New Infectious Etiologies for Posterior Uveitis

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Key Words

Arthropod borne-diseases • Posterior uveitis • Retinitis • Chorioretinitis • Vasculitis

Abstract

Emergent and resurgent arthropod vector-borne diseases are major causes of systemic morbidity and death and expanding worldwide. Among them, viral and bacterial agents including West Nile virus, Dengue fever, Chikungunya, Rift Valley fever, and rickettsioses have been recently associated with an array of ocular manifestations. These include anterior uveitis, retinitis, chorioretinitis, retinal vasculitis and optic nerve involvement. Proper clinical diagnosis of any of these infectious diseases is based on epidemiological data, history, systemic symptoms and signs, and the pattern of ocular involvement. The diagnosis is usually confirmed by the detection of a specific antibody in serum. Ocular involvement associated with emergent infections usually has a self-limited course, but it can result in persistent visual impairment. There is currently no proven specific treatment for arboviral diseases, and therapy is mostly supportive. Vaccination for humans against these viruses is still in the research phase. Doxycycline is the treatment of choice for rickettsial diseases. Prevention, including public measures to reduce the number of mosquitoes and personal protection,

remains the mainstay for arthropod vector disease control. Influenza A (H1N1) virus was responsible for a pandemic human influenza in 2009, and was recently associated with various posterior segment changes.

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Introduction

Arthropod vector-borne diseases are among the most important emergent and resurgent infections. They include a wide variety of viral, bacterial and parasitic diseases that are transmitted to humans by the bite of an arthropod such as a mosquito or tick. Most of them are prevalent in tropical and subtropical areas, but they tend to spread into new regions mainly due to climate changes and globalization. Systemic disease may range from mild febrile illness to severe, potentially lethal systemic involvement. Specific viral and bacterial arthropod vector-borne infections have been recently associated with posterior uveitis and other ocular manifestations [1–3]. They include viral diseases, namely West Nile virus (WNV) infection, Rift Valley fever (RVF), Dengue fever (DF), Chikungunya, and rickettsioses. There is currently no proven specific treatment for arboviral diseases, and therapy is mostly supportive. Prevention, including pub-

lic measures to reduce the number of mosquitoes and personal protection, remains the mainstay for arthropod vector disease control. In this article, we review the epidemiological, systemic, and ocular features of these selected arthropod vector-borne diseases relevant to the ophthalmologist. Influenza A (H1N1) virus-associated ocular disease will also be briefly discussed.

WNV Infection

WNV infection is a zoonotic disease caused by a single-stranded RNA flavivirus and transmitted to human by a mosquito vector (type *Culex*) with wild birds serving as its reservoir [1–3]. The virus is widely distributed in Africa, Europe, Australia and Asia, and since 1999 it has spread rapidly throughout the Western hemisphere, including the United States, Canada, Mexico and the Caribbean and into parts of Central and South America [1–3]. Most human infections are subclinical (80%) or manifest as febrile illness (20%) [1–3]. Severe neurological disease was reported to occur in less than 1% of patients and was frequently associated with advanced age and diabetes [3]. The diagnosis is confirmed by the detection of IgM antibody in serum or cerebrospinal fluid and/or by PCR [4].

Typical bilateral or rarely unilateral multifocal chorioretinitis is the most common ocular manifestation of WNV infection, occurring in almost 80% of patients with acute WNV infection associated with neurological illness [5, 6]. Most patients have no ocular symptoms or present with mildly reduced vision or floaters. Active chorioretinal lesions present as circular, deep, yellowish lesions on ophthalmoscopy (fig. 1), with early hypofluorescence and late staining on fluorescein angiography (FA) [5]. Inactive chorioretinal lesions appear as round, atrophic lesions with or without central pigmentation (fig. 2a), and they usually exhibit a typical ‘target-like appearance’ on FA (fig. 2b) with central hypofluorescence and peripheral hyperfluorescence [5]. Chorioretinal lesions vary in number and size, involving the midperiphery, with or without associated posterior pole involvement [5]. They are typically oriented radially in the nasal and peripheral fundus or arranged in a curvilinear pattern in the temporal posterior fundus [5]. The linear pattern of chorioretinitis appears to be related to the course of retinal nerve fibers [7]. Indocyanine green angiography shows well-delineated hypofluorescent choroidal spots with more lesions than those appreciated clinically or on FA [8]. Most patients with chorioretinitis are above

Fig. 1. Color fundus photograph of the right eye of a young patient with WNV infection shows superotemporal, linear clustering of deep, creamy, active chorioretinal lesions (arrows).

50 years of age and have diabetes mellitus, with a substantial proportion of them exhibiting associated diabetic retinopathy [9]. Although multifocal chorioretinitis is the most common ocular manifestation of WNV infection, other manifestations have been described, including retinal hemorrhages, focal or diffuse retinal vascular sheathing, vascular leakage, occlusive vasculitis, zones of atrophy and mottling of retinal pigment epithelium (RPE), macular edema, and optic neuritis [1–3, 5, 6]. Ocular disease associated with WNV infection usually has a self-limited course, and visual acuity returns to baseline in most patients [5]. However, persistent visual loss may occur due to foveal chorioretinal scar, choroidal neovascularization, vitreous hemorrhage, tractional retinal detachment, severe ischemic maculopathy, optic atrophy, and retrogeniculate damage [1–3, 5, 6, 10, 11]. Recently, one case of reactivation of WNV infection-related chorioretinitis has been reported [12].

There is, at present, no proven treatment for WNV infection. In cases of severe systemic disease, intensive supportive therapy is indicated [1–3, 13, 14]. Antiviral agents such as ribavirin and interferon were found to be active only in vitro [3]. Several clinical trials of interferon- α -2b, interferon beta, and high-titer intravenous immunoglobulin will allow new and more effective therapeutic approaches to emerge in future [13, 14].

Fig. 2. Color fundus photograph (a) and fluorescein angiogram (b) of the left eye of a diabetic patient with WNV infection show inactive multifocal chorioretinitis with typical linear clustering and 'target-like appearance' of chorioretinal lesions.

Specific ophthalmic treatments that may be required include topical steroids for anterior uveitis, peripheral retinal photocoagulation for neovascularization owing to occlusive vasculitis, pars plana vitrectomy for nonclearing vitreous hemorrhage or tractional retinal detachment, and intravitreal injection of antivascular endothelial growth factor agent for choroidal neovascularization or macular edema [11, 15].

Dengue Fever

DF is caused by the Dengue virus, a flavivirus transmitted by the *Aedes aegypti* mosquito. The disease is considered to be one of the most important Arthropod vector-borne diseases in the tropical and subtropical regions [1–3]. In addition to fever, DF may cause headache, myalgia, thrombocytopenia and Dengue shock syndrome [1–3]. The diagnosis of DF is based on the typical clinical presentation and a positive Dengue IgM serology [1–3]. Ocular involvement, usually bilateral, is common in patients with DF [1–3]. The patients may complain of a sudden decrease in vision, a central scotoma, or floaters. A subconjunctival hemorrhage, petechial in type and asso-

ciated with a platelet count of less than 50,000/ μ l is common [3]. Numerous posterior segment changes can occur in association with DF, including retinal hemorrhages, retinal vascular sheathing, yellow subretinal dots, RPE mottling, foveolitis (seen clinically as a round yellowish lesion at the fovea; fig. 3a), choroidal changes, optic disc swelling, optic neuritis, and neuroretinitis [1–3, 16–23]. There may also be cells in the anterior chamber or vitreous humor. The most common fluorescein angiographic findings include retinal vascular leakage and occlusion. Indocyanine green angiography shows hypofluorescent spots corresponding to the subretinal lesions seen clinically and additional spots in areas without clinically evident dots [17]. Large choroidal vasculopathy with hyperfluorescence and leakage is also common. Optical coherence tomography (OCT) is useful in detecting and monitoring the progress of foveolitis [24], showing a focal outer neurosensory RPE thickening corresponding to the round foveal yellowish lesion seen clinically (fig. 3b). OCT is also useful in the detection and evaluation of serous retinal detachment (SRD) and macular edema. Although the visual prognosis is good in most patients, Dengue-associated maculopathy and neuropathy may result in permanent visual impairment [24]. Ocular in-

Fig. 3. **a** Color fundus photograph of the left eye of a patient with DF shows a subretinal round, yellowish lesion at the fovea. **b** OCT shows a corresponding focal outer neurosensory RPE thickening (courtesy of Soon-Phaik Chee).

involvement in DF may be self-limiting [1–3] and there have been no prospective randomized trials on therapy to date. Treatment with topical, periocular, oral, intravenous steroids and immunoglobulins has been attempted with variable success [16, 18].

Chikungunya Virus Infection

Chikungunya virus is a single-stranded RNA virus of the genus *Alphavirus* in the family *Togaviridae* transmitted to humans by the bite of infected *Aedes* mosquitoes, primarily *A. aegypti* [1–3]. The virus has been associated with many epidemics in tropical regions of Africa, India, Southeast Asia and South America [1–3]. Chikungunya fever may manifest as an acute fever with headache, fatigue, myalgia, diffuse maculopapular rash, bleeding from the nose or gums, peripheral edema, joint pain neurological signs, acute hepatic failure, multiorgan failure, mother-to-child transmission, and vision-threatening ocular complications [1–3].

Ocular symptoms usually occur after a latent period of a month to a year; however, a few concurrent presentations have also been reported. Ocular involvement in Chikungunya is either unilateral or bilateral, affecting both genders in all age groups, with anterior uveitis and retinitis as the most common ocular manifestations [1–3, 25].

Chikungunya retinitis or retinochoroiditis is usually accompanied by mild vitritis and presents in the form of areas of retinal whitening in the posterior pole with sur-

rounding retinal and macular edema (fig. 4). Associated occlusive vasculitis, accurately detected by FA, is also common [1–3, 25–27]. Other posterior segment involvements include optic neuritis, neuroretinitis, central retinal artery occlusion, and exudative retinal detachment [25–29]. Although ocular manifestations have typically a benign clinical course, optic neuritis may result in permanent visual loss. Some investigators treat confluent retinitis with intravenous/oral acyclovir and oral prednisolone, although there is no evidence in the literature to support the efficacy of acyclovir or other antiviral agents against Chikungunya [1–3].

Rift Valley Fever

RVF is an arthropod-borne viral disease caused by *Bunyaviridae*. It is transmitted to humans through a bite by infected mosquitoes or through direct contact with infected animals. Several outbreaks have been reported in sub-Saharan and North Africa, and more recently in the Arabian Peninsula [1–3]. The main symptoms are fever with biphasic temperature curve, headache, arthralgia, myalgia, and gastrointestinal disturbances [1–3]. Other clinical presentations include a hemorrhagic fever with liver involvement, thrombocytopenia, icterus and bleeding tendencies, and a neurological involvement with encephalitis after a febrile episode with confusion and coma [1–3]. Ocular involvement has been reported to occur in 1–20% of RVF infections [1–3, 30]. The mean interval between the onset of RVF and visual symptoms

Color version available online

Fig. 4. Fundus photograph of the left eye of a patient with Chikungunya shows hyperemic optic disc, numerous white retinal lesions, superficial hemorrhages, and an incomplete macular star (courtesy of Padmamalini Mahendradas).

Color version available online

Fig. 5. Fundus photograph of the left eye of a patient with RVF shows macular retinitis with associated retinal vascular sheathing and retinal hemorrhages (courtesy of Emad Abboud).

ranges from 4 to 15 days. Macular or paramacular retinitis is the most common finding (fig. 5). Foci of retinitis show early hypofluorescence with late staining of retinal lesions and retinal vascular leakage on FA. Other posterior segment lesions include retinal hemorrhages, vitritis, optic disc edema, and retinal vasculitis [1–3, 30]. Symptoms resolve spontaneously within 2–3 weeks from the onset of systemic symptoms, but permanent visual loss is common, resulting from macular and paramacular scarring, vascular occlusion, or optic atrophy [1–3, 30].

Treatment is entirely supportive. For mild to moderate cases of RVF, simple analgesia and fluids can be administered [1–3]. For patients who develop severe disease, aggressive critical care including assisted ventilation and blood product transfusion is essential [1–3].

Rickettsioses

Rickettsioses are worldwide-distributed zoonoses due to obligate intracellular small Gram-negative bacteria. Most of them are transmitted to humans by the bite of contaminated arthropods such as ticks [1–3]. Rickettsial

agents are classified into three major categories: the spotted fever group, the typhus group, and the scrub typhus group [1–3]. A rickettsial disease should be suspected, during spring or summer, in the presence of the triad of high fever, headache and general malaise, and skin rash in a patient living in or traveling back from a region endemic for rickettsioses [1–3]. Ocular involvement is common in patients with rickettsioses, but since it is frequently asymptomatic and self-limited, it may be easily overlooked [1–3, 31–33]. Inner retinitis with or without associated mild or moderate vitritis is the most common clinical finding [1–3, 31–33]. It presents in the form of white retinal lesions typically adjacent to retinal vessels (fig. 6a) and variable in number, size and location. FA shows early hypofluorescence and late staining of large retinal lesions (fig. 6b) and slight hypofluorescence or isofluorescence of small retinal lesions [31, 32]. SRD, accurately detected by OCT, frequently accompanies large foci of rickettsial retinitis. Retinal vascular lesions in patients with rickettsial disease may include focal or diffuse vascular sheathing, vascular leakage, retinal hemorrhages, and retinal vascular occlusions, including branch retinal artery occlusion and branch retinal vein occlusion or

Fig. 6. a Color fundus photograph of the right eye of a patient with rickettsial disease shows white retinal lesions adjacent to the inferior vascular arcade and close to the optic disc associated with retinal hemorrhages. **b** Late-phase fluorescein angiogram shows staining of the retinal lesions with retinal vascular leakage and optic disc hyperfluorescence.

subocclusion, leading to retinal neovascularization and vitreous hemorrhage [1–3, 31–34]. A subclinical choroidal involvement in the form of multiple dark dots on FA was observed in more than 15% of patients with Mediterranean spotted fever [31]. Indocyanine green angiography shows small hypofluorescent spots in the intermediate and late phases, areas of hyperfluorescence, choroidal vascular filling defect, and choroidal vascular staining [32]. Other chorioretinal changes include cystoid macular edema and endophthalmitis [1–3, 31–34]. Optic disc involvement may include optic disc edema, optic disc staining, optic neuritis, neuroretinitis, and ischemic optic neuropathy [1–3, 35]. Ophthalmic involvement in rickettsioses often has a self-limited course. Foci of retinitis usually disappear without causing scarring in 3–10 weeks. Persistent decreased vision may occur in cases of retinal changes secondary to macular edema or SRD, retinal artery or vein occlusion, foveal chorioretinal scar, or optic neuropathy [1–3, 31–34]. Doxycycline is the drug of choice for the treatment of rickettsial diseases [1–3, 31, 32]. Systemic steroids may be required for severe ophthalmic involvement [1–3, 31, 32].

H1N1 Uveitis

Influenza A (H1N1) virus was the most common cause of human influenza in 2009. Patients infected with H1N1 may present with flu symptoms such as fever, cough and

body aches [36, 37]. Ocular involvement has been recently associated with H1N1 infection, as well as vaccination. It includes retinitis, choroiditis, submacular hemorrhages, macular edema, cotton wool spots, frosted branch angiitis, neuroretinitis, SRD, optic disc edema, and uveal effusion [36–41]. Ocular involvement is favorable in the majority of reported cases [36–41]. Frosted branch angiitis, macular edema, and uveal effusion may be treated with oral prednisone [38, 40].

Disclosure Statement

The authors have no financial interests to disclose.

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