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West Nile Virus Chorioretinitis in the Presence of Negative Cerebrospinal Fluid Polymerase Chain Reaction Results

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Abstract

Purpose: This work aims to evaluate the utility of nucleic acid amplification testing (NAAT) and serology in confirming West Nile Virus (WNV) infection in patients with suspected WNV chorioretinitis. **Methods:** A retrospective cross-sectional study was conducted of a cluster of patients who presented to the Retina Service of Massachusetts Eye and Ear between September and October 2018. **Results:** Three patients were identified with classic WNV chorioretinitis lesions with negative cerebrospinal fluid NAAT and positive serum serology findings. The diagnosis of WNV chorioretinitis was made based on the appearance of the fundus lesions and the presence of characteristic findings on fluorescein angiography as previously described in the literature. **Conclusions:** This report highlights 3 unique cases of WNV chorioretinitis in which NAAT of cerebrospinal fluid failed to identify WNV as the inciting agent. These cases stress the importance of serum serologic testing in diagnosing WNV infection.

Keywords

chorioretinitis, nucleic acid amplification testing, serology, West Nile Virus

Introduction

West Nile Virus (WNV) is an Arbovirus and a member of the *Flaviviridae* family, which also includes yellow fever, dengue, Zika, Japanese encephalitis, and St. Louis encephalitis viruses. WNV is introduced in human hosts by *Culex* mosquitoes that most commonly have bitten infected birds, the natural hosts. WNV enters cells via receptor-mediated endocytosis, releases its viral genomic RNA, and initiates its replication cycle.[1] WNV was first isolated in the West Nile region of Uganda in 1937.[2] The first reports in the Western hemisphere were during a meningoencephalitis outbreak in New York City in 1999, and since then the virus has spread westward across the United States. Over time, the infection has had an increased public health significance, with 48 of 50 states reporting cases in 2018 and 42 reported cases in Massachusetts alone.[3]

The incubation time is 3 to 14 days, and systemic infection is most commonly asymptomatic. When symptomatic, infection typically presents with fever, nausea, headache, and weakness. In rare cases, especially in the elderly or immunosuppressed, a severe meningoencephalitis may develop that is characterized by confusion, headache, stiff neck, back pain, and sometimes coma. Severe neurologic involvement can lead to death.

Ocular involvement, consisting of vitritis, optic neuritis, and multifocal chorioretinitis, was first reported in 2003.[4] WNV chorioretinitis tends to occur in older patients with diabetes and is more likely to occur in patients with encephalitis.[5] Active chorioretinal lesions appear round, deep, and creamy on examination, with early hypofluorescence and late staining on fluorescein angiography (FA). Inactive lesions appear atrophic with central hypofluorescence and a peripheral ring of hyperfluorescence.[4,6] These lesions are typically clustered in a linear pattern, closely following the course of retinal nerve fibers, suggesting spread from the central nervous system via the optic nerve to the retina and choroid.[7] Other hypotheses suggest hematogenous dissemination of viral particles via the choroidal circulation, resulting in a pattern of multifocal choroiditis.[8]

WNV infection is suspected in patients with the clinical symptoms described previously as well as a history of possible mosquito exposure. The diagnosis is confirmed by tests that detect the WNV, namely through the detection of WNV-specific immunoglobulin M (IgM) antibodies in serum or cerebrospinal fluid (CSF). Reverse transcriptase–polymerase chain reaction (RT-PCR) of serum or CSF can also be used to confirm infection, although negative results do not necessarily rule

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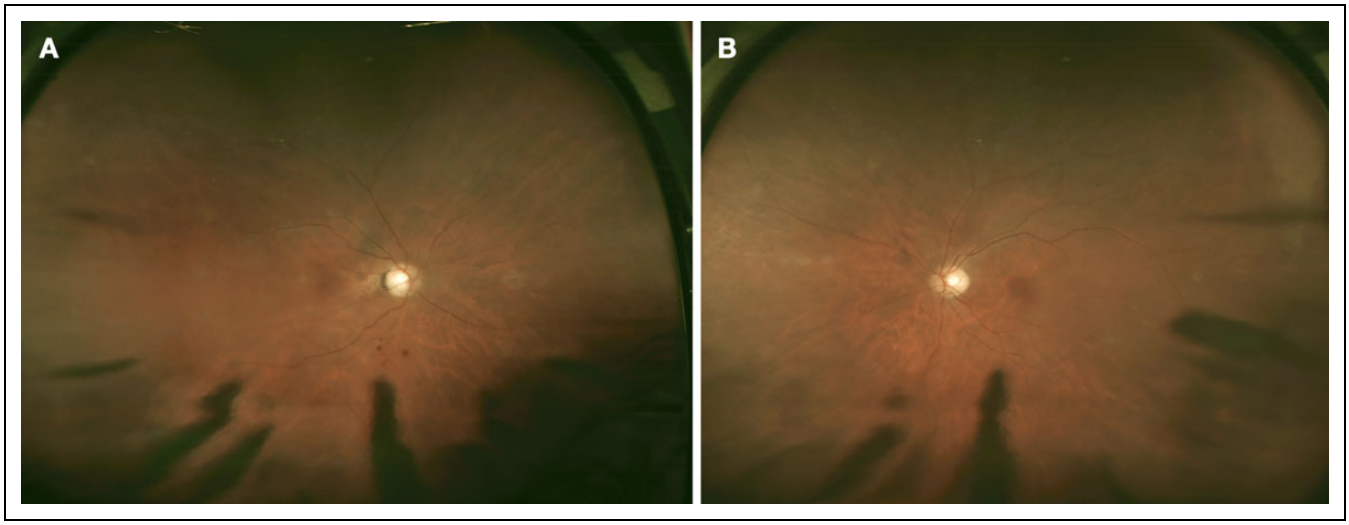

Figure 1. Color fundus photograph of the (A) right and (B) left eyes showing multiple round, deep, creamy chorioretinal lesions and scattered intraretinal hemorrhages (case 1). Shadowing from lenticular cortical spokes can be seen inferiorly.

out disease. In this study we describe 3 cases of WNV encephalitis with concurrent chorioretinitis in which CSF RT-PCR failed to identify a causative agent. In all 3 cases, serum antibody testing revealed immunoglobulin G (IgG) and IgM antibodies directed against the virus. Through these cases we aim to highlight the limited utility of CSF RT-PCR in establishing a diagnosis of WNV infection and the importance of serum antibody testing for prompt diagnosis.

Methods

This study is a retrospective review of medical records of a cluster of patients who presented to the Retina Service of Massachusetts Eye and Ear over a 4-week period between September and October 2018 (n = 3 patients, 6 eyes). All patients had CSF RT-PCR testing, which had negative results, and subsequent positivity via serum antibody testing. All patients underwent a complete dilated eye examination with ancillary testing including color fundus photography, FA, and optical coherence tomography (OCT). The diagnosis of WNV chorioretinitis was made based on the appearance of the fundus lesions and the presence of characteristic findings on FA as previously described in the literature. Subsequent testing results for serum WNV antibodies (IgG and IgM) were positive in all 3 patients.

Results

Case 1

A 63-year-old man with a history of hypertension, hyperlipidemia, type 2 diabetes, hepatitis C with cirrhosis, and a remote history of intravenous drug use was referred to the Retina Service for presumed branch retinal vein occlusion (BRVO) with macular edema in the right eye. He reported blurry vision in the right eye of approximately 2 months' duration. Two weeks prior to evaluation in the Retina Clinic, the patient presented to the emergency department with 6 days of headache, fever, stiff neck, and confusion. He was admitted for altered mental status and treated with intravenous vancomycin, ceftriaxone, ampicillin, and acyclovir. Findings from blood and CSF cultures were negative. CSF analysis revealed lymphocytic pleocytosis, elevated glucose, and elevated protein. CSF PCR for herpes simplex virus types 1 and 2, varicella zoster virus, and WNV had negative results. He was discharged with a diagnosis of meningoencephalitis of unknown etiology.

Eye examination was notable for visual acuity (VA) of 20/60 OD and 20/20 OS. Intraocular pressure (IOP) was normal in both eyes. Slit lamp examination showed mild nuclear sclerosis and cortical spokes (which can be seen on the images) in both eyes. Mild vitritis was present in both eyes. Fundus examination was notable for multiple round, deep, creamy chorioretinal lesions and a few scattered intraretinal hemorrhages in both eyes (Figure 1). FA showed multiple round "target" lesions, most with a hypofluorescent center and a hyperfluorescent peripheral ring, with some arranged in a linear pattern radiating outward in both eyes (Figure 2). In addition, focal vasculitis was noted in the macula of the right eye. OCT of the macula revealed cystoid macular edema (CME) in the right eye and a normal foveal contour without edema in the left eye (Figure 3, A and B, respectively).

On further questioning, the patient reported heavy exposure to mosquitoes 1 to 2 weeks prior to the emergency room presentation. Serum WNV IgG and IgM antibodies were ordered in the Retina Clinic. Results showed IgG of 3.09 (> 1.5 positive) and IgM greater than 5.00 (> 1.10 positive), confirming the diagnosis of WNV meningoencephalitis with concurrent chorioretinitis. An intravitreal injection of bevacizumab (1.25 mg/0.05 mL) was given in the right eye for WNV-associated vasculitis with macular edema. At follow-up 2 weeks later, the patient's VA remained stable at 20/60 OD with resolution of the macular edema but residual focal attenuation of the ellipsoid zone at the fovea. At 3 months' follow-up, his VA was 20/

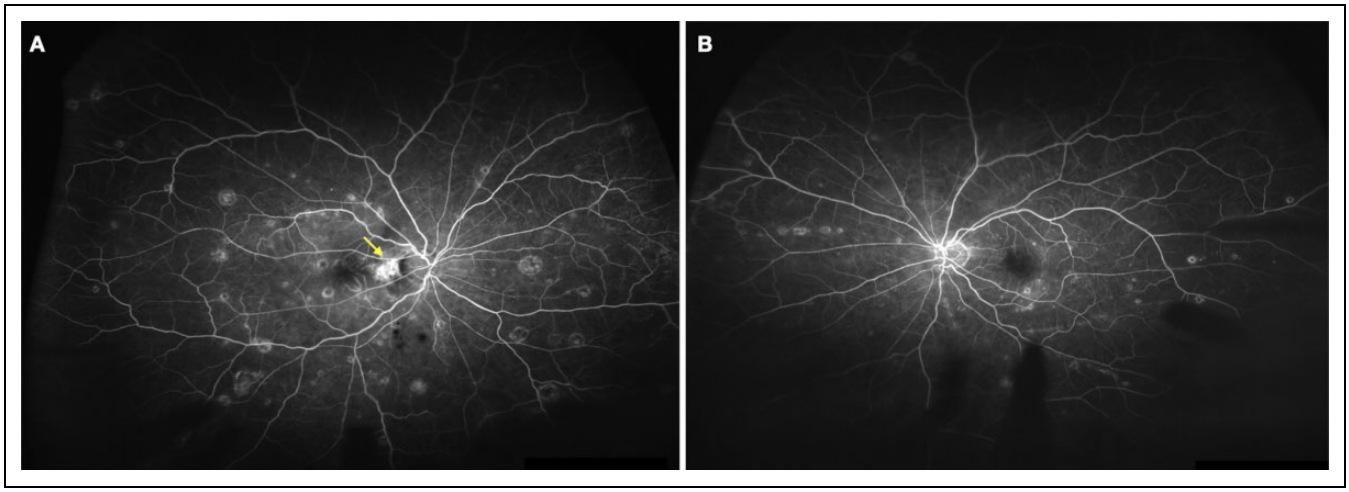

Figure 2. Fluorescein angiography of the (A) right and (B) left eyes notable for multiple round "target" lesions with a hypofluorescent center and hyperfluorescent ring in a linear pattern radiating outward (case 1). Focal vasculitis is seen nasal to the fovea in the right eye (arrow).

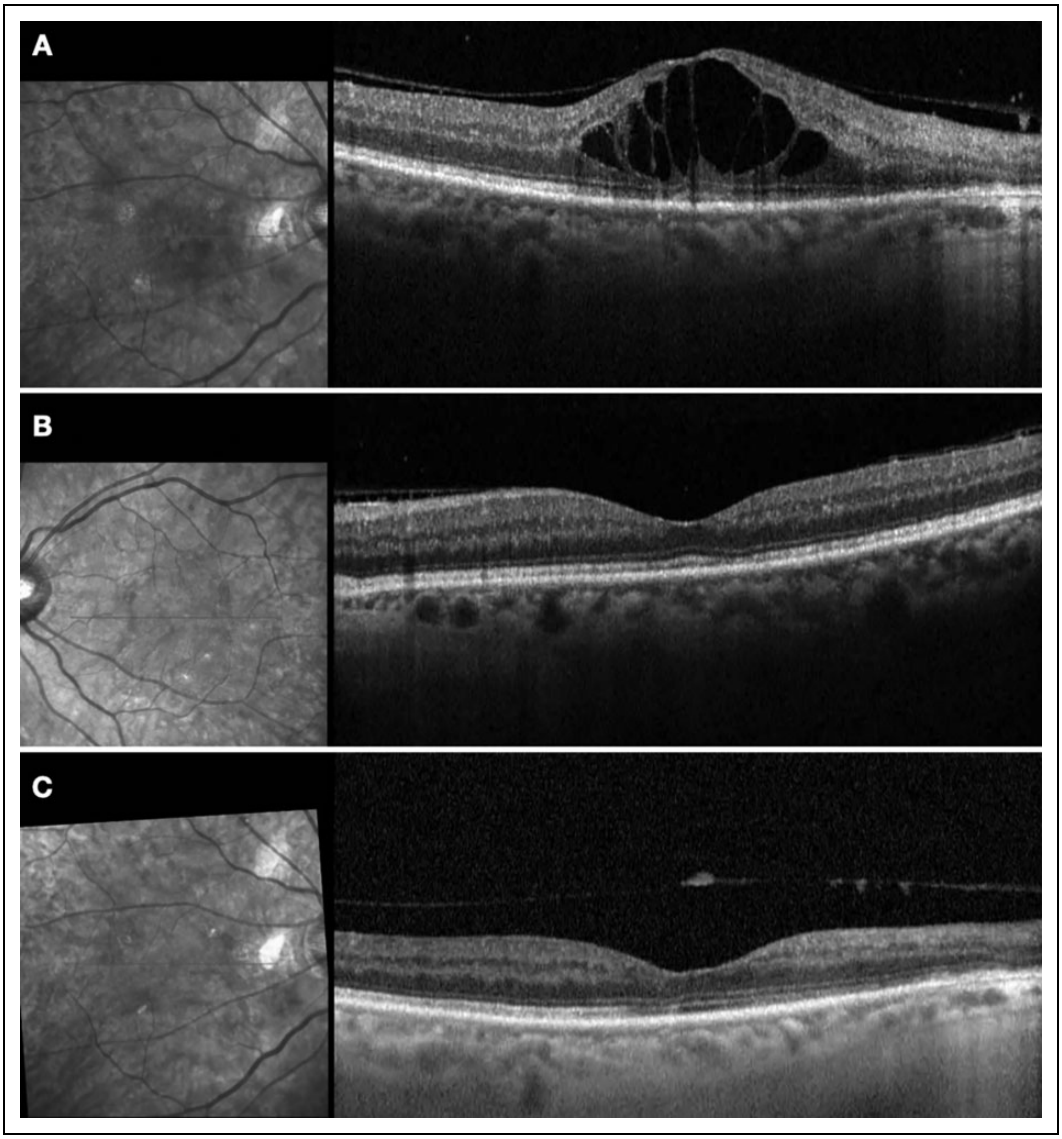

Figure 3. Optical coherence tomography showing cystoid macular edema in the (A) right eye and a normal foveal contour without edema in (B) the left eye (case 1). (C) There was resolution of the edema at 3 months with persistent ellipsoid zone disruption.

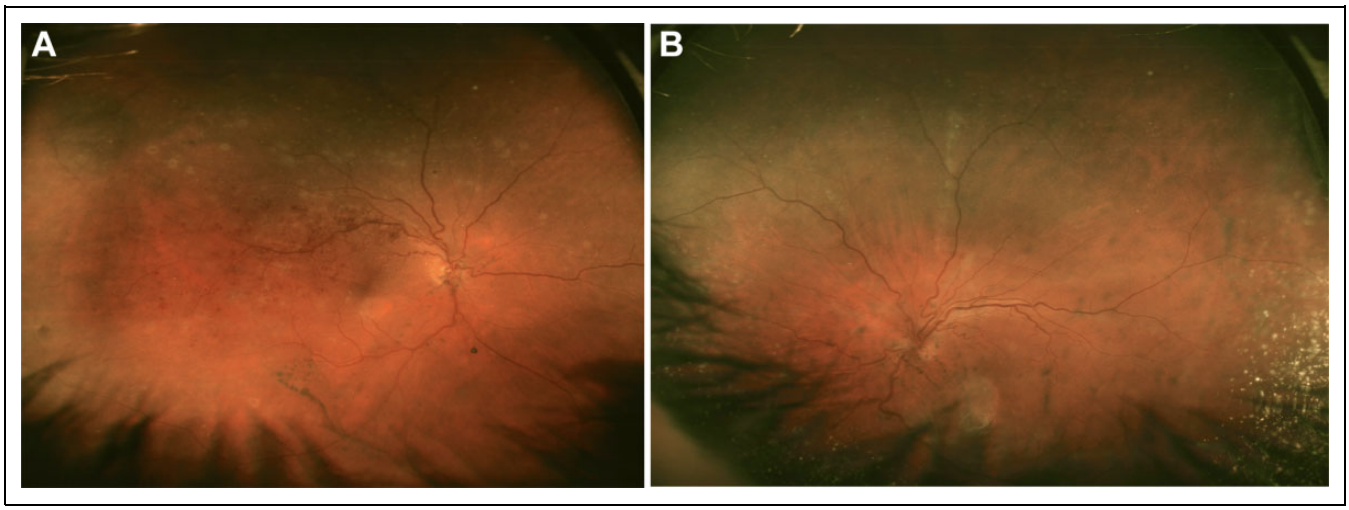

Figure 4. Color fundus photograph of (A) the right eye and (B) the left eye shows round, creamy chorioretinal lesions and intraretinal hemorrhages (case 2).

100 OD and 20/25 OS. OCT showed persistent attenuation of the ellipsoid zone at the fovea of the right eye (see Figure 3C). OCT of the left eye remained stable. At 6 months' follow-up, his VA was 20/80 OD and 20/25 OS. OCT showed mild recurrence of CME in the right eye, and a second intravitreal injection of bevacizumab (1.25 mg/0.05 mL) was given. The patient did not return for follow-up after the injection.

Case 2

An 83-year-old man with a history of hypertension, hyperlipidemia, coronary artery disease after coronary artery bypass grafting, heart failure, prostate cancer, and bladder cancer was referred to the Retina Service for presumed BRVO with macular edema in the right eye. He reported blurry vision in the right eye of approximately 2 months' duration. One month prior to evaluation in the Retina Clinic, the patient presented to the emergency department with 1 week of headache, fever, chills, and confusion. He was admitted for altered mental status and treated with intravenous vancomycin, cefepime, metronidazole, and azithromycin. Blood and CSF cultures were negative for bacteria and fungi. CSF analysis revealed lymphocytic pleocytosis and elevated protein. CSF RT-PCR result for WNV was negative. Serum WNV antibody testing showed IgG less than 1.3 (> 1.5 positive) and IgM greater than 5.00 (> 1.10 positive). He was diagnosed with WNV meningoencephalitis and treated with supportive therapy consisting of antipyretics and intravenous fluids as needed; antivirals and antibiotics were discontinued on results of positive antibody titers.

Eye examination was notable for a VA of 20/25 OD and 20/20 OS. IOP was normal in both eyes. Slit lamp examination showed mild nuclear sclerosis in both eyes. Mild vitritis was noted in the right eye, and asteroid hyalosis was present in the left eye. Fundus examination showed multiple round, deep, creamy chorioretinal lesions and intraretinal hemorrhages in both eyes (Figure 4). Venular dilation was noted in both eyes. A cluster of intraretinal hemorrhages was noted in the superotemporal macula of the right eye, possibly consistent with BRVO. FA showed "target" lesions with hypofluorescent centers and hyperfluorescent edges, mostly in a radiating pattern in both eyes (Figure 5). Late leakage was noted in the temporal macula of the right eye, consistent with macular edema. OCT of the macula revealed mild CME in the right eye (Figure 6A) and a normal foveal contour without edema in the left eye.

Given the patient's good VA and minimal macular edema on OCT, the right eye was observed. At follow-up 6 weeks later, his VA was 20/32 OD and there was significant improvement in the CME on OCT (Figure 6B). OCT of the left eye remained stable. At 6 months' follow-up, his VA was 20/30 OD with slight worsening of the CME on OCT. He was observed. At 9 months' follow-up, his VA was 20/40 OD with mild worsening of the CME on OCT. An intravitreal antivascular endothelial growth factor injection was offered to him, but he declined it. OCT of the left eye remained stable. His examination and vision remained stable at 1-year follow-up without further treatment.

Case 3

A 60-year-old man with no medical history presented to the emergency department with fever, chills, vomiting, and blurry vision in both eyes of 5 days' duration. He was seen by the Neurology Service and referred to the Retina Service. Eye examination was notable for VA of 20/100 OU. IOP in both eyes was normal. Slit lamp examination showed mild anterior chamber inflammation and mild nuclear sclerosis in both eyes. Moderate vitritis was present in both eyes. Fundus examination was notable for multiple round, deep, creamy chorioretinal lesions and a few scattered intraretinal hemorrhages in the right eye; there was marked asymmetry with minimal involvement in the left eye. FA showed multiple round "target" lesions with hypofluorescent centers and hyperfluorescent edges in the right

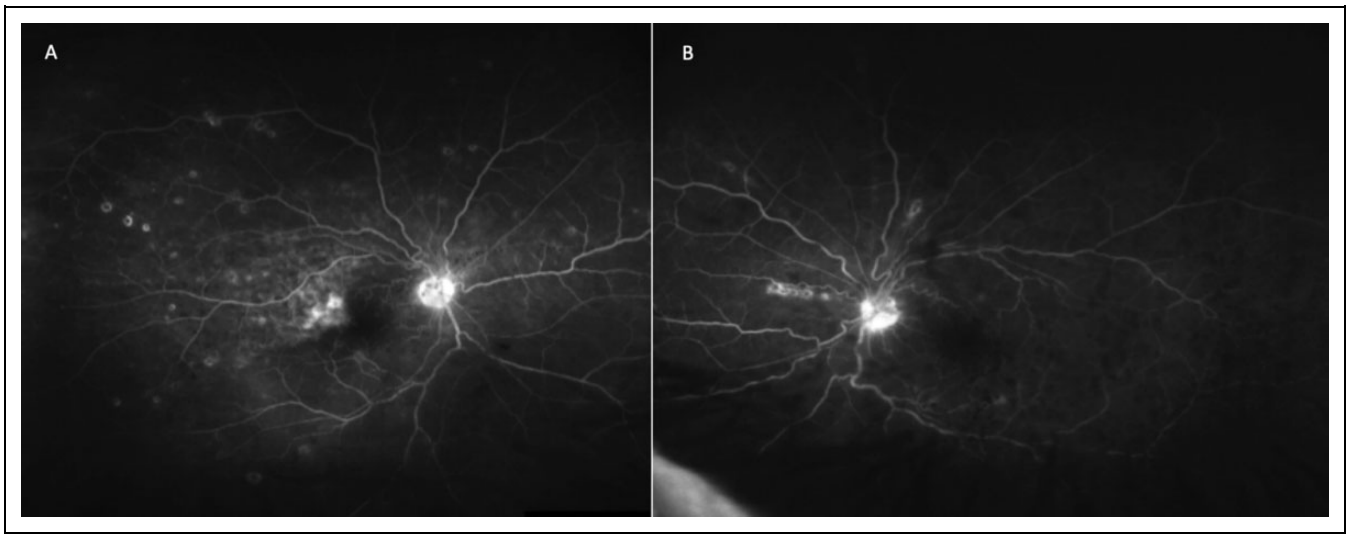

Figure 5. Fluorescein angiography of (A) the right eye and (B) the left eye shows multiple "target" lesions in a linear pattern (case 2).

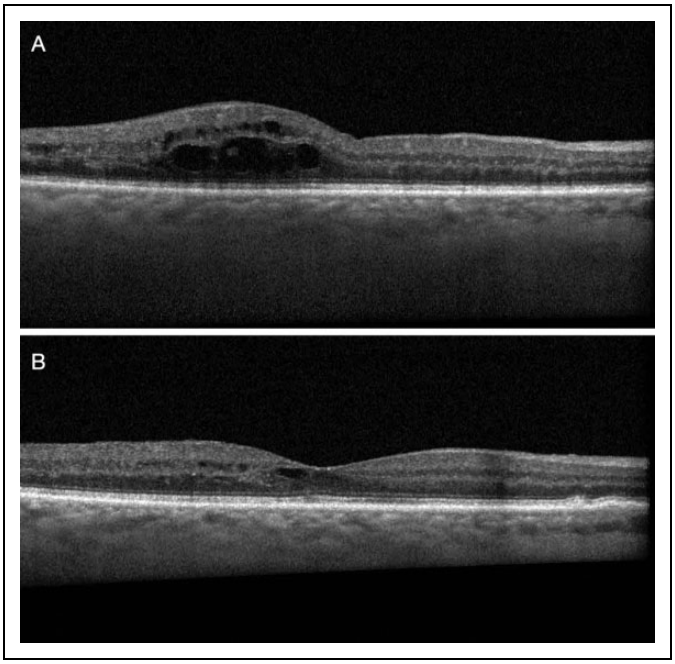

Figure 6. (A) Optical coherence tomography of the right eye shows mild cystoid macular edema and (B) its subsequent improvement at 6 weeks' follow-up (case 2).

eye, largely clustered in the nasal retina, and very few lesions in the left eye (Figure 7). OCT of the macula of both eyes was unremarkable. Based on the ocular findings, he was diagnosed with WNV and admitted to the hospital. On further questioning, he reported recent exposure to mosquitoes.

The patient was treated with supportive therapy and placed on topical prednisolone acetate and atropine. CSF analysis revealed lymphocytic pleocytosis and elevated protein. The result of CSF RT-PCR for WNV was negative. Serum WNV IgG and IgM antibody testing showed IgG of 2.85 (> 1.5 positive) and IgM of 4.77 (> 1.10 positive), confirming the diagnosis. At follow-up 2 weeks later, his VA improved to 20/40 OD and 20/25 OS, and 9 months later VA improved to 20/25 OD and 20/20 OS.

Conclusions

Serology is the most consistent technique to diagnose WNV infection.[9,10] It can be performed on serum or CSF. The enzyme-linked immunosorbent assay is most commonly used in clinical practice; cross-reactivity with other flaviviruses has been reported. A different technique known as plaque reduction and neutralization tests may also be used; however, it is costly and time-consuming relative to enzyme-linked immunosorbent assay.

Nucleic acid amplification testing (NAAT) can also be used to diagnose WNV infection by RT-PCR, and this can be performed on serum or CSF. NAAT, however, has a low positive rate after the first week of illness. In a study of 276 WNV cases in which 191 cases were tested both by serology and NAAT at first blood collection, 58.1% by serology and 45% by NAAT had positive results.[11] After the first week of illness, serology findings were positive in 98.4% of cases, and NAAT results were positive in 4.3% of cases. These findings suggest that NAAT has limited utility in diagnosing WNV, and serology is more likely to yield a positive result after the first week of illness. A study of 28 cases of serologically confirmed WNV infection found findings from RT-PCR to be positive in 16 of 28 cases in CSF samples compared with 4 of 28 in serum samples. Most of the positive cases had testing performed within the first 12 days of illness.[12]

A curious finding in case 1 was the localized vasculitis with CME in the right eye on initial evaluation. This has been described previously and appears to be an infrequent complication.[13-16] The pathophysiology is unclear, and other authors

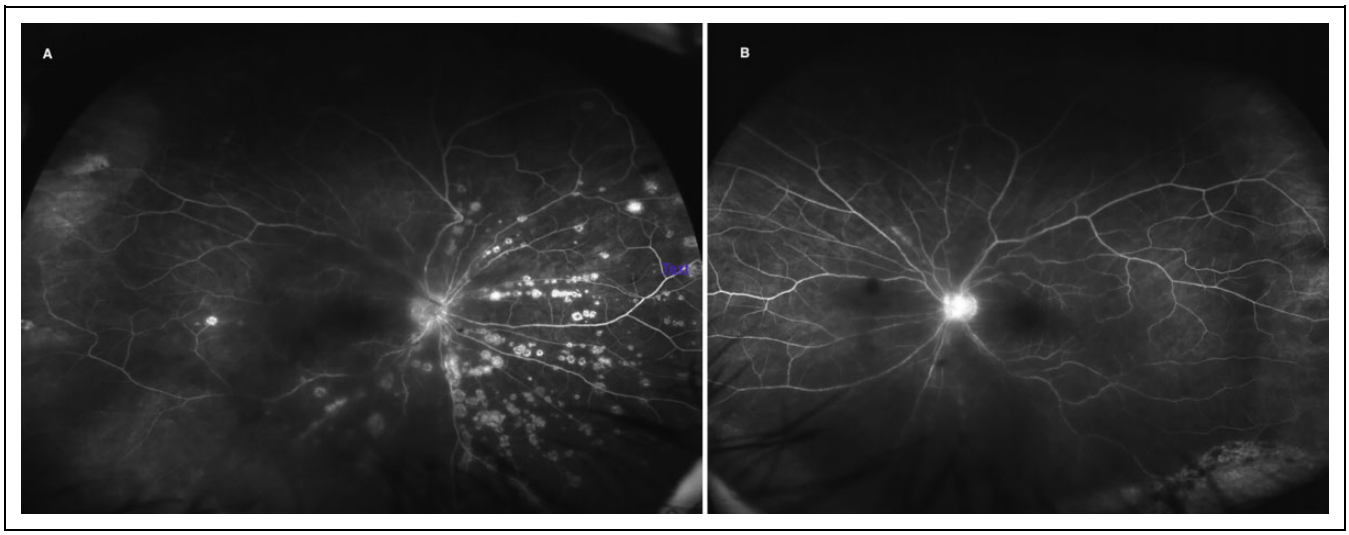

Figure 7. Fluorescein angiograph of both eyes shows many more "target" lesions in (A) the right eye compared with (B) the left eye (case 3).

have postulated that diabetes and hypertension may be contributing factors. In 2012, a case of WNV chorioretinitis with vasculitis and macular edema with resolution of the macular edema following intravitreal bevacizumab (1.25 mg/0.05 mL) injection was reported.[17] We believe case 1 is the second case involving resolution of WNV vasculitis-associated macular edema following intravitreal bevacizumab injection, suggesting the pathophysiology was at least in part vascular endothelial growth factor mediated. Unfortunately, VA ultimately declined in our patient, presumably because of photoreceptor loss, which was reflected by ellipsoid zone attenuation on OCT.

The macular edema noted in case 2 was also intriguing. The cluster of intraretinal hemorrhages in the superotemporal macula of the right eye, as well as the venular dilation, favored BRVO as a concurrent diagnosis, in which case it was reasonable to infer the macular edema was BRVO related. This was observed because the patient presented with good VA and a few small cysts on OCT, and the edema improved on subsequent follow-up, which is compatible with BRVO-associated macular edema. The relationship between this patient's presumed BRVO and WNV infection was unclear.

The Centers for Disease Control and Prevention released a report in August 2019 noting the incidence of WNV neuroinvasive disease to be 25% higher in 2018 than the median incidence during 2008 to 2017.[16] Accurate diagnosis of WNV infection is critical to differentiate and distinguish WNV from other neuroinvasive disease entities. Furthermore, accurate incident reporting of this disease may affect public health efforts aimed at controlling vector populations. As the annual prevalence of WNV in the United States has risen throughout the years, retina specialists should be aware of the distinct chorioretinal lesions and systemic testing to properly establish the diagnosis and treat the infection.

In summary, we present 3 unique cases of WNV chorioretinitis in which CSF RT-PCR failed to identify WNV as the inciting agent. These cases stress the importance of serology in diagnosing WNV infection, particularly after the first week of illness.

Authors' Note

This manuscript was presented at the Atlantic Coast Retina Club 2019 on January 10–12, 2019, in Boston, Massachusetts.

Ethical Approval

This study was exempt as determined by the Massachusetts Eye and Ear Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

Statement of Informed Consent

The study was deemed exempt per the Massachusetts Eye and Ear Institutional Review Board and informed consents were not obtained.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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