcephaly.[63,173,249–251]

Recently, cerebrospinal fluid of infants with microcephaly has been tested for ZIKV using the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) test,[250] following the Centers for Disease Control and Prevention protocol as described by Martin and colleagues.[165]

2.21.4. Treatment and outcomes—As yet, there are no data on treatment and long-term outcomes of ZIKV posterior uveitis. There is currently no vaccine for ZIKV. Environmental modifications and efforts to eradicate mosquitoes are important to reduce and prevent ZIKV-related microcephaly and ocular manifestations, as well as reduce the infection rates of other vector borne diseases such as dengue fever, chikungunya, and WNV. In areas where ZIKV is prevalent, clinicians should perform ophthalmologic examination on all microcephalic babies.[109] Further long-term follow-up studies have to be done to determine the optimal management and visual prognosis of ZIKV posterior uveitis.

2.22. Other rare viruses

2.22.1. Influenza A (H1N1) virus—Influenza H1N1 virus is a more recent variant strain of influenza that is most closely related to the swine influenza A viruses. H1N1 virus was the most common cause in a human influenza pandemic in 2009. Symptoms of H1N1

include fever, cough, sore throat, diarrhea, and vomiting.[152] Ocular involvement is rare and has been associated with H1N1 infection as well as influenza vaccination.[124,160,233]

Ocular symptoms include pain, redness, and decreased visual acuity.[200] On examination,[59,200] there may be dense anterior chamber inflammation, vitritis, peripheral retinal necrosis, choroiditis, submacular hemorrhages, macular edema, neuroretinitis, vaso-occlusive retinal vasculitis,[35] frosted branch angiitis,[110] exudative retinal detachment,[233] and optic neuritis.[142,206] Other ocular conditions associated with H1N1 include uveal effusion syndrome[202] and orbital inflammatory syndrome.[22] Visual loss may also be caused by simultaneous retinal and lateral geniculate body infarction.[29]

No proven treatment exists for influenza retinopathy. Treatment of influenza posterior uveitis with systemic corti-costeroids has been shown to reduce the inflammation.[233] Frosted branch angiitis and macular edema may be treated with oral prednisone.[110] The long-term outcomes are generally favorable in majority of the reported cases and H1N1 posterior uveitis carries a better visual prognosis than other viruses that cause acute retinitis.[59,110,200,233] Complications are few and include involvement of the fellow eye.[200]

2.22.2. Coxsackie B virus—Group B coxsackieviruses are single-stranded RNA *Enterovirus* from the Picornavirus family. These viruses cause a number of diseases ranging from asymptomatic, nonspecific febrile illnesses, rashes, and upper respiratory tract disease to aseptic meningitis and myocarditis.[101]

Posterior uveitis caused by coxsackieviruses is extremely rare. There have been few reports of chorioretinitis linked to coxsackievirus, first described by Hirakata and colleagues in 1990.[91] Symptoms include a viral prodrome consisting of fever, arthralgia, sore throat, headache, and diarrhea preceding ocular symptoms such as blurring of vision, meta-morphopsia, and photopsia. On fundus examination, there was a unilateral retinal vasculitis, papillitis, and chorioretinitis in one case caused by coxsackievirus B3,[61] and cream-colored parafoveal spots at level of the RPE with similar confluent spots in the midperiphery in another case caused by coxsackievirus B4.[113] In both cases, there was complete resolution of the lesions with excellent visual outcomes.[61,113]

Unilateral acute idiopathic maculopathy has also been associated with Coxsackie virus.[112] Unilateral acute idiopathic maculopathy is a rare cause of unilateral, sudden, painless vision loss in young immunocompetent adults. A viral prodrome is common and 50% of patients had positive titres for Coxsackie virus.[112] Initially there are irregular, circular areas of white-gray macular discoloration, serous macular detachment, or exudative neurosensory retinal detachment.[112] Several FFA studies showed findings of irregular RPE hyperfluorescence and hypofluorescence. Following resolution, there is a bull's eye pattern of pigmentary disturbance at the macula, well-circumscribed areas of RPE atrophy, and progressive hyperplasia with late staining on FFA. Indocyanine green angiography showed "moth-eaten" choroidal vasculature, and OCT showed partially reversible disruption of the outer photoreceptor layer. Nearly, all patients experienced spontaneous visual recovery, with improvement between 20/20 and 20/30 at final follow-up.[112]

2.22.3. Ebola virus—Ebola virus disease (EVD) is a severe hemorrhagic fever caused by 5 species of RNA *Ebolaviruses* from the Filoviridae family. Ebola virus infects human monocytes and causes a loss of endothelial barrier function. The first reported cases of EVD occurred in 1976. The current epidemic in West Africa that began in December, 2013, is the largest known. As of February, 2016, over 28,500 cases have been reported, with a fatality ratio of 50%–65%.[168,236,247,253]

EVD cases may be asymptomatic or manifest as high fever, diarrhea, myalgia, arthralgia, and conjunctival injection. Fatal cases present with shock and coagulopathy. Late complications in survivors include auditory, arthritic, cardiac, and ocular disease (including vision loss, conjunctivitis, and uveitis) that develop during convalescence.[168,236,247,253]

Hypertensive uveitis characterized by ocular pain, photophobia, hyperlacrimation, foreign body sensation, red eye, and progressive visual loss develops in as many as 20% of convalescent patients, who may be asymptomatic for up to 2 months. The presence of blurred vision, photophobia, red or itchy eye, or fever during acute EVD was associated with underlying uveitis during convalescence. Vitreous opacities, multiple, peripheral chorioretinal scars with hypopigmented halos, and small intraretinal hemorrhages were seen on posterior segment examination. Uveitis was diagnosed as posterior uveitis and panuveitis in up to 26% and 25% of patients with ocular symptoms, respectively.[132,168,236,247,253]

Ebola virus is detected by ELISA, reverse transcriptase PCR assay, or viral culture from the serum, semen, conjunctival swab, or aqueous humour samples. Ebola viral load at the time of EVD diagnosis is a key independent predictor of ocular symptoms and uveitis in patients during convalescence.[132,168,247,253] Posterior uveitis caused by Ebola virus can be treated with topical, oral, or periocular corticosteroids, mydriatics, and management of intraocular pressure with ocular hypotensive agents.[132,236,247,253] The mainstay of management of EVD is supportive (IV fluids, antipyretics, antibiotics, and blood transfusion) with isolation and strict barrier nursing.[156] Currently, no antiviral agents have proven efficacy in patients with EVD. The World Health Organization has published a list of potential drugs with demonstrated antiviral efficacy in *in vitro* or animal models and undergoing clinical trials. This includes direct antiviral agents (favipiravir−a RNA-dependent RNA polymerase inhibitor−and BCX4430), monoclonal antibodies (ZMapp), type I interferons, RNA interference–based drugs (TKM-Ebola and AVI-7537), and anticoagulant drugs (rNAPc2). So far, there is no conclusive evidence of efficacy in clinical trials with the above drugs, and further testing is required.[156,266]

In a study done by Tiffany and colleagues,[236] the visual acuity did not change during the follow-up period in majority of uveitis patients, worsened unilaterally in 4, and improved in 9 of 58 patients. Complications of Ebola posterior uveitis include recurrence of anterior uveitis that may evolve into a sight-threatening panuveitis, ocular hypertension, scleritis, and cataracts.[236,247]

3. Conclusion

Viruses are an important cause of infectious posterior uveitis. In the clinical setting, it is useful to consider common infectious etiologies and rule out infectious causes. The diagnosis of viral posterior uveitis is primarily based on typical clinical symptoms and signs. Laboratory tests are used to confirm the virus involved and aid in the subsequent management of the disease. Investigations of intraocular fluids such as PCR assays may be useful, especially in cases of atypical clinical presentations. The treatment of viral posterior uveitis is complex and requires careful monitoring to provide the appropriate balance of symptomatic treatment, systemic or ocular antiviral medication, corticosteroids, and management of complications to ensure optimal long-term visual outcomes.

4. Method of literature search

A search of Medline, using PubMed and Google Scholar was performed. Keywords that were included for the search were: “viruses,” “viral posterior uveitis,” “herpetic retinitis,” “acute retinal necrosis,” “progressive outer retinal necrosis,” “CMV retinitis,” “HIV retinitis,” “measles retinopathy,” “rubella retinopathy,” “dengue posterior uveitis,” “chikungunya posterior uveitis,” “Rift Valley retinitis,” “West Nile Virus chorioretinitis,” “Zika posterior uveitis,” “Ebola posterior uveitis,” “polymerase chain reaction.” Articles were selected based on clinical importance. Additional references of key articles were also included. Articles with non-English abstracts were excluded.

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Table 1

Epidemiology of uveitis

Author (year)	Gender, n (%)		Age (years)		Anatomic diagnosis, n (%)				Posterior uveitis				
									Laterality, n (%)		Infectious status, %		Viral etiology, n (%)
	Male	Female	Range	Mean (± SD)	Anterior	Intermediate	Posterior	Pan	Bilateral	Unilateral	Infectious	Noninfectious	
Pathanapitoon et al (2008)[188]	105 (52.5)	95 (47.5)	8–85	38.4	49 (24.5)	17 (8.5)	92 (46.0)	42 (21.0)	48 (52.2)	44 (47.8)	NR	NR	CMV: 54 (58.7) ARN: 7 (7.6)
Kianersi et al (2014)[131]	915 (45.4)	1101 (54.6)	2–98	33.76 ± 10.56	865 (42.9)	390 (19.3)	432 (21.4)	329 (16.3)	63 (14.6)	369 (85.4)	88.4	11.6	CMV: 4 (0.9) HIV: 1 (0.2)
Al-Shakarchi (2014)[12]	159 (50.0)	159 (50.0)	NR	36.2	78 (24.5)	20 (6.3)	123 (38.7)	97 (30.5)	63 (51.2)	60 (48.8)	69.9	30.1	ARN: 2 (1.6) CMV: 1 (0.8)
Liberman et al (2014)[150]	256 (41.9)	355 (58.1)	3–91	38.0 (median)	247 (40.4)	51 (8.3)	110 (18.0)	203 (33.2)	42 (38.2)	68 (61.8)	40.0	60.0	CMV: 5 (4.5) HSV: 2 (1.8)
Llorenç et al (2015)[153]	465 (45.5)	557 (54.5)	1–92	38.0 (median)	534 (52.3)	92 (9.0)	240 (23.5)	156 (15.3)	120 (50.0)	120 (50.0)	47.9	52.1	CMV: 9 (3.8) ARN: 6 (2.5) HIV: 5 (2.1) NNHR: 2 (0.8) PORN: 1 (0.4)
Venkatesh et al (2015)[248]	489 (61.1)	311 (38.9)	4–81	34.21 ± 13.94	413 (51.6)	131 (16.4)	162 (20.3)	94 (11.8)	84 (51.9)	78 (48.1)	51.2	48.8	HIV: 11 (6.8) CMV: 8 (4.9) ARN: 2 (1.2)
Dhibi et al (2016)[55]	390 (43.9)	498 (56.1)	6–94	39.6 ± 11	242 (27.3)	113 (12.7)	63 (7.1)	470 (52.9)	40 (63.5)	23 (36.5)	47.6	52.4	CMV: 1 (1.6)
Summary, n (%)	M: 2779 (47.5); F: 3076 (52.5); M:F ratio 1:1.1		Range: 1–98; mean: 36.4		2428 (41.5)	814 (13.9)	1222 (20.9)	1391 (23.7)	460 (37.6)	762 (62.4)	65.5	34.5	ARN: 17 (14.0) HIV: 17 (14.0) HSV: 2 (1.7) NNHR: 2 (1.7) PORN: 1 (0.8)

ARN, acute retinal necrosis; CMV, cytomegalovirus; F, female; HSV, herpes simplex virus; M, male; NNHR, nonnecrotizing herpetic retinitis; NR, not reported; PORN, progressive outer retinal necrosis.

Table 2

Retinitis after intraocular steroid injection

Author (year)	Age (years)	Gender	HIV status	Indication for corticosteroid	Time from corticosteroid to retinitis (months)	Established diagnosis	VA when retinitis first diagnosed	Treatment	Duration of follow-up (months)	VA at last visit
D'Alessandro et al (2002)[51]	45	M	+	Immune recovery uveitis	2	CMV retinitis	20/100	Intravenous ganciclovir	18	"Habitual visual acuity"
Saidel et al (2005)[208]	75	M	−	CME	4	CMV retinitis	20/400	Oral valganciclovir, intravitreal ganciclovir	6	20/400
Toh et al (2006)[237]	62	F	−	Choroidal neovascular membrane	6	HSV-1 retinitis	20/60	Intravenous acyclovir, oral acyclovir	3	20/120
Furukawa et al(2007)[66]	54	F	−	CME	3	CMV retinitis	1.0	Intravenous ganciclovir, intravitreal foscarnet, vitrectomy	14	0.5
Vertes et al (2010)[252]	78	F	−	CME	3	CMV retinitis	20/40	Intravenous ganciclovir, oral valganciclovir, intravitreal ganciclovir, vitrectomy, peripheral endolaser	8	20/25
Takakura et al (2014)[232]	65	M	−	VKH with steroid-induced cataracts	1.8	CMV retinitis	20/200	Intravitreal ganciclovir, oral valganciclovir	2	20/70
	37	F	−	Idiopathic posterior uveitis with CME	12	CMV retinitis	20/80	Intravitreal foscarnet, oral valganciclovir	2	20/80
	63	M	−	Granulomatous panuveitis with CME	2	CMV retinitis	20/40	Intravenous ganciclovir, oral prednisone, pars plana vitrectomy	84	20/200
	72	M	−	BRVO	1	CMV retinitis	20/60	Intravitreal ganciclovir	12	CF
	37	F	−	Chronic idiopathic iridocyclitis	2	ARN	20/30	Oral acyclovir, intravitreal ganciclovir	36	20/200
Summary; n (%)	Range: 37–78; mean: 58.8; median: 62.5	Male: female ratio 1:1	HIV positive: 1 (10.0)	CME: 5 (50.0); others: 5 (50.0)	Range: 1–12; mean: 3.7; median: 2.5	CMV retinitis: 8 (80.0); others: 2 (20.0)	≤20/40: 3 (30.0); 20/40–20/100: 4 (40.0); ≥20/100: 3 (30.0)	Systemic: 3 (30.0); intravitreal: 1 (10.0); both systemic and intravitreal: 6 (60.0)	Range: 2–84; mean: 18.5; median: 10	≤20/40: 1 (10.0); 20/40–20/100: 2 (20.0); ≥20/100: 7 (70.0)

M, male; F, female; CMV, cytomegalovirus; HSV, herpes simplex virus; ARN, acute retinal necrosis; VKH, Vogt-Koyanagi-Harada disease; C/BRVO, central/branch retinal vein occlusion; CME, cystoid macular edema; VA, visual acuity; CF, counting fingers.

Table 3

Demographics and clinical characteristics of Epstein-Barr virus chorioretinitis

Author (year)	Age (years)	Gender	Laterality	Immuno deficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Kelly et al (1989)[118]	17	M	U	Nil	Serology	Pain, blurred vision	RAPD, AC/vitreous cells, white fluffy retinitis, retinal hemorrhage, vitreous haze, vascular sheathing, optic disk edema	OS: CF 1/3 m	Oral clindamycin, prednisolone, acetazolomide, topical dexamethasone	Atrophic macular scar	0.25	6/36
Hershberger et al (2003)[89]	0.8	M	B	X-linked lymphoproliferative disorder	Serology, retinal biopsy	Unable to fix and follow	RAPD, posterior synechiae, rubeosis, hazy vitreous, widespread yellow-white retinal opacification, retinal hemorrhages, RD, optic nerve swelling and hemorrhage, vascular sheathing, atrophic RPE lesions	NR	Vitrectomy, bone marrow transplant	RD, phthisis bulbi	NR	NR
Kim et al (2011)[133]	65	F	B	Nil	Serology, vitreous biopsy	Sudden decreased vision	ERM, coalescing, yellow lesions at the level of the RPE in the macula	OD: 20/200; OS: CF	Oral valacyclovir, prednisone	RPE atrophy	6	OD: 20/80 OS: CF
Peponis et al (2012)[192]	67	M	B	EBV encephalitis	CSF PCR	Progressive decreased vision	Multiple, well-demarcated gray-white areas of retinal atrophy, multifocal chorioretinitis, optic neuritis	OD: 6/60; OS: HM	Ceftriaxone, ampicillin, acyclovir	Nil	2	OD: 6/18 OS: CF
Schmoll et al (2013)[213]	65	F	U	Aplastic anemia on immunosuppressive therapy	Anterior chamber paracentesis	Pain, redness, blurred vision	RAPD, anterior uveitis, hypotony, vitritis, focal retinitis, localized choroidal effusions, hemorrhagic arteriolitis	OS: PL	IV acyclovir, topical dexamethasone, oral prednisolone, oral famciclovir	Hypotony, progression of retinochoroiditis	1	PL
Weller et al (2015)[258]	30	M	U	Nil	Serology	Paracentral scotoma	Intraretinal, white sharp-edged macular lesion, surrounded by several smaller intraretinal white-yellow spots	20/20	IV/oral acyclovir, topical prednisolone	Nil	1	20/20
Summary; n, %	Mean: 40.8; range: 0.8–67	M: 4 (66.7); F: 2 (33.3)	B: 3 (50.0); U: 3 (50.0)	2 (33.3)	Serology, aqueous/vitreous PCR, retinal biopsy, CSF	Blurred vision, scotoma, pain, redness	RAPD, anterior chamber/ vitreous inflammation, chorioretinitis, hemorrhage, vasculitis, optic neuritis	Range: 20/20-PL	IV/oral acyclovir, oral valacyclovir, topical/systemic corticosteroids	Progression, RD, phthisis, hypotony, atrophy, macular scar	Mean: 2.05 Range: 0.25–6	Improved: 3 Stable: 2

M, male; AC, anterior chamber; B, bilateral; CF, counting fingers; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ERM, epiretinal membrane; F, female; HM, hand movement; IV, intravenous; NR, not reported; NPL, no light perception; OD, oculus dexter; OS, oculus sinister; PCR, polymerase chain reaction; PL, light perception; RD, retinal detachment; RPE, retinal pigment epithelium; RAPD, relative afferent pupillary defect; U, unilateral.

Table 4

Demographics and clinical characteristics of Acute Retinal Necrosis

Author (year)	Age (years)	Gender, n (%)	Laterality, n (%)	Immun odeficiency, n (%)	Viral etiology, n (%)	Method of diagnosis	Previous herpes infection, n (%)	Symptoms, n (%)	Signs, n (%)	VA at presentation	Treatment, n (%)	Complications, n (%)	Duration of follow-up (months)	VA at last visit
Tran et al (2004)[240]	Mean: 36; range: 10–57	M: 6; F: 5	B: 4 (27.2); U: 7	0	HSV-2: 11	Aqueous or vitreous biopsy	Neonatal herpes: 1; previous ARN: 3	NR	RPE abnormalities, neuroretinal atrophy, chorioretinal scars	Range: 20/25–CF; <20/60: 4; 20/70–20/400: 4; >20/400: 4	IV acyclovir/ foscarnet, intravitreal ganciclovir, oral valacyclovir, interferon, vitrectomy, laser	RD: 5 (41.7); ERM: 4 (33.3); cataract: 5 (41.7); optic nerve atrophy: 2 (16.7); CME: 1 (8.3)	Mean: 14.5; range: 5–22	Improved: 5 (41.7); <20/60: 4 (33.3); 20/70–20/400: 4 (33.3); >20/400: 4 (33.3)
Lau et al (2006)[146]	Mean: 49.5±3.5; median: 51; range: 18–83	M: 10; F: 12	B: 5 (22.7); U: 17	0	VZV alone: 9/18 (50.0); HSV alone: 4/18 (22.2); EBV + VZV: 3/18 (16.7)	Vitreous biopsy	Shingles: 2; cold sore: 1; Ramsay Hunt syndrome: 1; corneal dendritic ulcer: 1	Flu-like symptoms: 1 (4.5)	NR	Mean: 0.32 ± 0.05	Systemic corticosteroid, laser, IV and oral acyclovir, vitrectomy	RD: 14/27 (51.9); macular lesion: 7 (25.9); vitreoretinopathy: 7 (25.9); optic neuropathy: 3 (11.1); ERM: 1 (3.7); cataracts: 1 (3.7); glaucoma: 1 (3.7)	Mean: 48; range: 12–146	Mean: 0.38 ± 0.17
Muthiah et al (2007)[179]	Mean: 54.3; range: 13–85	M: 22 (71.0); F: 9 (29.0)	B: 3 (9.7); U: 28 (90.3)	7 (22.6)	VZV: 9; HSV-1: 3; HSV-2: 2; HSV-1 + HSV-2: 1; HSV + VZV: 1	Aqueous or vitreous biopsy	Herpes simplex keratitis: (9.7); herpes zoster ophthalmicus: (20.7); cold sore: (25.0); genital ulcers: (4.5); encephalitis: (15.4); chicken pox: (70.6); Shingles: (29.4)	Sudden visual loss: (85.1); photophobia: (54.5); flu-like symptoms: (26.1); ocular pain: (25.8); red eye: (16.1)	AC activity: 25 (80.6); vitreous cells: 26 (83.9); peripheral retinal involvement: 25 (80.6)	Range: 6/5–NPL	IV antivirals (acyclovir, ganciclovir, and cidofovir): 23 (85.2); oral antivirals (acyclovir and valacyclovir): 4 (14.8); systemic steroids: 16 (51.6); aspirin: 2 (6.5); laser: 5	RD: 9/12 (75.0); hypotony, CME, rubeosis	12	Worsened: 15/34 (44.1); improved: 9/34 (26.5)
Hillenkamp et al (2009)[90]	Mean: 58 ± 21; range: 17–96	M: 16; F: 11	B: 3; U: 24	NR	VZV alone: 23; HSV alone: 4; VZV + EBV: 2; VZV + HSV:1	Vitreous biopsy	NR	NR	NR	Mean: 1.09 ± 0.83; range: 0.1–3.0	IV acyclovir + oral prednisolone: 32; vitrectomy, intravitreal acyclovir, laser: 10	RD: 22/30 (73.0); phthisis: 2/30	Mean: 38 ± 53; range: 1–216	Mean: 1.46 ± 0.88; range: 0.18–3.0
Meghpara et al (2010)[172]	Mean: 42 ± 19; range: 9–77	M: 5; F: 15	B: 5 (25.0); U: 15 (75.0)	0	VZV: 2; CMV: 1	Vitreous biopsy	Chicken pox: 7 (35.0); cold sore: 5; shingles: 2; genital ulcers: 1; pharyngeal herpes: 1	NR	Retinal involvement: <25%: 11 (44.0), 25–50%: 8 (32.0), >50%: 6 (24.0); optic disk swelling: 6	NR	IV acyclovir/ foscarnet: 14 (70.0); oral acyclovir/ valacyclovir/ famciclovir: 19 (95.0); intravitreal	RD: 5 (25.0)	Mean: 20.4 ± 20.5; range: 0.3–57.9	Improved: 4; worsened: 5

Author (year)	Age (years)	Gender, n (%)	Laterality, n (%)	Immun odeficiency, n (%)	Viral etiology, n (%)	Method of diagnosis	Previous herpes infection, n (%)	Symptoms, n (%)	Signs, n (%)	VA at presentation	Treatment, n (%)	Complications, n (%)	Duration of follow-up (months)	VA at last visit
											ganciclovir/ foscarnet: 11 ganciclovir implants: 2 (8.0%); laser: 6 (24.0) (44.0);			
Cochrane et al (2012)[42]	Range: 10–94	M: 25 (55.6); F: 20 (44.4)	B: 7 (15.6); U: 38 (84.4)	13 (28.9)	VZV alone: 15; HSV alone: 9; CMV alone: 2; EBV alone: 1; VZV+EBV: 2; VZV +CMV: 1	Aqueous tap, vitreous biopsy, or CSF lumbar puncture	Chicken pox: 9 (20.2); Shingles/ herpes zoster ophthalmicus: 6 (13.3); encephalitis/ meningitis: 7 (15.6)	NR	NR	NR	Oral antivirals: 11 (24.4; 8 with valacyclovir); IV antivirals: 34; intravitreal antivirals (foscarnet): 21 (46.7); oral steroids: 26 (57.8); aspirin: 14/43 (32.6); laser: 10 (23.2)	RD: 16/52 (30.8); phthisis: 2/42 (4.7)	6	<6/60: 21 (47.7)
Roy et al (2014)[205]	Mean: 36.0; range: 6–70	M: 38 (71.7); F: 15 (28.3)	B: 9 (17.0); U: 44 (83.0)	2	VZV: 28 (45.2); HSV: 19 (30.6)	Aqueous or vitreous biopsy	Chicken pox: 4 (7.5); herpes encephalitis: 1	Hazy vision: 53 (100.0); headache/ periocular pain: 10 (18.9); viral fever: 4 (7.5)	Retinal necrosis	Mean: 2.02	Oral steroids, systemic acyclovir, laser, vitreoretinal surgery	RD: 41 (66.1); proliferative vitreoretinopathy: 14 (35.0); optic atrophy: 10 (29.4); phthisis: 4 (11.7); hypotony: 3 (8.8); macular scar: 1 (2.9)	Mean: 27; range: 6–120	Mean: 1.78; <6/60: 28 (45.1)
Summary; n, %	Mean: 46.0; range: 6–96	M: 122 (58.4); F: 87 (41.6)	B: 36 (17.2); U: 173 (82.8)	22 (12.1)	VZV alone: 86 (41.1); HSV alone: 53 (25.4); CMV: 4 (1.9); EBV: 8 (3.8)	Aqueous or vitreous biopsy, CSF	Chicken pox: 42 (20.1); shingles: 19 (9.1); cold sore: 14 (6.7); herpes encephalitis: 13 (6.2); others: neonatal herpes, herpes simplex keratitis, genital ulcers	Vision loss, ocular pain, photophobia, flu-like symptoms, red eye	AC inflammation; retinal necrosis, RPE abnormality, neuroretinal atrophy, chorioretinal scars	Range: 6/5-NPL	Systemic/ intravitreal antivirals, systemic/topic steroids, aspirin, prophylactic laser, vitrectomy	RD: 112 (53.6); phthisis: 8 (3.8); macular lesion: 13 (6.2); optic neuropathy/atrophy: 15 (7.2); cataracts:6 (2.9); others: CME, rubeosis, vitreoretinopathy	Mean: 23.7; range: 0.3–216	Majority worsen or no improvement

AC, anterior chamber; ARN, acute retinal necrosis; B, bilateral; CME, cystoid macular edema; CF, counting fingers; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ERM, epiretinal membrane; F, female; HM, hand movement; HSV, herpes simplex virus; IV, intravenous; M, male; NR, not reported; NPL, no light perception; PCR, polymerase chain reaction; PL, light perception; RD, retinal detachment; U, unilateral; VA, visual acuity; VZV, varicella zoster virus.

Table 5

Diagnostic criteria of acute retinal necrosis by the American Uveitis Society

Clinical characteristics that must be seen	Characteristics that support but are not required for diagnosis
• One or more focus of retinal necrosis with discrete borders located in the peripheral retina (primarily involving the area adjacent to, or outside of, the major temporal vascular arcades). • Rapid progression of disease (advancement of lesion borders or development of new foci of necrosis) if antiviral therapy is not given • Circumferential spread of disease • Evidence of occlusive vasculopathy with arteriolar involvement • Prominent inflammatory reaction in the vitreous and anterior chambers	• Optic neuropathy/atrophy • Scleritis • Pain

Table 6

Antiviral treatment modalities for herpes human virus posterior uveitis

Type of drug	Route of administration	Doses	Duration	Mechanism of action	Indications	Side effects
Antivirals						
Acyclovir induction[6,26,56]	Intravenous	10 mg/kg every 8 hours or 1500 mg/m^2 per day	5 to 10 days	A nucleoside analog that selectively inhibits replication of HSV, VZV and EBV. Acyclovir is converted into acyclovir triphosphate, which inhibits viral DNA polymerase, resulting in chain terminations and mutations.	ARN, PORN	Reversible rise in serum creatinine levels, urinary calculi, elevation in liver function tests, central nervous system toxicity such as lethargy, delirium, seizures.
Acyclovir maintenance[6,26,56]	Oral	800 mg 5 times daily	6 weeks		ARN, PORN	
Acyclovir[7,258]	Oral	400 mg 5 times daily 800 mg 5 times daily	4 weeks, then tapered slowly 4–8 months		EBV chorioretinitis NNHR	
Valacyclovir[2,6,15,27,60,79,133]	Oral	1 g 3 times daily or 2 g 4 times daily	Slowly tapered over 2–6 months	The L-valyl ester of acyclovir is rapidly converted to acyclovir, producing acyclovir blood levels 3–5 times greater, with bioavailability of 54% compared with 20% for acyclovir.	ARN, PORN, NNHR, EBV chorioretinitis	Headache, gastrointestinal disturbances, nausea, with similar side effects as acyclovir but to a lesser extent.
Famciclovir[6,15,60,213]	Oral	500 mg 3 times daily	Slowly tapered over 2–6 months	Rapidly converted to a highly bioavailable penciclovir which is converted to a triphosphate that preferentially inhibits viral DNA polymerase.	ARN, EBV chorioretinitis	Well-tolerated, similar side effect profile as acyclovir.
Foscarnet[265]	Intravitreal	2.4 mg/0.1 mL	2–4 injections	A pyrophosphate analog that selectively inhibits pyrophosphate binding site on viral DNA polymerases of HHVs but is not activated by thymidine kinase.	ARN, PORN, EBV chorioretinitis	Systemic foscarnet may cause nephrotoxicity, hypocalcemia, anemia and, nausea. Risks of intravitreal injections include cataract, infection, vitreous hemorrhage, retinal detachment.
Ganciclovir[134,155,171,193]	Intravitreal	4 mg/0.1 mL or 400 mg twice per week	2–4 injections	An acyclic analog of the nucleoside guanosine. Differs from acyclovir by the lack of hydroxyl group on the acyclic side chain, with enhanced activity against CMV, but similar activity against HSV and VZV.	ARN, PORN	Greater systemic toxicity and cytotoxicity including neutropenia, anemia, nephrotoxicity, diarrhea. Risks of intravitreal injections as previously described.

ARN, acute retinal necrosis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHVs, human herpesviruses; HSV, herpes simplex virus; NNHR, nonnecrotizing herpetic retinitis; OD, oculus dexter; OS, oculus sinister; VZV, varicella zoster virus; PORN, progressive outer retinal necrosis.

Table 7

Demographics and clinical characteristics of progressive outer retinal necrosis

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Viral etiology	Method of diagnosis	Previous herpes infection	Symptoms	Signs	VA at presen-tation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Pavesio et al (1995)[191]	33	M	B	HIV + CD4+ count: 1 cell/mm^3	VZV	Vitreous biopsy	Thoracic shingles	Acute vision loss	Parafoveal white lesion with central cherry red spot, optic disk edema, peripheral confluent satellite lesions	OD: 6/6; OS: 1/60	IV acyclovir/ foscarnet, intravitreal acyclovir, laser photocoagulation, vitrectomy	RD	2	OU: NPL
	37	M	U (OD)	HIV + CD4+ count: 14 cells/mm^3	VZV	Vitreous biopsy	Concurrent left CMV retinitis	Acute vision loss	Mild right anterior uveitis, bilateral vitritis, large white macular lesion, multiple peripheral white lesions	OD: PL	IV acyclovir, intravitreal acyclovir	RD	12	"Poor visual prognosis"
Greven et al (1995)[75]	41	M	B	HIV+	VZV	Retinal biopsy	Herpes zoster dermatitis	Vision loss, paracentral scotoma	Outer retinal and choroidal infiltrates	OU: 20/25	Trimethoprim/ sulfamethoxazole, IV acyclovir, pyrimethamine, pentamidine, clindamycin, IV ganciclovir	Retinal and optic atrophy, RD	4	OU: NPL
Kalpoe et al (2005)[114]	24	M	B	Stem cell transplant	VZV	Aqueous tap	Cutaneous herpes zoster	Acute vision loss	AC cells, yellow chorioretinal dots, exudative RD; coalescing peripheral retinal necrosis	OS: 0.2; OD: 1.0	IV acyclovir, tobradex, vitrectomy, IV and intravitreal foscarnet, laser	Involvement of fellow (OD) eye after 4 weeks	6	OS: 1/300; OD: 0.4
Khot et al (2006)[128]	51	M	B	Stem cell transplant	VZV	Vitreous biopsy	Thoracic shingles	Left visual field defect	RAPD, extensive peripheral pigmented mottling, hemorrhage	OU: 6/9	IV foscarnet, prednisolone, IV ganciclovir/cidofovir, intravitreal foscarnet, IVIG, oral valacyclovir	RD, optic disk edema, macular involvement	1	OD: 6/60; OS: NPL
Turno-Kręcicka et al (2015)[244]	41	F	B	Kidney transplant	VZV; BK virus	Vitreous biopsy	Mucocutaneous HSV infections	Progressive vision loss	Mild vitritis, white deep retinal infiltrate in posterior pole, retinal atrophy, vascular sheathing	OD: 20/35; OS: 20/100	IV ganciclovir, intravitreal ganciclovir, vitrectomy	RD	1	OD: NPL; OS: PL
Tseng et al (2015)[241]	45	M	B	HIV+	VZV	Aqueous tap	Cutaneous herpes zoster	Progressive vision loss	Multifocal, patchy choroidal, and deep retinal opacification with dot and blot hemorrhage	OD: HM; OS: PL	Oral/IV/intravitreal ganciclovir, sulfamethoxazole, trimethoprim, HAART, aspirin, IV valganciclovir/ famciclovir, laser	Obliterative vasculitis, CRVO	1	OU: NPL
Summary; n, %	Mean: 38.9; range: 24–51	M: 6 (85.7); F: 1 (14.3)	B: 6 (85.7); U: 1 (14.3)	HIV: 4; Transplant: 3	VZV	Vitreous biopsy, aqueous tap, retinal biopsy	Herpes zoster	Vision loss, scotoma, visual field defect	Minimal AC/ vitreous inflammation, multifocal white-yellow choroidal and retinal lesions, hemorrhage	Range: 6/6-PL	Systemic/intravitreal antivirals, laser, vitrectomy	RD: 5 (71.4); optic disk involvement, CRVO, involvement of fellow eye	Mean: 3.9; range: 1–12	Worsened: 7

AC, anterior chamber; ARN, acute retinal necrosis; B, bilateral; CMV, cytomegalovirus; CRVO, central retinal vein occlusion; F, female; HAART, highly active antiretroviral therapy; HSV, herpes simplex virus; HM, hand movement; IV, intravenous; IVIG, intravenous immunoglobulin; M, male; NR, not reported; NPL, no light perception; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PORN, progressive outer retinal necrosis; RD, retinal detachment; U, unilateral; VZV, varicella zoster virus.

Table 8

Demographics and clinical characteristics of cytomegalovirus retinitis

Author (year)	Age (years)	Gender	Laterality	Immunodeficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Kuo et al (2004)[140]	Mean: 50; Median: 58; range: 14–74	M: 13; F: 5	B: 12; U: 6	Immunosuppressive drugs: 18	NR	Blurred vision, floaters, scotoma	Necrotizing retinitis, intraretinal hemorrhage, with granular or edematous borders	>20/50: 11 (37%); >20/200: 5 (20%)	IV ganciclovir, ganciclovir implant, intraocular foscarnet, sub-Tenon corticosteroid	Involvement of second eye, RD, IRU, posterior subcapsular cataract, CME, ERM, optic atrophy	12	>20/50: 17 (58%); >20/200: 13 (45%)
Jabs et al (2004)[108]	Mean: 41	M: 224; F: 47	B: 97; U: 174	HIV+: 271; CD4+ <50: 34.0%; CD4+ 50–99: 12.7%; CD4+ 100–199: 17.5%; CD4+ ≥200: 35.8%	Clinical	NR	Necrotizing retinitis, atrophic and gliotic scar	NR	Ganciclovir implant: 42.2%; systemic ganciclovir: 17.5%; Intravitreal injection: 3.0%; HAART: 79.8%	Progression of retinitis, involvement of second eye, RD, IRU	NR	NR
Pathanapitoon et al (2013)[189]	Mean: 49; range: 29–65	M: 11; F: 7	B: 4; U: 14	Immunosuppressive drugs: 11; primary immunodeficiency: 1	Aqueous PCR	NR	Focal hemorrhagic retinitis, granular retinitis, ARN, vitritis, retinal arteritis, frosted branch angiitis	NR	Systemic/intraocular ganciclovir, vitrectomy	ERM, RD, traction	Mean: 24; range: 3–60	NR
Schneider et al (2013)[214]	Mean: 71.0; median: 74; range: 48–83	M: 4; F: 1	B: 1; U: 4	Immunosuppressive drugs: 2	Aqueous/vitreous PCR, retinal biopsy	Progressive vision loss, floaters, scotoma	Slowly progressive granular retinitis, occlusive panretinal vasculitis, retinal hemorrhages, optic neuritis	OS: PL OD: HM OS: 20/25 OD: 20/30 OS: 5/200	IV ganciclovir, oral valganciclovir, intravitreal foscarnet, panretinal photocoagulation, vitrectomy	Retinal neovascularization, vitreous hemorrhage, RD, phthisis	Mean: 13.2; range: 7–21	OS: HM OD: HM OS: 20/20 OD: 20/30 OS: HM
Jabs et al (2013)[106]	Median: 40.0; range: 34–45	M: 196; F: 54	B: 88; U: 162	HIV+: 250; median CD4+ count: 20	Clinical	NR	Full thickness necrotizing retinitis	Mean: 20/42	HAART, oral valganciclovir, IV ganciclovir/ cidofovir/foscarnet, intravitreal ganciclovir/ foscarnet, ganciclovir implant	RD, IRU, visual field loss, second eye involvement	Mean: 60; range: 20.4–90	>20/40: 27.8%; >20/200: 12.4%
Agarwal et al (2014)[4]	Mean: 33.7 ± 15.7; range: 11–63	M: 6; F: 4	B: 8; U: 2	Immunosuppressive drugs: 8	Clinical, vitreous PCR	Blurred vision, floaters	Vascular sheathing, CMV lesions	Mean: 0.51 ± 0.41; range: 0–1.9	Intravitreal ganciclovir	IRU, posterior subcapsular cataracts, RD, CME, ERM	Mean: 9.46 ± 12.42	Mean: 0.43 ± 0.52; range: 0–1.9
Huang et al (2015)[100]	Mean: 38 ± 9; range: 18–60	M: 58; F: 9	B: 37; U: 30	HIV+: 67; mean CD4+ count: 31.7 ± 33.9	NR	Ocular discomfort, blurred vision, visual field defects, floaters	Perivascular yellowish white necrotic retinal infiltration with granular borders, intraretinal hemorrhages, retinal vasculitis, optic neuritis	<0.05: 23; 0.05–0.3: 31; >0.3: 44	HAART, IV ganciclovir/foscarnet, oral/ intravitreal ganciclovir	Macular necrosis, RD, cataracts, IRU	Range: 5–44	No improvement: 26 (33.3%); improved: 39 (50.0%); <0.05: 28.9%
Summary; n, %	Mean: 47.1; range: 11–83	M: 512 (80.1); F: 127 (19.9)	B: 247 (38.7); U: 392 (61.3)	HIV+: 588 (92.0); immunosuppressive drugs: 39 (6.1)	Clinical, aqueous/vitreous PCR	Blurred vision, floaters, scotoma, ocular discomfort	Necrotizing retinitis, retinal hemorrhage, vasculitis, optic neuritis	Range: 20/20-PL	HAART, systemic/intraocular valganciclovir, ganciclovir, cidofovir, foscarnet, vitrectomy, corticosteroid	Progression, second eye involvement, RD, IRU, CME, ERM, cataracts, phthisis, neovascularization, optic atrophy	Mean: 23.7; range: 3–90	Majority no improvement

ARN, acute retinal necrosis; B, bilateral; CMV, cytomegalovirus; CME, cystoid macular edema; EBV, Epstein-Barr virus; ERM, epiretinal membrane; F, female; HAART, highly active antiretroviral therapy; HM, hand movement; HSV, herpes simplex virus; IV, intravenous; IRU, immune recovery uveitis; M, male; NPL, no light perception; NR, not reported; OD, oculus dexter; OS, oculus sinister; PL, light perception; PORN, progressive outer retinal necrosis; RD, retinal detachment; RPE, retinal pigment epithelium; U, unilateral.

Table 9

Demographics and clinical characteristics of nonnecrotizing herpetic retinitis

Author (year)	Age (years)	Gender	Laterality	Immunodeficiency	Viral etiology	Method of diagnosis	Previous herpes infection	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Bodaghi et al (2003)[27]	Mean: 53.2; range: 29–82	M: 1; F: 4	B: 4; U: 1	HIV−; immunosuppressive drugs/ corticosteroids: 5	VZV: 3; HSV-1: 2	Aqueous tap	Herpetic keratitis	NR	Mild to moderate vitritis, diffuse retinal vasculitis, papillitis, macular edema; granulomatous anterior uveitis; unilateral glaucoma	Case 1: OD 20/60 Case 2: OU 20/60 Case 3: OU 20/40 Case 4: OD CF, OS 20/50 Case 5: OD 20/200, OS 20/100	Oral valacyclovir, low-dose steroids	NR	Mean: 11.2; range: 6–16	Case 1: OD 20/30 Case 2: OU 20/40 Case 3: OU 20/30 Case 4: OD CF, OS 20/40 Case 5: OU 20/60
Wickremasinghe et al (2009)[262]	48	M	U	NR	VZV	Vitreous biopsy	Herpetic anterior uveitis for 15 years	Blurred vision, pain	Sectorial iris atrophy, mutton fat KPs, 1+ AC cells, flare, multiple discrete arteriolar sheathing	6/12	Oral acyclovir, topical prednisolone, timolol	NR	7	6/12
	76	M	U	NR	VZV	Vitreous biopsy	Herpetic anterior uveitis for 2 months	Blurred vision	Localized corneal stromal edema, KPs, iris atrophy 1/2 + AC cells, vitreous cells, arteriolar sheathing	6/18	Oral acyclovir, topical steroid	Persistent stromal corneal edema	1	6/12
Wensing et al (2011)[259]	Mean: 55; range: 19–81	M: 6; F: 3	B: 2; U: 7	Immunosuppressive drugs/corticosteroids: 3	VZV: 7; HSV: 2	PCR and GWC	Herpetic encephalitis	NR	Vasculitis: 3; papillitis: 2; vitritis, panuveitis without any distinct features	NR	Oral valacyclovir, corticosteroids, vitrectomy, laser	RD: 1; CME: 2; retinal atrophy	6	0.3–0.8
Albert et al (2015)[7]	19	F	B	NR	HSV-1	Aqueous tap	NR	NR	Severe bilateral occlusive vasculitis, vitreous/ intraretinal hemorrhage, peripheral neovascularization	OU 20/20	Oral corticosteroid, laser photocoagulation, immunosuppressive drugs, vitrectomy, oral acyclovir	Multiple recurrences of occlusive vasculitis with hemorrhage, CME	132	OU 20/20
	11	M	U	Tetralogy of Fallot	VZV	Vitreous biopsy	NR	NR	Inferior occlusive retinal vasculitis, optic disk/ retinal neovascularization, severe vitritis	OD 20/50	Vitrectomy, photocoagulation, oral acyclovir, topical corticosteroids	CME, recurrence of anterior uveitis, band keratopathy, posterior subcapsular cataract	168	OD 20/200
Summary; n, %	Mean: 43.7; range: 11–82	M: 10 (55.6); F: 8 (44.4)	B: 7 (38.9); U: 11 (61.1)	Immunodeficiency: 8	VZV: 13 (72.2); HSV: 5 (27.8)	Aqueous tap, vitreous biopsy	Herpes keratitis, anterior uveitis, encephalitis	Blurred vision, pain	Vitritis, retinal vasculitis, papillitis, hemorrhages, neovascularization	Range: 20/20–20/200	Oral (val)acyclovir, topical/systemic steroids, vitrectomy	Recurrences, CME, RD, band keratopathy, cataracts	Mean: 54.2; range: 1–168	Improved: 6; worsened: 1

AC, anterior chamber; B, bilateral; CF, counting fingers; CME, cystoid macular edema; F, female; GWC, Goldmann-Witmer coefficient; HSV, herpes simplex virus; KPs, keratic precipitates; M, male; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; RD, retinal detachment; PCR, polymerase chain reaction; U, unilateral; VA, visual acuity; VZV, varicella zoster virus.

Table 10

Demographics and clinical characteristics of measles retinopathy

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Associated conditions	Method of diagnosis	Symptoms	Signs	VA at presen-tation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Scheie et al (1972)[212]	6	F	B	Nil	Measles	Clinical	Blurred vision	Blurred optic disk margins, diffuse retinal edema, attenuated arterioles, scattered retinal hemorrhages, macular star	OU: HM	ACTH, cortisone, tetracycline	Retinitis pigmentosa, visual field defect	54	OD: 6/9; OS: 6/12
Tomoda et al (1997)[238]	10	M	B	Nil	Measles at 8 months, SSPE	CSF, EEG	Visual loss	Macular degeneration, chorioretinitis	NR	Corticosteroids, interferon alpha	NR	12	NR
Nguyen et al (1999)[182]	9	M	B	Nil	SSPE	Serology, CSF, EEG	Neurologic symptoms	RAPD, optic disk edema, multifocal, translucent pigment, epithelial-level lesions	OD: 20/800; OS: 20/30	Isoprinosine	NR	NR	NR
Serdaroglu et al (2005)[216]	17	M	B	Nil	Measles at 1.5 years, SSPE	CSF, EEG	Visual disorder, poor memory, jerky movements	Yellow-white retinitis-like lesion with hemorrhage	OD: CF 3 m; OS: 20/200	Oral corticosteroid, IVIG, isoprinosine	Macular pigment mottling	6	Died
	14	M	B	Nil	Measles at 2 years	CSF	Blurred vision, headache	Macular retinitis, macular edema, yellow-white lesions	OD: 20/400; OS: 20/200	Beta interferon, isoprinosine	Hypopigmented/hyperpigmented mottling	18	OU: 20/20
Babu et al (2007)[17]	20	M	B	Nil	SSPE	Serology, CSF, EEG	Sudden painless vision loss	Macular gray-white retinal lesions with geographic borders, yellow exudates, optic disk pallor	OD: 20/400; OS: 20/30	Sedatives, antiepileptics	NR	3	Died
	25	M	B	Nil	Measles at 7 years	Serology, CSF, EEG	Progressive vision loss	Macular RPE atrophy	OD: 20/200 OS: 20/800	Antiseizure, isoprinosine, interferon	NR	6	No improvement
Yuksel et al (2011)[271]	Mean: 6.6 ± 2.5	M: 19; F: 6	B: 22; U: 3	Nil	SSPE	CSF, EEG	Alternating exotropia	Retinal edema, vessel tortuosity, RPE changes, optic disk edema, optic atrophy, chorioretinitis	NR	NR	NR	NR	NR
Yimenicioglu et al (2012)[268]	15	M	B	Nil	Measles at 8 months, SSPE	CSF, EEG	Decreased vision, amnesia	Atrophic macular pigmentary changes, active macular retinitis, hyperpigmentation	NR	Isoprinosine, vitamin A/C/E	Nil	1	NR
Baillif et al (2012)[18]	39	M	B	Nil	Measles with neurologic symptoms at 4 years, SSPE	CSF, EEG	Sudden blurred vision	Diffuse RPE alteration, attenuated vessels, optic atrophy, retinal occlusive vasculitis, hemorrhages	OD: PL; OS: 20/400	Acyclovir, prednisone, isoprinosine, interferon alpha, ribavirin	Macular scar	3	OD: PL; OS: CF; died
Summary; n, %	Mean: 16.2; range: 6–39	M: 27 (79.4); F: 7 (20.6)	B: 31 (91.2); U: 3 (8.8)	Nil	Measles, SSPE	Serology, CSF, EEG	Vision loss, neurological signs	Chorioretinitis, retinitis, retinal edema, vasculitis, hemorrhage, optic disk edema	Range: 20/30-PL	Isoprinosine, interferon alpha, corticosteroids	Retinitis pigmentosa, macular scar	Mean: 12.9; range: 1–54	Majority worsen or die

ACTH, adrenocorticotropic hormone; B, bilateral; CF, counting fingers; CSF, cerebrospinal fluid; EEG, electroencephalogram; F, female; HM, hand movement; IVIG, intravenous immunoglobulin; M, male; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PL, light perception; RPE, retinal pigment epithelium; RAPD, relative afferent pupillary defect; SSPE, subacute sclerosing panencephalitis; U, unilateral; VA, visual acuity.

Table 11

Demographics and clinical characteristics of rubella retinopathy

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Associated conditions	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Kresky et al (1967)[138]	Mean: 4.5	M: 3	B	Nil	Congenital rubella	Serology	Hearing loss	Abnormal areas of depigmentation and hyperpigmentation in macula, “salt and pepper” retinitis	OU: 20/20; OD: 20/80; OS: 20/40	NR	Strabismus, nystagmus, nuclear cataracts	NR	NR
Collis et al (1970)[45]	1.4, 1.1	NR	B	Nil	Congenital rubella	Serology	Blindness, hearing loss	Hazy cornea, pigmentary retinopathy, diffuse black granular pigmentation	NR	NR	Cataracts, iris atrophy	17, 13	NR
Orth et al (1980)[186]	11	M	B	Nil	Congenital rubella	NR	Profound deafness, sudden vision loss	Macular pigment mottling, loss of foveolar reflex, yellow fibrotic scar, punctate hemorrhage	OD 20/20; OS 3/400	NR	Disciform scar, band keratopathy, snowflake cataracts	NR	NR
	11	M	U				Hearing loss, decreased vision	Diffuse pigment epithelial mottling, salt and pepper appearance, yellow fibrotic macular scar	OS 20/400		Disciform scar		
	12	M	B				Deaf, vision loss	Salt and pepper pigmentary mottling, loss of macular ring and foveolar reflex, serous RD, subretinal hemorrhage	OD 20/400; OS 20/20		Nil		
Hayashi et al (1982)[86]	50	M	B	Betame-thasone for 20 days	Acquired rubella	Serology	Decreased visual acuity	Localized dark-gray atrophic lesions at posterior pole, diffuse RD, anterior uveitis	NR	Nil	Atrophic RPE	3	“normal”
Hirano et al (2000)[92]	7	F	B	Nil	Congenital rubella	NR	Sudden visual loss	Rubella retinopathy	NR	NR	Neovascular maculopathy	10	NR
	12	F	B	Nil	Congenital rubella	NR	Visual loss	Rubella retinopathy,	NR	NR	Nil	10	NR

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Associated conditions	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
								neovascular maculopathy					
Wang et al (2002)[256]	36	M	B	Nil	Congenital rubella	NR	Decreased visual acuity, central scotoma, metamorphopsia	Diffuse mottling with RPE clumping, submacular hemorrhage	OD: 20/200; OS: 20/25	Photodynamic therapy (verteporfin)	Subfoveal choroidal neovascularization, subretinal fibrosis	5	OD: 20/60
Khurana et al (2006)[129]	39	F	B	Nil	Congenital rubella	NR	Congenital hearing loss, no visual problems	Granular, pigmentary mottling, punctuate hypopigmentation and hyperpigmentation consistent with “salt and pepper” retinopathy	OU 20/20	Nil	Nil	4	20/20
Damasceno et al (2010)[52]	28	M	U	Nil	Acquired rubella	Serology	Sudden vision loss, preceding flu-like illness	RAPD, fine KPs, AC cells, mild vitritis, resolving neuroretinitis, macular star, retinal edema, vasculitis, papillitis	OD: 20/200	Prednisone	“Salt and pepper” fundus	2	OD: 20/60
Summary; n, %	Mean: 17.8; range: 1.1–50	M: 9 (75.0); F: 3 (25.0)	B: 11 (84.6); U: 2 (15.4)	Nil, Cortico-steroid	Congenital: 11 (84.6); acquired: 2 (15.4)	Serology	Vision loss, scotoma, metamorphopsia, hearing loss	Salt and pepper fundus, yellow fibrotic scar, retinal edema, hemorrhage, vasculitis, papillitis	Range: 20/20–20/400	Nil, corticosteroids, PDT	Salt and pepper pigmentary retinopathy, disciform scar, choroidal neovascularization	Mean: 8; range: 2–17	Majority improve or remain stable

AC, anterior chamber; B, bilateral; F, female; KPs, keratic precipitates; M, male; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PDT, photodynamic therapy; RAPD, relative afferent pupillary defect; RD, retinal detachment; RPE, retinal pigment epithelium; U, unilateral; VA, visual acuity.

Table 12

Demographics and clinical characteristics of dengue posterior uveitis

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Lim et al (2004)[151]	Mean: 35.8; range: 24–61	M: 1; F: 5	B: 5; U: 1	Nil	Serology	Blurring of vision, scotoma	Maculopathy with choroidopathy: small, intraretinal, whitish lesions, localized retinal and RPE disturbance, hemorrhages, vascular sheathing	Range: 20/30-HM	Corticosteroids (topical, periocular, oral)	RPE discoloration	Mean: 2.4; range: 0.5–4	Partial recovery: 3; stable: 2
Siqueira et al (2004)[223]	32	F	B	Nil	Serology	Blurred vision	Peripheral vascular sheathing, preretinal hemorrhage, cotton wool spots in macula	OD: 20/100; OS: 20/200	Oral antiplatelet (acetylsalicylic acid), vitrectomy, panretinal photocoagulation	Vitreous hemorrhage, preretinal neovascularization	24	“Poor”
Chlebicki et al (2005)[37]	Mean: 34; range: 21–49	M: 1; F: 3	B: 4	Nil	Serology, PCR	Reduced visual acuity, metamorphopsia	Blot hemorrhages within the vascular arcades	NR	Supportive, platelet transfusion	Metamorphopsia	2	6/6: 3; partial recovery: 1
Teoh et al (2006)[234]	Mean: 29.8; range: 20–40	M: 3; F: 1	B: 4	Nil	PCR, serology	Sudden painless blurring of vision	Focal macular chorioretinitis, macular edema, vasculitis, flame hemorrhage	OD: 20/400; OS: CF 1 ft OU: 20/20 OD: 20/20; OS: 20/400 OD: 20/40; OS: 20/200	Supportive, oral prednisone, IV methylprednisolone	Paracentral scotoma	Mean: 5.3; range: 3–6	NR
Gupta et al (2011)[82]	Mean: 29; range: 14–45	M: 1; F: 2	B: 2; U: 1	Nil	Clinical, serology	Sudden, painless vision loss	Retinal/ subhyaloid hemorrhages in macular area and vascular arcades, retinal edema, small whitish dot-like retinal lesions	OU: CF 0.5 m OD: 6/36; OS: 6/24 OS: CF 2 m	Oral steroids, observation	Nil	Range: 1.5–3	OD: 20/30; OS: 20/60 OU: 6/12 OU: 6/12 NR

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Juanarita et al (2012)[111]	24	F	B	Nil	Serology	Sudden painless vision loss	Multiple retinal hemorrhages at macula, elevation of fovea, subretinal fluid	OD: 6/30; OS: 6/120	Supportive	Multiple retinal yellowish deposits at fovea	1	OD: 6/7.5; OS: 6/120
Tabbara (2012)[231]	32	M: 2	B: 2	Nil	Serology	Blurred vision, floaters	Multifocal chorioretinitis, retinal vasculitis, cotton wool spots, flame-shaped hemorrhages, CME	OD: 20/100; OS: 20/40	Supportive	CME, nummular pigmented scars	1.5	OD: 20/50; OS: 20/25
	45							OD: 20/30; OS: 20/40			2	OD: 20/20; OS: 20/30
Koh et al (2013)[136]	Mean: 27 ± 9; range: 14–40	M: 7; F: 4	B: 5; U: 6	Nil	Serology	Blurring of vision: 7; floaters: 2; redness: 1	Retinal hemorrhage: 15; cotton wool spots: 15; RPE change: 5; optic disk swelling: 3; foveolitis: 3; hyperemia: 2	Median: 6/7.5; range: 6/6-CF	Supportive, oral/topical/IV corticosteroids	Optic atrophy, persistent scotoma	Range: 0.4–12	Range: 6/6-NPL; 6/12 or better: 95.2%
Summary; n, %	Mean: 32.1; range: 14–61	M: 15 (46.9); F: 17 (53.1)	B: 24 (75.0); U: 8 (25.0)	Nil	Serology, PCR, clinical	Blurred vision, floaters, redness, metamorphopsia	Chorioretinitis, maculopathy, hemorrhages, vasculitis, retinal edema, cotton wool spots, foveolitis	Range: 6/6-CF	Supportive, corticosteroids	Neovascularization, vitreous hemorrhage, nummular scars, persistent scotoma	Mean: 5.5; range: 0.4–24	Majority improved

B, bilateral; CME, cystoid macular edema; CF, counting fingers; F, female; HM, hand movement; IV, intravenous; M, male; NR, not reported; NPL, no light perception; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PCR, polymerase chain reaction; RPE, retinal pigment epithelium; U, unilateral; VA, visual acuity.

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Table 13

Demographics and clinical characteristics of chikungunya posterior uveitis

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Lalitha et al (2007)[143]	Mean: 44.8; range: 22–57	M: 21; F: 16	B: 7; U: 30	Nil	Clinical, serology	Blurring of vision	Retinitis with vitritis: 2; optic neuritis: 4; multifocal choroiditis with CME: 2; exudative RD: 2; neuroretinitis: 1; CRAO: 1	Range: 20/20-PL; 20/20 –20/120: 24; <20/200: 7; <HM: 3	Topical/systemic corticosteroids	RD, CRAO, optic neuritis/ atrophy	Range: 0.5–3	Improved: 11; same: 12; worse: 3
Chanana et al (2007)[33]	16	M	B	Nil	Serology	Decreased vision	Macular choroiditis with submacular exudates	OD: 20/400; OS: 20/40	Oral prednisolone	Nil	1.5	OD: 20/120; OS: 20/30
Mittal et al (2007)[174]	Mean: 45.8 ± 15.6; range: 22–68	M: 9; F: 5	B: 5; U: 9	Nil	Serology	Blurred vision: 19; impaired color vision: 19; pain: 3; diplopia: 1; redness: 1	Papillitis: 8; neuroretinitis: 3	Range: 6/6-CF; 6/6–6/12: 3; 6/18–6/60: 5; <6.60: 11	IV methylprednisolone, oral prednisolone	Optic atrophy, disk pallor/ edema	0.75	Improved: 10; >6/12: 12
Mahendradas et al (2008)[158]	Mean: 43; range: 32–55	M: 2; F: 1	B: 1; U: 2	Nil	Serology	Blurring of vision	Viral retinitis: 3; vitritis, hyperemic disk, area of confluent retinal opacity in posterior pole, retinal and macular edema, hemorrhage	OU: 20/2000 OS: 20/20000 OD: 20/200	Systemic acyclovir, oral prednisolone	Serous RD	1.5	OD: 20/20; OS: 20/40 OS: 20/60 OD: 20/40
Murthy et al (2008)[177]	35	M	B	Nil	Serology (aqueous tap positive for HSV)	Decreased vision	RAPD, retinitis, hemorrhages in posterior pole, hyperemia and blurring of disk margins (neuroretinitis)	OD: CF 2 m; OS: 20/20	IV/oral acyclovir, intravitreal ganciclovir, oral steroids	Nil	5	OD: 20/120; OS: 20/20
Mahesh et al (2009)[159]	48	F	B	Nil	Serology (ELISA and PCR)	Decreased vision	Optic disk edema, intraretinal hemorrhages, peripapillary cotton wool spots, retinitis with macular star	OD: 20/80; OS: 20/60	Symptomatic, oral prednisolone	Nil	2	OD: 20/30; OS: 20/20
Rose et al (2011)[203]	Mean: 35.6; range: 22–45	M: 7; F: 1	B: 3; U: 5	Nil	Clinical, serology	Sudden blurring of vision, scotoma	Papillitis: 7; neuroretinitis: 1; RAPD, disk edema, hemorrhage	Range: 6/6-PL	IV methylprednisolone, oral prednisolone	Nil	1	Improved >6/12: 9

Author (year)	Age (years)	Gender	Laterality	Immuno-deficiency	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Nair et al (2012)[180]	65	M	B	Nil	PCR	Decreased vision	Neuroretinitis, cotton wool spots, hemorrhages, grade 2 vitreous haze	OD: 20/200; OS: 20/400	Oral steroids, oral acyclovir	Nil	0.75	NR; “partial resolution”
Summary; n, %	Mean: 41.7; range: 16–68	M: 42 (63.6); F: 24 (36.4)	B: 20; U: 46	Nil	Clinical, serology, ELISA, PCR	Blurring of vision, pain, diplopia, scotoma, redness	Vitritis, retinitis, multifocal choroiditis, neuroretinitis, retinal edema, hemorrhage	Range: 20/20-PL	Corticosteroids, acyclovir	RD, optic atrophy, CRAO	Mean: 1.8; range: 0.5–3	Improved: 37; (56.1)

B, bilateral; CME, cystoid macular edema; CF, counting fingers; CRAO, central retinal artery occlusion; ELISA, enzyme-linked immunosorbent assay; F, female; HM, hand movement; HSV, herpes simplex virus; IV, intravenous; M, male; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PCR, polymerase chain reaction; PL, light perception; RAPD, relative afferent pupillary defect; RD, retinal detachment; U, unilateral; VA, visual acuity.

Table 14

Demographics and clinical characteristics of Rift Valley retinitis

Author (year)	Age (years)	Gender	Laterality	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Freed et al (1951)[62]	38	M	U	Serology	Blurred vision, retro-orbital pain	Dense white elliptical macular mass, slightly raised, well demarcated, small thrombosed inferior temporal capillary localized to macula	NR	Aureomycin	Persistent central scotoma	2.5	NR
Schrire (1951)[215]	Mean: 35.8; range: 28e50	M: 6	U: 6	Serology	Central scotoma, decreased vision, floaters	Large yellowish macular swelling, small hemorrhage	OS: CF 1 m	NR	Persistent central scotoma	Mean: 1.0; range: 0.8–2	OS: 6/36
						Large elevated yellowish macular mass	OS: CF 1 m				OS: CF 1 m
						Small macular exudate with central hemorrhage	OS: 6/12				OS: 6/12
						Large paramacular exudate	OS: 6/18				OS: 6/12
						Large paramacular exudate	OD: 6/18				OD: 6/6
						Vitreous haze, RD	OD: CF 1 m				OD: PL
Siam et al (1980)[220]	50	M	U	Serology	Reduced vision	Vitreous turbidity, extensive exudate-like lesion in macular area, edema, hemorrhages	OD: CF 0.5 m	NR	NR	1	NR
	51	M	U	Serology	Reduced vision	Scattered, paramacular exudate-like lesions	OD: 6/60				
Siam et al (1980)[221]	Mean: 48.4; range: 26–55	M: 7	B: 4; U: 3	Serology	Reduced vision	Para/macular exudate-like lesions, hemorrhage, retinal edema, vasculitis, peripapillary choroidal ischemia, KPs, vitreous haze	OD: CF 0.5 m	NR	Para/macular scar, occlusive vasculitis, optic atrophy	Range: 1.5–6	OD: CF 0.5 m
							OD: 3/60				OD: 6/9
							OD: 2/60				OD: 6/60
							OD: 1/60; OS: 2/60				OD: 1/60; OS: 6/36
							OD: 1/60; OS: 6/9				OD: 6/36; OS: 6/9
							OD: 1/60; OS: CF 0.5 m				OD: 6/36; OS: CF 0.5 m
							OU: NPL				OU: NPL
Al-Hazmi et al (2005)[8]	Mean: 53.2 ± 15.64; range: 14e80	M: 111; F: 32	B: 69; U: 74	Serology	Blurred vision, floaters, scotoma	Macular retinitis: 151; paramacular retinitis: 61; retinal hemorrhage: 85; vitreous inflammation: 55; optic disk edema: 32; retinal vasculitis: 15	Range: 20/80-PL	Supportive care with IV fluid, antimicrobials, blood transfusion, hemodialysis, or	Chorioretinal scar, vascular occlusion, optic atrophy	9	Improved: 14; worsened: 17; same: 79

Author (year)	Age (years)	Gender	Laterality	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Summary; n, %	Mean: 46.1; range: 14e80	M: 127 (79.9); F: 32 (20.1)	B: 73 (45.9); U: 86 (54.1)	Serology	Blurred vision, scotoma, floaters, retro-orbital pain	Para/macular exudative retinitis, retinal hemorrhage, vasculitis, retinal/optic disk edema, vitreous inflammation	Range: 6/9-PL	Supportive mechanical ventilation	Para/macular/chorioretinal scar, vascular occlusion, optic atrophy, persistent central scotoma	Range: 1e9	Improved: 22; worsened: 18; same: 83

B, bilateral; CF, counting fingers; F, female; IV, intravenous; KPs, keratic precipitates; M, male; NPL, no light perception; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; PL, light perception; RD, retinal detachment; U, unilateral; VA, visual acuity.

Table 15

Demographics and clinical characteristics of West Nile virus chorioretinitis

Author (year)	Age (years)	Gender	Laterality	Associated conditions	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Bains et al (2003)[19]	62	F	B	WNV infection	Serology	Floaters	Deep, flat, creamy whitish yellow outer chorioretinal lesions, moderate vitritis, small intraretinal hemorrhages	OD 20/25; OS 20/40	Topical prednisolone	Chorioretinal scars	0.5	OD 20/25; OS 20/30
Hershberger et al (2003)[88]	61	F	B	WNV infection	Serology	Blurred vision	AC cells and flare, creamy/partially atrophic nummular chorioretinal lesions	OD 20/30; OS 20/25	Topical prednisolone	Chorioretinal scars	1	NR
	56	M	B	WNV meningoencephalitis	Serology	Floaters	Optic disk edema, retinal hemorrhages, small white deep chorioretinal lesions	OU 20/25	Topical prednisolone	Chorioretinal scars	4	NR
Anninger et al (2003)[13]	55	F	B	WNV meningoencephalitis	Serology	Blurred vision	Diffuse creamy yellow chorioretinal lesions	OD 20/80; OS 20/50	Nil	Visual field loss, optic neuritis	6	OU 20/25
Anninger et al (2004)[14]	55	F	B	WNV meningoencephalitis	Serology	Visual field loss, blurred vision, ocular pain	Pale optic nerves, vitreous cavity cells, diffuse creamy yellow chorioretinal lesions	OD 20/80; OS 20/40	Nil	Optic atrophy	12	OD 20/60; OS: "recovered"
Khairallah et al (2004)[122]	Mean: 53; range: 22–74	M: 20; F: 9	B: 23	WNV infection/meningoencephalitis	Serology	Floaters: 8; blurred vision: 6; redness: 6; visual field defect: 1; diplopia: 1	Bilateral multifocal chorioretinitis: 23; retinal hemorrhages: 21; vascular sheathing: 4; optic disk swelling: 2	Mean: 20/32; range: 20/20–20/100	Ribavirin	Chorioretinal scars	NR	Mean: 20/25
Khairallah et al (2006)[126]	Mean: 47.2; range: 29–62	M: 7; F: 5	B: 12	WNV infection	Serology	Floaters: 4; blurred vision: 2; redness: 2	Multifocal chorioretinitis with linear clustering of noncontiguous, contiguous, or confluent lesions	Mean: 20/25; range: 20/20–20/50	NR	NR	NR	NR
Garg et al (2006)[69]	44	F	B	WNV meningoencephalitis	CSF	Vision loss	Arterial attenuation, intraretinal hemorrhages, cotton wool spots, ischemic whitening of macula	OD 20/30; OS CF	NR	NR	NR	NR
	68	F	B	WNV infection	Serology	Blurred vision	Arterial attenuation, scattered chorioretinal lesions, intraretinal hemorrhages	OD 20/60; OS 20/25				
	57	M	B	WNV meningoencephalitis	CSF	Vision loss	Arterial attenuation, intraretinal hemorrhages, ischemic whitening of macula, cotton wool spots, retinal/disk neovascularization	OD 20/25; OS HM	Panretinal photocoagulation, vitrectomy	Tractional RD, vitreous hemorrhage	18	OD 20/100; OS 20/200
Khairallah et al (2007)[127]	Median: 57	M: 17; F:15	NR	WNV meningoencephalitis: 27	Serology	NR	Chorioretinal lesions	NR	NR	CME	24	NR
Seth et al (2007)[217]	81	M	B	WNV encephalitis	Serology	Decreased vision	Mild vitritis, round, cream-colored chorioretinal lesions	OD: NR; OS 20/400	Intravitreal bevacizumab for CNV	Chorioretinal scars, CNV	59	OS: HM 2 ft
Sivakumar et al (2013)[224]	Mean: 37; median: 35; range: 9–65	M: 22; F: 15	B: 14; U: 23	WNV meningoencephalitis: 2	Serology	Decreased vision, ocular pain	Areas of discrete, superficial, white multifocal choroiditis, retinal edema, vasculitis, retinal hemorrhages, optic disk hyperemia, neuroretinitis, serous RD	Mean logMAR: 1.26	Oral prednisolone	Retinal atrophy, vascular occlusion, retinitis, neovascularization	Range:2–6	Mean logMAR: 1.00; improved: 16; same: 28; worsened: 2

Author (year)	Age (years)	Gender	Laterality	Associated conditions	Method of diagnosis	Symptoms	Signs	VA at presentation	Treatment	Complications	Duration of follow-up (months)	VA at last visit
Summary; n, %	Mean: 56.4; range: 9–74	M: 69 (58.0); F: 50 (42.0)	B: 58 (71.6); U: 23 (28.4)	WNV infection/meningoencephalitis	Serology, CSF	Floaters, blurred vision, redness, visual field defect, diplopia, pain	White-yellow chorioretinal lesions, retinal hemorrhages, retinal/optic disk edema, vasculitis, serous RD, neuroretinitis	Range: 20/20-HM	Topical/oral prednisolone, photocoagulation, vitrectomy	Chorioretinal scars, optic atrophy, RD, vitreous hemorrhage, CNV, neovascularization	Range: 0.5–59	Majority improved

AC, anterior chamber; B, bilateral; CF, counting fingers; CME, cystoid macular edema; CNV, choroidal neovascularization; CSF, cerebrospinal fluid; F, female; HM, hand movement; M, male; NR, not reported; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque; RD, retinal detachment; U, unilateral; VA, visual acuity; WNV, West Nile virus.