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Emerging infectious uveitis: Chikungunya, Dengue, Zika, Ebola

Genevieve F. Oliver, FRANZCO
Jillian M. Carr, PhD
Justine R. Smith, FRANZCO, PhD

Flinders University College of Medicine & Public Health, Adelaide, Australia

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Corresponding Author:
Justine R. Smith, FRANZCO, PhD

Address: Eye & Vision Health, Flinders University College of Medicine and Public Health, Flinders Medical Centre Room 4E-431, Flinders Drive, Bedford Park, SA 5042, Australia
Telephone: 61-8-8204-4300
Email: justine.smith@flinders.edu.au
Abstract

Recently recognised forms of uveitis include intraocular inflammations that occur during or following one of several emerging infectious diseases: chikungunya fever, dengue, Zika virus disease and Ebola virus disease. Anterior, intermediate, posterior and pan-uveitis have been described in individuals infected with chikungunya virus. Persons who contract dengue or Zika viruses also may develop different types of uveitis in the course of the infection: maculopathy is a common manifestation of dengue eye disease, and Zika eye disease may cause hypertensive anterior uveitis or mimic a white dot syndrome. Up to one-third of Ebola survivors develop aggressive uveitis, which is frequently associated with vision loss and complicated by cataract. There are no specific anti-viral drugs for these forms of uveitis, and thus treatment is largely supportive. In this article, we summarise the systemic infectious diseases and virology, and describe the clinical presentations, outcomes and management of emerging viral forms of uveitis.
Introduction

New forms of eye disease continue to be described on a regular basis, in large part due to the considerable advances that are occurring in diagnostic medicine, as well as in biomedical science. In the field of uveitis in particular, most recent new diagnoses have been in the area of infectious uveitis, including re-definition of well-established forms of uveitis and description of new forms associated with systemic infections: Fuchs uveitis syndrome and Possner-Schlossman syndrome have been linked to infections with rubella virus and cytomegalovirus; and infections with human immunodeficiency virus, Epstein-Barr virus and Parvovirus B19 have been associated with different types of uveitis.\(^1\) Recently, several emerging viral infections have been linked to uveitis. Per the US Centers for Disease Control and Prevention definition, an emerging infection is one “whose incidence in humans has increased in past 2 decades or threatens to increase in the near future” and that “respects no national boundaries”\(^2\). These diseases may result from: (1) evolution of existing microbes; (2) appearance of new infections in areas that are changing ecologically; (3) spread of infections to new regions or population groups; and (4) re-emergence of pathogens as a result of drug resistance or failed public health measures.\(^2\) The emerging virus infections that have been linked to uveitis include Chikungunya fever, Dengue, Ebola virus disease and Zika infection.\(^3-6\)

Chikungunya Fever

Overview of chikungunya fever

Chikungunya fever is the infectious disease caused by chikungunya virus (CHIKV)\(^7\).

Although the disease has been identified throughout the world – related to global travel
– it is endemic in Africa, South and South-East Asia, India, and South and Central America.\(^8\) Recent outbreaks between 2005 and 2007 in India, and between 2014 and 2016 in South America have involved millions of persons.\(^9\) The virus circulates in non-human primate and small mammal reservoirs, from which there may be spread to humans. It is carried by multiple mosquito species, most commonly *Aedes aegypti* and *Aedes albopictus*.\(^7\) The majority of infected individuals become symptomatic, and do so within a few days of infection: disease is characterized by a high fever, headache, rash, myalgia and a characteristic arthralgia for which chikungunya virus is named.\(^8\) This arthralgia affects the extremities, and is severe and deforming. After recovery, approximately one-half of affected persons develop a long-term arthritis. Fatality of chikungunya fever is estimated at one in 1000, and fatalities generally occur in very young or elderly patients, or in adults with other health problems, who may develop multi-organ involvement including encephalopathy.\(^8\) There is no specific anti-viral drug treatment for chikungunya fever, and there is no vaccination that protects against CHIKV. Thus treatment is supportive, and patients with chronic arthritis may require immunosuppression.\(^8\)

**Chikungunya virology**

Chikungunya virus is a member of the *Togaviridae* family and *Alphavirus* genus, and consistent with the systemic manifestations of chikungunya fever, it is classified in the Semliki Forest Virus group of the Old World alphaviruses.\(^10\) The virion is spherical, measuring approximately 70 nm in diameter, with a lipid envelope and an 11.5 kb positive-sense, single-stranded, RNA genome.\(^7,8\) It enters different cell types, such as those in muscle, joints and skin, via receptor-mediated endocytosis.\(^7,8\) The CHIKV RNA genome provides transcripts that are translated into the non-structural proteins of the
replication complex, which transcribes a negative-sense RNA, and subsequently new positive-sense RNA genomes and subgenomic RNA. The latter are translated into the structural elements of CHIKV: capsid and envelope glycoproteins, E1 and E2. Viral particles are assembled at the cell surface from cytoplasmic encapsidated RNA genomes and glycosylated E1/E2 proteins arising from the Golgi apparatus, with new virions released by budding at the cell membrane.

**Chikungunya fever-associated uveitis**

Although non-specific ocular symptoms – including photophobia and retro-orbital pain – and conjunctivitis have been recognized for some time in patients with chikungunya fever, the first descriptions of CHIKV-associated uveitis and other ocular inflammatory syndromes were published just 10 years ago, following the large outbreak in India. Ophthalmic clinical groups based in Tamil Nadu and Bangalore published detailed descriptions of uveitis, keratitis and episcleritis, and neuroretinitis and optic neuritis that began within 4-6 weeks of the onset of chikungunya fever, which was confirmed through serological testing. A recent paper from the same region – that coined the term, “retinitis post febrile illness” or “epidemic retinitis”, for retinal inflammation occurring in seasonal-limited outbreaks in tropical regions of the world – attributed approximately 20% of this condition to infection with CHIKV. Mahendradas and colleagues have published a comprehensive review of the ocular manifestations of chikungunya fever.

Uveitis is the most common ocular involvement reported in patients with chikungunya fever. Anterior, intermediate, posterior and pan-uveitis all have been reported in association with CHIKV infection, although overall, anterior uveitis is the most
The anterior uveitis may be unilateral or bilateral; both granulomatous and non-granulomatous forms of anterior uveitis occur, and pigmented keratic precipitates are a frequent feature. Iris atrophy does not appear to be a common feature, but has been reported in the form of bilateral Fuchs’ heterochromic iridocyclitis with iris nodules and cataract. Intraocular pressure is often elevated. Confocal microscopy shows dendritic keratic precipitates. A spectrum of posterior uveitis phenotypes has been described following CHIKV infection, involving one or both eyes, and presenting as unifocal or multifocal, retinitis or choroiditis. In some cases, the presentation may mimic herpetic retinitis. Retinal vasculitis may occur, and may be complicated by retinal haemorrhage or retinal vascular obstruction, and optical coherence tomography (OCT)-angiography has demonstrated choriocapillaris flow deficits. Cystoid macular oedema and serous retinal detachment may complicate the inflammation. Both unilateral and bilateral neuroretinitis – characterized by optic disc swelling and a macular star – have been reported. Acute macular neuroretinopathy also has been observed in the context of chikungunya fever, with wedge-shaped, paracentral macular lesions.

Other forms of inflammatory eye disease have been reported in patients with chikungunya fever. Keratitis with epithelial dendrites, mimicking herpetic keratitis, but occurring bilaterally, is described. External eye manifestations that have been observed include: rheumatoid factor-negative, anti-nuclear antibody-negative, nodular anterior scleritis; and lagophthalmos with exposure keratitis. Bilateral and unilateral forms of optic neuritis are possible, including papillitis, retrobulbar neuritis and retrochiasmal neuritis. These optic neuropathies cause relative afferent pupillary defects and colour vision deficits, as well as a variety of visual field defects: central or centrocaecal
scotomas, peripheral field defects, and combined central and peripheral field loss. External ophthalmoplegia is another neuro-inflammatory syndrome reported in CHIKV-infected patients.\textsuperscript{14}

Making the diagnosis of CHIKV-associated inflammatory eye disease begins with information from the history, including residence in or recent travel to an endemic area, and recent febrile illness with typical musculoskeletal symptoms. The inflammatory eye disease is often non-specific, although presentations mimicking herpetic uveitis, but occurring bilaterally, may raise the suspicion. In several published series, systemic testing has involved serological testing for CHIKV immunoglobulin (Ig) M,\textsuperscript{3,13,14} which is generally detectable within the first week and for multiple months after the onset of the systemic illness.\textsuperscript{8} Although reverse transcription (RT)- polymerase chain reaction (PCR) for virus is commonly used to diagnose the systemic illness,\textsuperscript{8} it may be less useful for the eye disease, since this may present after the resolution of the viraemia. Several reports have described the successful use of RT-PCR analysis of aqueous to detect viral RNA in cases of CHIKV-associated anterior uveitis.\textsuperscript{18,23} Ruling out forms of uveitis that may mimic the presentation, is a standard principle when assessing any form of uveitis, and thus testing for herpetic viruses in particular, plus other locally endemic viruses, as well as the masqueraders, syphilis and tuberculosis, may be appropriate.

When treatment has been given to persons with CHIKV-associated inflammatory eye disease, this generally has been directed at the inflammation and/or its complications. Patients with anterior uveitis have been treated with topical prednisolone acetate, diclofenac sodium, as well as a topical cycloplegic and topical anti-glaucoma drops.\textsuperscript{3,13} Episcleritis has been managed with topical diclofenac sodium and systemic
indomethacin.³ For posterior eye involvements, including uveitis and optic neuritis, patients have been treated with oral prednisolone, preceded by intravenous methylprednisolone for optic nerve involvement.³,13,14 Some patients with retinal involvement also have been given acyclovir.³ Since this drug does not have anti-CHIKV activity, therapeutic effect seems unlikely, and the primary value would be to cover the possibility of a herpetic infection in cases of retinitis.

Ocular inflammation in chikungunya fever typically resolves within approximately 3 months.¹⁶ Patients initially present with a wide range of visual acuities, from normal to 6/60 or worse, including perception of only hand movements or light.³,13,14 Typically anterior segment disease is associated with good visual acuity, while posterior segment disease is not, but there are exceptional cases of good vision in patients who present with posterior uveitis, neuroretinitis and optic neuritis. There is similarly a wide range of visual acuities measured following resolution of the inflammation, although a majority of patients retain or recover vision.³,13,14 Poor outcomes typically occur in patients with optic neuritis, particularly when presentation is delayed.¹⁴

Dengue

Overview of Dengue
The most common vector-borne disease, dengue, affects an estimated 390 million persons annually.²⁴ Half the global population live in areas of transmission, and three-quarters of these people reside in the Asia-Pacific region.²⁵ Dengue virus (DENV) exists as four serotypes (i.e. DENV1, DENV2, DENV3 and DENV4), all of which are capable of epidemic spread.²⁶ While infection confers lifelong immunity to the infecting serotype,
subsequent infection with a different serotype may be severe, since antibodies may not effectively neutralize the virus, and instead facilitate its entry into the cell and enhance viral production. Classification of the infectious disease has been simplified to dengue, with warning signs, and severe dengue. Up to a week after the bite of infected *Aedes* species mosquitoes, individuals develop fever, rash, myalgia and arthralgia that can last for 7 days before defervescence. The 48-hour critical phase follows, during which vascular and metabolic derangements may occur, and supportive care in the form of fluid replacement may be required. Convalescence may be associated with hepatic and cardiac complications, and post-viral fatigue. No anti-viral drugs are effective against DENV. The first vaccine was registered in 2015, but this was linked to reports of deaths: post-hoc analysis identified a subgroup of DENV-naïve children who were paradoxically at higher risk of severe dengue after vaccination. While mortality from dengue, with intravenous rehydration when appropriate, should be near zero, reported deaths have increased over the last decade and the average case-fatality rate is 2.5%.

**Dengue virology**

Dengue virus – which is a member of the *Flaviridae* family and *Flavivirus* genus – is relatively small, at 50 nm in size. A lipid envelope encloses the nucleocapsid, housing an 11 kb single-stranded positive-sense RNA genome. Using receptor-mediated endocytosis to enter cells, DENV binds the C-type lectin CD209 antigen receptor on the dendritic cell, which is its primary target, and uses phosphatidylserine receptors on epithelial and other cells. Within the endosome, pH-dependent fusion allows release of viral RNA into the cytoplasm. The genome is translated into a polyprotein and cleaved by host and viral proteases to produce three structural and 7 non-structural proteins. The replication strategy of DENV is to hijack the endoplasmic reticulum, remodeling it to
create invaginations that protect from host recognition.\textsuperscript{25} Within these pockets, viral genomic RNA and structural proteins are mass-produced. Virions are assembled, and subsequently taxied through the increasingly acidic trans-Golgi network, before being released as mature virus particles from the cell through exocytosis.

**Dengue-associated uveitis**

A spectrum of ocular disease associated with DENV infection has been reported in the literature, ranging from haemorrhagic to inflammatory manifestations.\textsuperscript{30} The most common ocular complications involve haemorrhage. Conjunctival haemorrhage is widespread amongst persons with dengue, but visually significant haemorrhagic complications involve the posterior segment of the eye. Uveitis has been associated with dengue, and is diverse in its presentation.\textsuperscript{30} Anterior uveitis is reported to affect infected persons who are otherwise healthy, and may present up to 5 months after onset of systemic symptoms. Visual recovery is favourable with topical corticosteroid therapy and cycloplegia. Posterior and panuveitis usually present within the first few weeks of systemic symptoms. Patients may be systemically unwell: serous retinal detachments with panuveitis have been described in association with hepatitis, pericarditis and severe hypokalaemia.\textsuperscript{31,32} Choroidal effusions can be extreme and have been described in a patient presenting with bilateral acute secondary angle closure.\textsuperscript{33}

Causes of visual symptoms in patients with DENV infection are variable, but commonly reflect macular involvement. During the 2004-2005 Singapore epidemic, a majority of 50 symptomatic ophthalmology outpatients complained of blurred vision, and one-third reported visual field defects.\textsuperscript{30} Macular oedema occurred in three-quarters of these individuals, while macular haemorrhages were present in two-thirds, and vasculitis was
documented in one-quarter. Of those who had daily platelet levels, all became visually symptomatic within one day of their lowest count. A smaller study during the same epidemic found bilateral but asymmetric macular disease in three-quarters of symptomatic patients presenting to eye services. Almost two-thirds of these patients presented with central or paracentral scotomas. Retinal venous occlusions occurred in 25% of eyes; venular sheathing was observed in 45%; and arteriolar sheathing was present in 4%. Foveolitis – with a yellow or orange subretinal dot – is a particularly characteristic form of dengue maculopathy that was documented in 28% of the patients.

Cross-sectional studies performed during epidemics provide the best estimate of the prevalence of dengue-associated maculopathy. During the 2005 Singapore epidemic, DENV1 was the most common circulating serotype, and during this time nearly 200 hospital inpatients with dengue were examined ophthalmoscopically. While persons in the community and those with life-threatening thrombocytopaenia were excluded from examination, maculopathy was present in 10% of this DENV-seropositive patient group. Affected individuals had a mean complement C3 level that was significantly lower than levels measured in those without maculopathy. Curiously, those with maculopathy tended to be young adults, and were either asymptomatic or had ignored their symptoms. A similar, albeit smaller cross-sectional study conducted during the 2007 Singapore epidemic, when DENV2 was the predominate serotype in circulation, identified no cases maculopathy in DENV-seropositive inpatients. These individuals tended to be older, and had milder liver impairment compared to the 2005 cohort, suggesting that maculopathy and ocular complications might be related to DENV serotype or virulence.
The tissue features of dengue-related maculopathy have been examined in a study that employed Fourier-domain OCT to image the retinas of 74 eyes from 41 patients. Visual changes tended to coincide with the nadir of thrombocytopenia, about 7 days after onset of systemic symptoms. Three phenotypes of maculopathy were described: Type 1, diffuse retinal thickening; Type 2, cystoid macular oedema; and Type 3, foveitis with outer retinal thickening and hyper-reflectivity. All Types were associated with scotomas, and at 2 years, 60% of eyes had persistent scotomas. “Doughnut” scotoma were typical of eyes with Type 3 maculopathy, all of which retained visual field defects at 2 years.

Retinal vasculitis usually presents within a week of systemic symptoms in patients who may have thrombocytopenia, but are otherwise well, and visual recovery depends on the degree of maculopathy and ischaemia. Presentations of posterior uveitis affect the outer retina, and include acute posterior multifocal placoid pigment epitheliopathy, acute zonal occult outer retinopathy and retinochoroiditis. Cases of acute macular neuroretinopathy have been reported in patients with dengue. Persistent scotomas with a normal ocular examination have also been documented. Electrophysiological studies have confirmed involvement of the middle and outer retina in DENV-associated retinopathy, usually affecting the fovea, and with relative sparing of the inner retina.

The long-term visual prognosis of DENV-related ocular complications is variable, but most patients have a positive outcome. One study of 65 eyes of 50 consecutive patients with DENV infection and a spectrum of ocular complications showed that over 80% of patients had a visual acuities of 6/12 or better at one year. Thirteen patients with panretinal vasculitis were treated with systemic corticosteroids, including 6 individuals who took a course of oral prednisolone, and 7 individuals were also treated with pulsed
intravenous methylprednisolone. No adverse effects were reported, but despite treatment, 11 eyes of 7 patients treated with intravenous corticosteroid had visual acuities between 6/12 and 6/60 at final follow-up. Those with anterior segment inflammation had a more favourable course, and 7 individuals treated with topical corticosteroid experienced resolution at one week with no relapse after cessation. A separate study of DENV-related maculopathy detailed visual recovery in a cohort of patients who were managed expectantly. Overall, visual acuity improved from better than 6/12 in 42% of eyes at presentation, to 62% at 1 month, and over 80% at 2 years. Those who presented with foveolitis had a relatively poor prognosis, with approximately one-half of eyes recovering visual acuity to 6/12 or better, and all patients reporting persistent scotomas.

An infection with DENV may be confirmed by detecting viral RNA in the serum using RT-PCR from up to 48 hours before the onset of fever until 6 days following the onset of constitutional symptoms. Serologic testing may identify DENV antibodies after this time: DENV IgM appear within the week after fever begins and persist for approximately 3 months, while DENV IgG develop more slowly, unless infection is secondary. Ocular fluids may be tested in case of diagnostic uncertainty, although there were no PCR-confirmed DENV infections in one published report that involved aqueous sampling in cases of epidemic retinitis.
Zika virus disease

Overview of Zika virus disease

From its discovery in Uganda in 1947, Zika virus (ZIKV) caused only 14 documented cases of human infection until 2007, when an outbreak of rash, arthralgia and conjunctivitis occurred in Yap Island, Micronesia. Almost three-quarters of residents had serological evidence of ZIKV infection. Six years later, ZIKV infected 30,000 people in French Polynesia, and by early 2015, ZIKV had reached South America. During the 2015-2016 South American epidemic, 40,000 pregnant women were infected with ZIKV, and 4,000 diagnoses of ZIKV-associated microcephaly were confirmed in Brazil. Now an official teratogen, ZIKV can be transmitted sexually and transplacentally. Pregnant women who contract ZIKV risk preterm birth, miscarriage, and a congenital Zika syndrome that consists of intrauterine growth retardation, microcephaly, brain, auditory, skeletal, and ocular abnormalities. Children with congenital Zika syndrome have widespread functional disabilities and an unknown prognosis.

Like DENV, ZIKV is transmitted by the daytime-biting Aedes mosquito species. Incubation lasts up to two weeks, and infection is subclinical in 80% of individuals. The most common symptom is a maculopapular rash, which may be accompanied by low-grade fever, malaise, headache, non-purulent conjunctivitis, myalgia, and arthralgia, lasting up to a week. There is currently no vaccine against ZIKV, and treatment is supportive. In adults, the major complication of ZIKV infection is Guillain-Barré syndrome, an acute immune-mediated migrating polyradiculopathy affecting motor and sensory functions, usually occurring within a week of viral symptoms.
Polynesian epidemic was responsible for a 20-fold increase in Guillain-Barré syndrome, with an estimated risk of 0.24 per 1,000 ZIKV infections.\footnote{46}

**Zika virology**

Zika virus has two lineages that circulate in different cycles.\footnote{51} In Africa, ZIKV propagates through sylvatic transmission - between *Aedes* mosquito vectors and non-human primate reservoirs, and humans are sporadic hosts. Beyond Africa, ZIKV cycles through urban transmission between domesticated *Aedes aegypti* vectors and human reservoirs. Like DENV, ZIKV is a single-stranded RNA flavivirus, which shares many features. Zika virus has a lipid envelope enclosing its nucleocapsid, and an 11 kb genome.\footnote{50} It displays an affinity for neural progenitor cells and the capacity to infect a broad range of cell types.\footnote{52} The virion enters the cell through endocytosis, and within the cytoplasm, the genome is translated into one polyprotein and cleaved to produce three structural and 7 non-structural proteins that are required for viral replication and the formation of new virus particles.\footnote{50}

**Zika virus-associated uveitis**

Infants with congenital Zika syndrome present with a range of ocular abnormalities, but the two classic retinal appearances are well-circumscribed atrophy and pigment mottling at the macula.\footnote{53} Regardless of ocular involvement, all infants with congenital Zika syndrome have displayed significant visual impairment, suggesting that cortical rather than ocular dysgenesis is the most common cause of blindness.\footnote{49} In adults, ocular complications of ZIKV infection tend to be mild and self-limiting. Retro-orbital pain and conjunctivitis are common, affecting 40\% in one study.\footnote{54} Uveitis is an uncommon
complication of ZIKV infection, with less than 20 cases published in the literature. Visual outcomes are favourable, and recurrence has not been documented.

Anterior uveitis in ZIKV infection is associated with high intraocular pressure.\textsuperscript{5,55,56} A 39-year old male Brazilian physician presented one week after the onset of constitutional symptoms with bilateral hypertensive anterior uveitis that completely resolved with anti-hypertensive and corticosteroid eye drops.\textsuperscript{55} A similar report described a male presenting with bilateral anterior uveitis 8 days after onset of a rash. Remarkably, ZIKV was confirmed through RT-PCR of aqueous fluid taken by anterior chamber paracentesis.\textsuperscript{5} Upon review after a further 8 days, the uveitis had responded to topical corticosteroid, and no virus was detected in a second paracentesis. Two patients were described with bilateral acute hypertensive anterior uveitis, occurring 10 days after onset of systemic symptoms.\textsuperscript{56} Aqueous tested negatively for ZIKV by RT-PCR in one patient, but positively in the other. The uveitis in both patients improved with topical corticosteroids and anti-hypertensive drugs. In all patients, visual acuity returned to baseline with the topical treatment.

Various presentations of posterior uveitis have been described in association with ZIKV infection.\textsuperscript{57-61} A healthy 20-year old woman in Trinidad presented with bilateral neuroretinitis during the 2015-2016 South American ZIKV epidemic.\textsuperscript{57} Her ocular symptoms began a month after a viral illness, and she presented with a relative afferent pupil defect, and bilateral optic disc oedema and macular stars. All investigations, including MRI brain, were normal with the exception of serum ZIKV IgM. Subsequent clinical course was not reported. An woman living in Puerto Rico during the same epidemic, who was immunocompromised following chemotherapy for lymphoma,
presented with bilateral panuveitis, including chorioretinal lesions suggestive of acute posterior multifocal placoid pigment epitheliopathy. Diagnostic anterior chamber paracentesis excluded herpes simplex virus and cytomegalovirus; *Toxoplasma gondii* and DENV serology were negative; and recurrent lymphoma was excluded. Serum ZIKV RT-PCR confirmed the diagnosis, and the anterior chamber inflammation was treated with topical corticosteroids. After 5 months, visual acuity had finally returned to baseline, and the chorioretinal lesions were healed.

A healthy 26-year old tourist returning from Puerto Rico in 2016 presented with bilateral posterior uveitis, one week after the onset of systemic symptoms, when aqueous fluid tested negatively for ZIKV. There were peripheral chorioretinal lesions, which appeared nodular and were hyperfluorescent, and appeared hyperreflective by OCT. While the visual acuity remained at 6/6, he was mildly symptomatic of the eye involvement. Unilateral anterior vitreous cells were treated with a short course of topical corticosteroid, and the choroidal lesions showed evidence of regression by 5 months. Two case reports describe men with unilateral acute idiopathic maculopathy, presenting 10 days after onset of systemic features. Both had unilateral loss of vision, and disruption of the outer retinal and retinal pigment epithelial architecture on OCT. Symptoms resolved, and visual acuity returned to baseline with conservative management. At final follow-up, one patient had residual changes in the ellipsoid zone of the retina at 3 weeks, while the other had a normal OCT at 6 weeks.

Zika virus has been isolated in tears during the acute phase of infection. Eleven Chinese tourists to Venezuela returned with serum RT-PCR-confirmed ZIKV. Their serum viral load was undetectable after 5 days of symptoms, whereas conjunctival swab samples
contained ZIKV until the 7th day after fever onset. A study in Singapore of 29 individuals with serum and/or urine RT-PCR-confirmed infection found ZIKV RNA in 10% of conjunctival swabs one month after fever onset. These patients had been symptomatic with either conjunctivitis or retro-global pain.

The diagnosis of ZIKV-associated uveitis is challenging. For individuals returning from tropical regions, the differential diagnosis includes DENV and CHIKV-related disease. Due to a lack of symptoms in the majority of ZIKV infections, an index of suspicion is required to diagnose ZIKV uveitis in those presenting with undifferentiated anterior uveitis and a history of travel to endemic regions. Using RT-PCR, viral RNA can be detected from serum during viraemia that occurs a few days before symptom onset and may last up to a week. As viraemia wanes, serum IgM can be detected from 2 to 12 weeks after exposure using IgM capture enzyme-linked immunosorbent assay. Ocular fluid testing has aided diagnosis in ZIKV anterior uveitis, but the virus is variably detected using RT-PCR. Comparison of serum and intraocular levels of anti-ZIKV antibody using the Goldmann-Witmer coefficient has not been described, but might be a useful tool for diagnosis.

Ebola virus disease

Overview of Ebola virus disease

The 2014-2016 West African Ebola epidemic affected 28,500 individuals and claimed over 11,000 lives. Prior to this epidemic, 13 outbreaks with a total of 1,460 cases of Zaire ebolavirus (EBOV) infections had been documented since its discovery in 1976. Although the bat is assumed to be the reservoir for EBOV, transmission also occurs by
direct contact between infected individuals or animals. Ebola virus disease is a haemorrhagic illness that manifests up to 3 weeks after infection, initially as fever, sore throat, headache, myalgia and fatigue. Diarrhoea, vomiting, rash and bleeding complications follow. Diagnosis generally involves detection of viral RNA by RT-PCR in the blood. Hepatic, respiratory and renal impairments are common, and death results from shock, with electrolyte, metabolic and coagulation derangements. The case fatality rate in the West Africa epidemic ranged up to 74%, while those individuals repatriated to Europe and the US for treatment experienced a survival rate close to 90%. Survivors begin to recover a few weeks after the onset of symptoms, but the persistence of live EBOV in immune-privileged sites, such as reproductive organs, placenta and central nervous system, poses an enormous burden for public health. Survivors also experience severe fatigue, myalgia, arthralgia, gastric pain, auditory and psychiatric sequelae, as well as ocular complications.

Treatment of Ebola virus disease is supportive, and no anti-viral drugs have proven to be effective. A vaccine expressing EBOV surface glycoprotein in a recombinant vesicular stomatitis virus vector was implemented in three phase II/III trials across West Africa in 2015. These trials were designed to deliver the vaccine to high-risk populations, while also evaluating safety and efficacy data. In Sierra Leone, almost 8,000 participants were immunized in a randomized, non-blinded, ring-vaccination trial without placebo. No participants contracted Ebola virus infection, and there were no vaccine-related serious adverse events. This was a remarkable feat considering the challenge of conducting a large trial in developing countries during a global health crisis.
Ebola virology

The *Ebolavirus* genus falls within the *Filoviridae* family and *Mononegavirales* order, and describes enveloped, non-segmented, negative-polarity RNA viruses.\(^7^1\) Five antigenically-distinct Ebola species have been identified: *Zaire, Sudan, Reston, Tai Forest,* and *Bundibugyo ebolavirus.* *Zaire ebolavirus* is responsible for the most epidemics, and has three recognized strains, of which Makona was the causative agent in the 2014-2016 West Africa epidemic.\(^6^5\) Named for the filamentous form, EBOV is relatively large, with a diameter of 98 nm and a length that may extend beyond 20 \(\mu\)m.\(^7^1\) The genome is 19 kb long, encoding 7 genes and exhibiting polyploidy, harbouring multiple copies of the genome within an extremely long virus.\(^7^1\) The virion attaches to a variety of host cell surface molecules, is assumed into the endosome, and finally released into the cell cytoplasm. Transcription, translation and replication of the genome occur in the cytoplasm, producing virions that bud from the host cell surface.

Post-Ebola uveitis

The association of uveitis with Ebola virus disease was widely recognized with the case of the US physician repatriated from Sierra Leone in 2014 with Ebola virus disease.\(^7^2\) He survived multi-organ failure, and 9 weeks after resolution of viraemia presented with photophobia and a foreign body sensation. He had no intraocular inflammation at that time, but was noted to have multiple scattered peripheral chorioretinal scars. One month later, he presented with a unilateral hypertensive anterior uveitis that progressed despite intensive topical treatment, and was complicated by iris heterochromia. An anterior chamber paracentesis was performed, and EBOV was detected in the aqueous fluid by RT-PCR and culture. Concurrently, a conjunctival swab and tear sample both returned negative for viral RNA. The ocular condition deteriorated,
with scleritis and panuveitis, and the patient was treated with systemic corticosteroids and an experimental anti-viral drug, favipiravir. Three months after onset, the uveitis resolved, the iris heterochromia reversed, and the visual acuity returned to 6/4.8.

A similar case in 2014 involved another US physician, who was evacuated from Liberia with EBOV infection. He presented two weeks after discharge from hospital, and 40 days after the onset of Ebola virus disease, with a unilateral anterior uveitis that worsened to involve the posterior segment with vitritis and macular oedema. He was HLA-B27-positive. After treatment with oral prednisolone, visual acuity improved from 6/60 to 6/6. He did not have an anterior chamber paracentesis to investigate for intraocular virus, but EBOV RNA was detected by RT-PCR in a semen sample.

Prior to the 2014-2016 West African outbreak, uveitis had been associated with EBOV infection. During the 1995 EBOV epidemic in the Democratic Republic of Congo, uveitis was observed in 3 of 20 survivors, and a fourth case was also reported. These patients had anterior, posterior and pan- uveitis, presenting 42 to 72 days after onset of systemic symptoms. Another series of 19 survivors of that epidemic reported one case of uveitis. The uveitis and visual recovery were not described in detail.

Ocular symptoms after Ebola virus disease are common, involving up to 60% of survivors in Sierra Leone. A study of 96 Ebola virus disease survivors in Liberia found that three-quarters reported blurry vision, while over half reported photophobia, tearing and/or eye pain. However, the main ocular complication of EBOV infection was uveitis, with over 180 cases being documented in survivors of the 2014-2016 West African epidemic. Reported rates of uveitis in Ebola survivors vary, but the condition may affects as many as one-third of these individuals, who present on average
3 to 8 weeks after discharge from the Ebola treatment unit.\textsuperscript{68,76,77} Risk factors for developing uveitis include a high viral load whilst in the treatment unit, presumed conjunctivitis during the acute phase of disease and older age.\textsuperscript{68,74,76} In one study, uveitis was 10 times more likely if survivors had experienced red eyes during their acute disease.\textsuperscript{68} Length of admission to the treatment unit, and systemic manifestations – including hair loss, hearing impairment, arthralgias and arthritis – were not associated with the development of uveitis.\textsuperscript{6}

In the 2014-2016 West African epidemic, uveitis was most often unilateral, but bilateral disease was also observed.\textsuperscript{76} Anatomic location was anterior in almost half of cases, while posterior and pan-uveitis each accounted for approximately one-quarter.\textsuperscript{76,77} Most patients were treated with local and systemic corticosteroids and cycloplegia, and recurrences were reported, but uncommon.\textsuperscript{77,80} Other ocular manifestations in survivors included episcleritis, interstitial keratitis, nystagmus, motility disorders and optic neuropathy.\textsuperscript{6,77} Hyperpigmented retinal pigment epithelial scars with hypopigmented borders are more common in survivors who develop uveitis.\textsuperscript{6}

The visual prognosis for Ebola survivors is poor, and those who develop uveitis have significantly worse vision than those who do not. In one study of 96 survivors, nearly 40\% of those with uveitis were blind, and vision was significantly worse in these patients compared to those without uveitis.\textsuperscript{6} Blindness is a significant cause of morbidity in a population already carrying a burden of psychological and systemic disease. White cataract is associated with hypotony in survivors, and surgery in these eyes may increase the risk of phthisis bulbi.\textsuperscript{81} Cataract may develop in those with or without
uveitis, and the implications of viral persistence in the eye mean that cataract surgery is often delayed.

Given the association of cataract with uveitis in Ebola survivors, a study of viral persistence in intraocular fluid was performed in 50 people who were candidates for intraocular surgery to ascertain the safety of cataract surgery in this group. Of 46 survivors with cataract, three-quarters had cataract surgery. Median visual acuity improved from hand motions to 6/9 by the 4th postoperative month. Five patients retained poor vision due to vitreoretinal pathology. Importantly, this study showed that persistence of EBOV in the ocular fluid was not permanent, as is the case at other immune-privileged sites. All 50 Ebola survivors tested negative for EBOV RNA in aqueous and vitreous samples, when tested at a median of 18 or 34 months following the acute disease.

Conclusion

While molecular biological testing, including RT-PCR and immunoassays, are providing reliable means to diagnose the emerging viral forms of uveitis, treatment of these conditions continues to be challenging. Corticosteroid therapies may be effective in limiting the inflammation. However, knowledge that the uveitis may reflect the presence of virus within the eye means decisions around timing of such treatment in the absence of specific anti-viral treatment are difficult. Understanding how these viruses access, replicate and persist within, and finally are cleared from the eye may provide a useful basis for specific medical approaches to these diseases. Initial studies using human retinal cells and new in vivo models, most commonly in rodents, are providing
illuminating information in this regard. While this work is in its infancy, research from several groups has focused on the potential role of the human retinal pigment epithelial cell as a key cell in providing access to the eye, supporting DENV, ZIKV and EBOV replication and induction of a strong innate anti-viral response.\textsuperscript{82-84} Studies of infections induced in mice by local or systemic ZIKV inoculation demonstrate that Mueller cells, as well as retinal pigment epithelial cells, also may be primary targets for these viruses.\textsuperscript{85,86} As these investigations expand, they may identify opportunities to develop novel anti-viral drugs targeted at key pathogenic viral and/or infected host cell molecules.
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