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# Non-congenital severe ocular complications of Zika virus infection

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## CASE SUMMARY

In 2016, during a major Zika virus (ZIKV) outbreak in Maracaibo, Venezuela, a 49-year-old woman and an unrelated 4-year-old boy developed bilateral optic neuritis 2–3 weeks after presenting an acute febrile illness characterized by low-grade fever, rash and myalgia [1]. Both patients presented sudden, painless bilateral loss of vision with no corneal or uveal abnormalities. Fundoscopic examination revealed oedema of the optic nerve and optic disc pallor. Optical coherence tomography confirmed bilateral optic nerve head swelling in the case of the adult, but it was not carried out in the child. Automated perimetry performed in the adult revealed bilateral diffuse visual field loss. Magnetic resonance imaging of the brain in both cases was unremarkable. Both patients were diagnosed with bilateral optic neuritis of possible infectious or parainfectious origin. Differential diagnoses that were considered and subsequently discarded included arteritic and non-arteritic ischaemic optic neuropathy, and brain disorders such as multiple sclerosis and brain tumours. Both patients were seropositive for anti-ZIKV IgG and seronegative for anti-ZIKV IgM. In addition, both patients were positive for anti-dengue virus (DENV) IgG for all four DENV serotypes. Management included intravenous methylprednisolone for 3 days, followed by oral prednisolone for 11 days. Although the patients presented a modest improvement in their vision, they continued to have visual impairment after several months of follow-up [1].

## QUESTION

Which of the following statements is accurate about non-congenital severe ocular complications of Zika virus (ZIKV) infection?

## ANSWER OPTIONS

1. They are unique to ZIKV infection and readily distinguishable from complications caused by other flaviviruses.
2. Serious ocular complications are related to the severity of the acute exanthematous illness.
3. The diagnosis can be conclusively established by detecting anti-Zika IgM and/or IgG in the patient's serum.
4. These complications can lead to permanent visual impairment.
5. There is specific treatment for ocular manifestations caused by ZIKV infection.

## DISCUSSION

**Correct Answer:** 4. These complications can lead to permanent visual impairment.

ZIKV is a mosquito-borne RNA virus belonging to the genus *Flavivirus* of the family *Flaviviridae* [2]. The classical

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**Keywords:** Zika virus; dengue; Arbovirus; *Flavivirus*; uveitis; optic neuritis; vision loss; steroid treatment.

**Abbreviations:** DENV, dengue virus; ZIKV, Zika virus.

**Table 1.** Non-congenital ocular complications of common Arbovirus infections

| Type of virus     | Complication                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zika              | Uveitis [1, 41, 42]; macular atrophy [46]; chorioretinal scar [47]; chorioretinal macular atrophy [43]                                                                                                                                                                                                                                                                                         |
| Dengue            | Maculopathy or neuropathy [3–8]; macular oedema, retinal detachment, retinal vascular occlusion, choroidal changes, optic disk swelling, optic neuritis and neuroretinitis [3–7, 9–20]                                                                                                                                                                                                         |
| Chikungunya       | Optic neuropathy [21]; conjunctivitis, episcleritis, keratitis, panuveitis, multifocal choroiditis, optic neuritis, neuroretinitis, central retinal artery occlusion, panophthalmitis, lagophthalmos and sixth nerve palsy [22–24]                                                                                                                                                             |
| West Nile         | Foveal chorioretinal scar, choroidal neovascularization [25]; vitreous haemorrhage secondary to retinal neovascularization, severe ischaemic maculopathy [26]; macular oedema, optic atrophy or retrogenulate damage; occlusive vasculitis [27–29]; uveitis [30]; vitritis [31]; chorioretinitis [31–35]; multifocal choroiditis [36]; chorioretinal lesions [37]; and optic neuritis [38, 39] |
| Rift Valley fever | Macular or paramacular scarring, retinal vascular occlusion or optic atrophy [9–11, 40]                                                                                                                                                                                                                                                                                                        |

clinical picture of ZIKV infection includes fever, exanthema, headache and conjunctivitis. The most common non-congenital, ocular manifestation of ZIKV infection is a self-limiting conjunctivitis. Serious ocular complications have been reported for other arboviruses, such as DENV [3–20], chikungunya virus [21–24], West Nile virus [25–39] and Rift Valley fever virus [9–11, 40] (Table 1). To date, there is no specific ocular lesion that is pathognomonic for ZIKV infection [41–45].

Non-congenital ocular complications are infrequent, but serious, consequences of ZIKV and other arboviral infections. The complications may appear at the end of the acute febrile illness, but more commonly occur within 2 weeks to 1 month after the onset of symptoms. There is no evidence to suggest that serious ocular complications correlate with the severity of the acute febrile illness. One study, however, found that the white cell count and serum albumin are significant predictors of ocular complications of DENV [46].

Serological testing for arboviral diseases should be performed in all patients with ocular complications and a recent history of acute febrile exanthematous infection, who live, or have travelled to, endemic regions. The presence of IgM to ZIKV strongly suggests that the ocular manifestation is associated with this virus. A causative aetiology, however, can only be established by documenting the presence of the virus in body fluids, either by cell culture or by PCR. It should be noted that other viruses, such as herpes simplex virus and human immunodeficiency virus, can also cause retinal damage and optic neuritis. Furthermore, as in the cases presented here, the diagnosis is complicated by cross-reactivity among flaviviruses, and by the co-circulation of arboviruses.

Most patients with ocular complications of arboviral infections recover completely. Nevertheless, physicians should be aware that a small percentage of patients have permanent damage with long-life visual impairment.

There is no specific or established treatment for optic neuritis caused by any arboviral infection. Systemic steroids may be used to reduce inflammation and resulting ischaemia. Corticosteroids have been used in combination with

acyclovir to treat chikungunya-associated optic neuritis, but efficacy has not been proven [47].

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#### Conflicts of interest

The authors declare that there are no conflicts of interest.

#### Ethical statement

Our study consists of observations only and no intervention/change to patient care was made.

#### References

- de Moraes CG, Pettito M, Yopez JB, Sakuntabhai A, Simon-Loriere E *et al.* Optic neuropathy and congenital glaucoma associated with probable Zika virus infection in Venezuelan patients. *JMM Case Rep* 2018;5:jmmcr.0.005145.
- Musso D, Gubler DJ. Zika virus. *Clin Microbiol Rev* 2016;29:487–524.
- Cruz-Villegas V, Berrocal AM, Davis JL. Bilateral choroidal effusions associated with dengue fever. *Retina* 2003;23:576–578.
- Lim WK, Mathur R, Koh A, Yeoh R, Chee SP. Ocular manifestations of dengue fever. *Ophthalmology* 2004;111:2057–2064.
- Bacsal KE, Chee SP, Cheng CL, Flores JV. Dengue-associated maculopathy. *Arch Ophthalmol* 2007;125:501–510.
- Beral L, Laurence B, Merle H, Harold M, David T *et al.* Ocular complications of dengue fever. *Ophthalmology* 2008;115:1100–1101.
- Teoh SC, Chee CK, Laude A, Goh KY, Barkham T *et al.* Optical coherence tomography patterns as predictors of visual outcome in dengue-related maculopathy. *Retina* 2010;30:390–398.
- Chia A, Luu CD, Mathur R, Cheng B, Chee SP. Electrophysiological findings in patients with dengue-related maculopathy. *Arch Ophthalmol* 2006;124:1421–1426.
- Khairallah M, Jelliti B, Jenzeri S. Emergent infectious uveitis. *Middle East Afr J Ophthalmol* 2009;16:225–238.
- Khairallah M, Chee SP, Rathinam SR, Attia S, Nadella V. Novel infectious agents causing uveitis. *Int Ophthalmol* 2010;30:465–483.
- Khairallah M, Yahia SB, Attia S. Arthropod vector-borne uveitis in the developing world. *Int Ophthalmol Clin* 2010;50:125–144.
- Chan DP, Teoh SC, Tan CS, Nah GK, Rajagopalan R *et al.* Ophthalmic complications of dengue. *Emerg Infect Dis* 2006;12:285–289.
- Siqueira RC, Vitral NP, Campos WR, Oréfice F, de Moraes Figueiredo LT. Ocular manifestations in dengue fever. *Ocul Immunol Inflamm* 2004;12:323–327.

14. Chlebicki MP, Ang B, Barkham T, Laude A. Retinal hemorrhages in 4 patients with dengue fever. *Emerg Infect Dis* 2005;11:770–772.
15. Loh BK, Bacsal K, Chee SP, Cheng BC, Wong D. Foveolitis associated with dengue fever: a case series. *Ophthalmologica* 2008;222:317–320.
16. Kanungo S, Shukla D, Kim R. Branch retinal artery occlusion secondary to dengue fever. *Indian J Ophthalmol* 2008;56:73–74.
17. de Amorim Garcia CA, Gomes AH, de Oliveira AG. Bilateral stellar neuroretinitis in a patient with dengue fever. *Eye* 2006;20:1382–1383.
18. Venkatramani J, Lim WK. Bilateral vitreous haemorrhage associated with dengue fever. *Eye* 2006;20:1405–1406.
19. Sanjay S, Wagle AM, Au Eong KG. Dengue optic neuropathy. *Ophthalmology* 2009;116:170.
20. Tabbara K. Dengue retinochoroiditis. *Ann Saudi Med* 2012;32:530–533.
21. Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. *J Ophthalmic Inflamm Infect* 2013;3:35.
22. Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM et al. Ocular manifestations associated with chikungunya. *Ophthalmology* 2008;115:287–291.
23. Lalitha P, Rathinam S, Banushree K, Maheshkumar S, Vijayakumar R et al. Ocular involvement associated with an epidemic outbreak of chikungunya virus infection. *Am J Ophthalmol* 2007;144:552–556.
24. Mittal A, Mittal S, Bharati MJ, Ramakrishnan R, Saravanan S et al. Optic neuritis associated with chikungunya virus infection in South India. *Arch Ophthalmol* 2007;125:1381–1386.
25. Seth RK, Stoessel KM, Adelman RA. Choroidal neovascularization associated with West Nile virus chorioretinitis. *Semin Ophthalmol* 2007;22:81–84.
26. Khairallah M, Ben Yahia S, Attia S, Zaouali S, Jelliti B et al. Indocyanine green angiographic features in multifocal chorioretinitis associated with West Nile virus infection. *Retina* 2006;26:358–359.
27. Kaiser PK, Lee MS, Martin DA. Occlusive vasculitis in a patient with concomitant West Nile virus infection. *Am J Ophthalmol* 2003;136:928–930.
28. Teitelbaum BA, Newman TL, Tresley DJ. Occlusive retinal vasculitis in a patient with West Nile virus. *Clin Exp Optom* 2007;90:463–467.
29. Gohari AR, Willson RL, Gitter KA. West Nile virus occlusive retinal vasculitis. *Retin Cases Brief Rep* 2011;5:209–212.
30. Kuchtey RW, Kosmorsky GS, Martin D, Lee MS. Uveitis associated with West Nile virus infection. *Arch Ophthalmol* 2003;121:1648–1649.
31. Bains HS, Jampol LM, Caughron MC, Parnell JR. Vitritis and chorioretinitis in a patient with West Nile virus infection. *Arch Ophthalmol* 2003;121:205–207.
32. Adelman RA, Membreno JH, Afshari NA, Stoessel KM. West Nile virus chorioretinitis. *Retina* 2003;23:100–101.
33. Shaikh S, Trese MT. West Nile virus chorioretinitis. *Br J Ophthalmol* 2004;88:1599–1560.
34. Eidsness RB, Stockl F, Colleaux KM. West Nile chorioretinitis. *Can J Ophthalmol* 2005;40:721–724.
35. Myers JP, Leveque TK, Johnson MW. Extensive chorioretinitis and severe vision loss associated with West Nile virus meningoencephalitis. *Arch Ophthalmol* 2005;123:1754–1756.
36. Vandenbelt S, Shaikh S, Capone A, Williams GA. Multifocal chorioiditis associated with West Nile virus encephalitis. *Retina* 2003;23:97–99.
37. Khairallah M, Ben Yahia S, Ladjimi A, Zeghidi H, Ben Romdhane F et al. Chorioretinal involvement in patients with West Nile virus infection. *Ophthalmology* 2004;111:2065–2070.
38. Vaispapis V, Blum A, Soboh S, Ashkenazi H. West Nile virus meningoencephalitis with optic neuritis. *Arch Intern Med* 2002;162:606–a–6607.
39. Gilad R, Lampl Y, Sadeh M, Paul M, Dan M. Optic neuritis complicating West Nile virus meningitis in a young adult. *Infection* 2003;31:55–56.
40. Al-Hazmi A, Al-Rajhi AA, Abboud EB, Ayoola EA, Al-Hazmi M et al. Ocular complications of Rift Valley fever outbreak in Saudi Arabia. *Ophthalmology* 2005;112:313–318.
41. Furtado JM, Espósito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA. Uveitis associated with Zika virus infection. *N Engl J Med* 2016;375:394–396.
42. Kodati S, Palmore TN, Spellman FA, Cunningham D, Weistrop B et al. Bilateral posterior uveitis associated with Zika virus infection. *The Lancet* 2017;389:125–126.
43. Parke DW, Almeida DR, Albin TA, Ventura CV, Berrocal AM et al. Serologically confirmed Zika-related unilateral acute maculopathy in an adult. *Ophthalmology* 2016;123:2432–2433.
44. Wong CW, Ng SR, Cheung CM, Wong TY, Mathur R. Zika-related maculopathy. *Retin Cases Brief Rep* 2017;doi: 10.1097/ICB.0000000000000552
45. Marquezan MC, Ventura CV, Sheffield JS, Golden WC, Omiadze R et al. Ocular effects of Zika virus—a review. *Surv Ophthalmol* 2018;63:166–173.
46. Seet RC, Quek AM, Lim EC. Symptoms and risk factors of ocular complications following dengue infection. *J Clin Virol* 2007;38:101–105.
47. Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM et al. Ocular manifestations associated with chikungunya. *Ophthalmology* 2008;115:287–291.

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