

Ocular Disease Associated with West Nile Virus Infection

Moncef Khairallah*, Rim Kahloun, Imen Ksaa, Nesrine Abroug, Bechir Jelliti and Salim Ben Yahia

Department of Ophthalmology, Fattouma Bourguiba University Hospital, Faculty of Medicine, University of Monastir, Monastir, Tunisia

*Corresponding author: Moncef Khairallah, MD, Department of Ophthalmology, Fattouma Bourguiba University Hospital, 5019 Monastir, Tunisia, Tel: 00 216 73 461 144; E-mail: moncef.khairallah@rns.tn

Received date: March 5, 2014; Accepted date: April 16, 2014; Published date: April 24, 2014

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Abstract

Chorioretinal involvement, frequently asymptomatic and self-limited, is common in patients with West Nile virus (WNV) infection associated with neurologic illness. A bilateral multifocal chorioretinitis, with typical clinical and fluorescein angiographic features, is the most common finding, but numerous other ocular manifestations can occur. Diabetes mellitus appears to be a potential risk factor for developing severe neurologic disease and also severe chorioretinitis. The unique pattern of multifocal chorioretinitis can help establish an early diagnosis of the disease while serologic testing is pending. This might be of utmost importance in the near future for early initiation of promising drugs currently under investigation. Therefore, an ocular examination, including dilated fundus examination and fluorescein angiography in selected cases, should be part of the routine evaluation of patients with clinically suspected WNV infection. WNV infection should be considered in the differential diagnosis of multifocal chorioretinitis in patients living in or returning from specific endemic regions.

Keywords: West Nile virus; Meningoencephalitis; Multifocal chorioretinitis; Retinal vasculitis

Introduction

West Nile virus (WNV) was first isolated from a febrile adult woman in the West Nile District of Uganda in 1937 [1]. The virus responsible of the disease belongs to the genus *Flavivirus*, family *Flaviviridae*. It is a single stranded RNA virus and can have antigenically similar with other virus of the Japanese encephalitis serocomplex, which are Japanese encephalitis virus, Saint Louis encephalitis virus, Murray Valley encephalitis virus and Kunjin virus [2]. Hundreds of wild and domestic avian species including Passerines mainly the *Corvidae* family, Gulls, Flamingos, Pelicans, Hawks and Owls, and companion Birds have been described as susceptible to WNV infection. The reported seroprevalence in birds is usually higher among migratory than resident birds. This leads to suggest that migratory birds may play a pivotal role in spreading WNV infection [2]. The virus is maintained in nature through a bird-mosquito-bird transmission cycle. However, mosquitoes (primarily the *Culex* species) can transmit the virus from the natural hosts to humans and other mammals, mainly horses. Other less common routes of transmission have been recognized including blood transfusion [3], organ transplantation [4], transplacental transmission [5], laboratory transmission, and breast feeding [6,7].

In this article, we review the epidemiological, systemic, and ocular features of WNV infection.

Epidemiology

After the first case isolated in 1937 [1], an outbreak in nursing home residents in Israel took place during 1957 causing meningoencephalitis [6]. Then, the first major epidemic in Europe appeared in Romania in 1996 [8], followed by several outbreaks worldwide. Russia was involved in 1999 [9], United States in August

1999 [10], Algeria in 1994 and 1997 [11], Tunisia in 1997 and 2003 [12], the Czech Republic in 1997 [13], the Democratic Republic of the Congo in 1998 [14], Israel in 2000 [6], Sudan in 2002 [15], the United States between 2002 and 2007 [7], Canada in 2002, 2003, and 2007 [7], Greece in 2010 and 2011 [16], Croatia, and Serbia in 2012 [17]. In each of these outbreaks, mortality among patients with meningitis and encephalitis was approximately 10% and occurred more often in elderly patients [6].

Epizootics of disease in horses occurred in Morocco in 1996 [18], Italy in 1998 [19], the United States in 1999-2001 [10], and France in 2000 [20]. Furthermore, birds were infected in Israel in 1997-2001 [21] and in the United States in 1999-2002 [7].

Since 2000, the Arbo NET national surveillance system has tracked WNV in the United States. From 1999 to 2013, a total 780 000 confirmed and probable cases of WNV disease, including 16,196 of neuroinvasive disease cases with 1549 deaths, were reported to the Centers for Disease Control and Prevention (CDC) from all states [22].

The most cases of WNV infection were caused by lineage 1 of the virus, whereas lineage 2 was involved in African enzootic strains [6].

Systemic disease

Following the incubation period which ranges from 3 to 14 days, systemic disease has three possible presentations: asymptomatic disease, West Nile fever and meningoencephalitis.

About 80% of human infections are apparently asymptomatic. Only approximately 20% of people infected become symptomatic with a flu-like syndrome in most cases [2]. This syndrome includes high-grade fever, headache, myalgia, arthralgia, malaise, nausea, vomiting, diarrhea, skin rash, weakness, lymphadenopathy, and pharyngitis. Rarely, hepatitis, pancreatitis, myocarditis, myositis, orchitis, and nephritis were reported [23].

The acute illness is typically self-limiting within a week [2,6]. However, an onset of mental status changes, cerebral dysfunction, and even coma indicates the neurologic disease.

Severe, potentially lethal, neurologic involvement was initially reported to occur in less than 1% of infected individuals, but over time, WNV infection has increased in severity [7].

Neurologic disease may take the form of aseptic meningitis and/or encephalitis, or myelitis, or poliomyelitis-like disease [23]. WNV encephalitis and/or meningitis are characterized by rapid onset of headache, photophobia, back pain, confusion and continued fever. WNV poliomyelitis-like syndrome is characterized by acute onset of asymmetric weakness and absent reflexes without pain resulting in an acute flaccid paralysis syndrome which may lead to a respiratory failure [2,22,23]. Movement disorders such as tremor, myoclonus, and parkinsonism have been also reported [6].

Ocular disease

Since the first descriptions of ocular involvement secondary to WNV infection in 2002 and 2003, several ophthalmologic findings have been recognized, including chorioretinitis, anterior uveitis, retinal vasculitis, optic neuritis, and congenital chorioretinal scarring [6,12,24-47].

Chorioretinitis

A bilateral or rarely unilateral multifocal chorioretinitis, with typical clinical and fluorescein angiographic features, is the most common finding, occurring in almost 80% of patients with acute WNV infection associated with neurologic illness [29]. Most patients have no ocular symptoms or present with mildly reduced vision. An associated mild to moderate vitreous inflammation is frequently observed. The chorioretinal lesions commonly develop early in the course of the disease, appearing to be active (35%) or already inactive (65%) at presentation [29]. Active chorioretinal lesions appear as circular, deep, creamy lesions on ophthalmoscopy, with early hypofluorescence and late staining on fluorescein angiography [29]. Inactive chorioretinal lesions typically are partially atrophic and partially pigmented with a "target-like appearance": central hypofluorescence by blockage from pigment and peripheral hyperfluorescence [29] (Figure 1). Some atrophic lesions are not pigmented. The lesions vary in number from less than 20 to more than 50 per eye [29]. Chorioretinal lesions involve the midzone and/or periphery in almost all eyes. The posterior pole is involved in nearly 2/3 of eyes. Most of the lesions measuring 200 to 500 μm , large lesion size range from 1000 to 1500 μm [29]. Linear clustering of chorioretinal lesions is a prominent feature, occurring in more than 80% of eyes with chorioretinitis. The streaks vary in number, from one to more than 3 per eye, and in length approximately from 2 to 15 mm [29]. They typically are oriented radially in the nasal and peripheral fundus or arranged in a curvilinear pattern in the temporal posterior fundus [29]. The linear pattern of chorioretinitis appears to be related to the course of retinal nerve fibers, suggesting a contiguous spread of central nerve system disease [42]. Indocyanine green angiography shows well delineated hypofluorescent choroidal lesions, which are more numerous than those appreciated by fluorescein angiography or clinically [43] (Figure 1). Diabetes mellitus appears to be a potential risk factor for developing multifocal chorioretinitis, with more than 20% of patients having diabetic retinopathy in association with multifocal chorioretinitis. It was also associated with more severe

chorioretinal involvement [44]. Typical multifocal chorioretinitis has a specific marker of WNV infection, particularly in patients who present with meningoencephalitis [48].

Other ophthalmic manifestations

Other findings have been reported in WNV infection including iridocyclitis in the absence of chorioretinitis, retinitis, retinal hemorrhages, focal or diffuse vascular sheathing, vascular leakage, macular edema, occlusive vasculitis, and segmental wedge-shaped zones of atrophy and mottling of the retinal pigment epithelium [28,33,36,37,49]. WNV-associated optic nerve involvement may occur, including optic neuritis, neuroretinitis, optic disc swelling, and optic disc staining on fluorescein angiography [28]. Other reported neuro-ophthalmic manifestations include ocular nerve palsy and nystagmus [28]. Congenital chorioretinal scarring secondary to intrauterine transmission of WNV infection has been reported [24].

Diagnosis

Diagnosis of WNV infection requires a high index of suspicion and specific laboratory testing. The most common efficient diagnostic method is detection of WNV-specific IgM antibody in serum or cerebrospinal fluid using the antibody-capture enzyme-linked immunoabsorbent assay [2,23]. Since IgM antibody does not cross the blood-brain barrier, its presence in the cerebrospinal fluid strongly suggests infection of the central nervous system. Based on CDC guidelines (www.cdc.gov/ncidod/dvbid/westnile/resources/wnv-guidelines-aug-2003.pdf), the diagnosis of WNV meningoencephalitis is confirmed if the IgM from cerebrospinal fluid is positive for WNV. Flaviviruses may exhibit antigenic cross-reactivity; therefore persons, who have recently been vaccinated with yellow fever or Japanese encephalitis vaccines or have infections with related flaviviruses, may generate a false-positive result in the serum. The plaque-reduction neutralisation test can help distinguish false-positive results of MAC-ELISA or other assays as well as to help to distinguish serologic cross-reactions among the flaviviruses [2,22]. Recently, PCR-based detection systems for the rapid detection of WNV infection in clinical specimens that are negative for virus isolation have been reported, suggesting that nucleic acid-based assays hold great promise for the detection of WNV infection [41]. In addition, other PCR-based methods, including RT-PCR, real time RT-PCR, reverse transcription loop-mediated isothermal gene amplification (RT-LAMP) assay, and qRT-PCR have been developed for the detection of WNV RNA [41,50,51].

Cerebrospinal fluid generally shows normal glucose, elevated protein, pleocytosis (>5 leukocytes/ μL) [22]. The unique pattern of multifocal chorioretinitis can help establish an early diagnosis of the disease while serologic testing is pending [49].

Differential diagnosis

The differential diagnosis of WNV systemic disease include other arthropod-borne viral encephalitides, enteroviral aseptic meningitis, herpesvirus encephalitis, encephalopathy from systemic illnesses (Legionnaires' disease, rickettsiosis, Epstein-Barr virus infectious mononucleosis, and systemic lupus erythematosus), epidural abscess, hypertensive encephalopathy, and drug-induced meningitis. Many infectious and inflammatory conditions may present with chorioretinitis. The differential diagnosis includes syphilis, tuberculosis, histoplasmosis, sarcoidosis, and idiopathic multifocal chorioretinitis [6,29]. WNV associated chorioretinitis can be

distinguished from these entities on the basis of history, systemic signs and symptoms, and particularly the unique pattern of chorioretinitis [29].

Treatment

There is, at present, no proven treatment for WNV infection. In cases of severe systemic disease, intensive supportive therapy is indicated, often involving hospitalization, intravenous fluids, respiratory support, prevention of secondary infections, and good nursing care [23].

Clinical trials of interferon a-2b, interferon b, high-titer intravenous immunoglobulin, and pluripotent immunomodulator AS101 will allow new and more effective therapeutic approaches to emerge in future [52-54].

Specific ophthalmic treatment may be required: topical steroids for anterior uveitis, peripheral retinal photocoagulation for neovascularization due to occlusive vasculitis, pars plana vitrectomy for non-clearing vitreous hemorrhage or tractional retinal detachment, and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agent for Choroidal neovascularization (CNV) or macular edema [34,55].

Prevention is the mainstay of WNV infection control: measures to reduce the number of mosquitoes (draining standing water, larvicides), personal protection (repellents, window screen, protective clothing). Vaccination, a possible long-term solution, is still in the research phase [56-58].

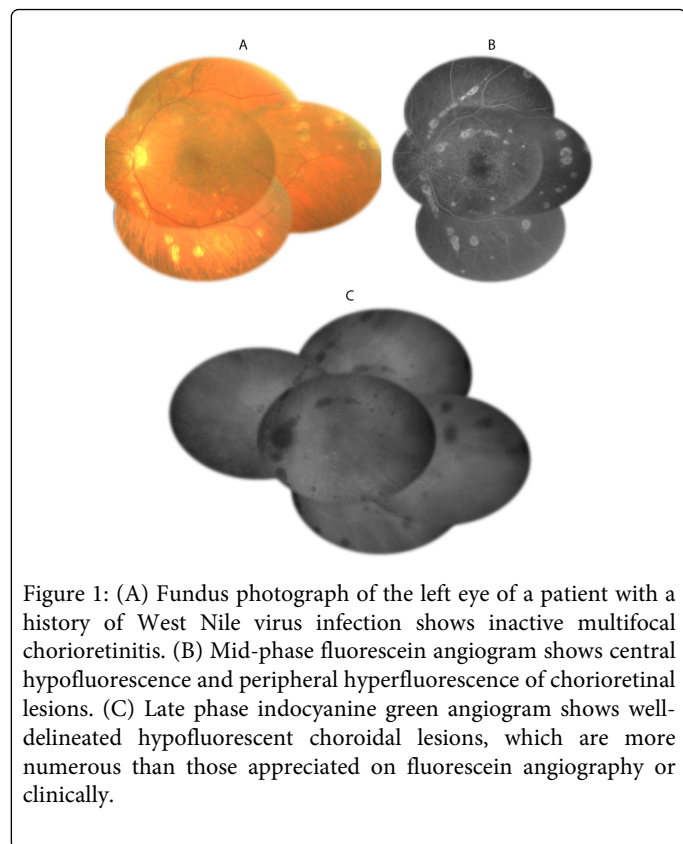


Figure 1: (A) Fundus photograph of the left eye of a patient with a history of West Nile virus infection shows inactive multifocal chorioretinitis. (B) Mid-phase fluorescein angiogram shows central hypofluorescence and peripheral hyperfluorescence of chorioretinal lesions. (C) Late phase indocyanine green angiogram shows well-delineated hypofluorescent choroidal lesions, which are more numerous than those appreciated on fluorescein angiography or clinically.

Prognosis

Prognosis of WNV systemic disease is good in most patients. Full recovery is the norm for patients with uncomplicated West Nile fever or meningitis; however, initial symptoms, particularly extreme fatigue, may be prolonged [22]. However, severe cases may result in neurologic sequelae or death, especially in patients who are elderly or debilitated [7,22]. Advanced age is the most important risk factor for death, ranging from 0.8% among those aged less than 40 years to 17% among those aged at least 70 years [22]. Encephalitis with severe muscle weakness, changes in the level of consciousness, diabetes, cardiovascular disease, hepatitis C virus infection, and immunosuppression are possible risk factors for death [22].

Ocular involvement usually has a self-limited course. Active chorioretinal lesions at presentation evolved to the typical inactive stage [6,29]. Some inactive lesions become more prominent on both ophthalmoscopy and fluorescein angiography. Visual acuity returns to baseline in most patients [29]. However, persistent visual impairment may occur due to a foveal chorioretinal scar, CNV, complications of occlusive retinal vasculitis, such as vitreous hemorrhage secondary to retinal neovascularization, severe ischemic maculopathy, optic atrophy, or retrogeniculate damage [34,36,37]. Recently, one case of reactivation of WNV infection-related chorioretinitis has been reported [45].

Conclusion

Chorioretinal involvement, frequently asymptomatic and self-limited, is present in almost 80% of patients with WNV infection associated with neurologic disease. The unique pattern of multifocal chorioretinitis can help establish an early diagnosis of the disease while serologic testing is pending. Therefore, an ocular examination, including ophthalmoscopy and fluorescein angiography in selected cases, should be part of the routine evaluation of patients with clinically suspected WNV infection.

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