

Zika Virus Infection in the Eye

Xu P^{1,2*}¹Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, Texas, United States²Department of Ophthalmology and Visual Sciences, University of Texas Medical Branch, Galveston, Texas, United States***Corresponding authors:** Pei Xu, Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, Texas, United States, E-mail: pegggy83422@gmail.com**Received date:** January 11, 2017; **Accepted date:** January 31, 2017; **Published date:** February 03, 2017**Copyright:** © 2017 Xu P. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Zika virus (ZIKV) infection is becoming one of the greatest concerns nowadays all over the world due to its rapid geographic spread and the involvement of central nervous system (CNS) in newborns and adults. Since the first report of outbreak in Brazil in 2015, microcephaly, Guillain-Barre syndrome (GBS) and ocular anomalies have been associated with ZIKV infection, although approximately 80% of cases appeared to be asymptomatic. As to eye lesions, it is still undefined whether they are the results of microcephaly or caused by ZIKV infection directly. In this review, the current literature on newborn and adults ophthalmic findings associated with ZIKV infection were summarized and discussed.

Keywords: Zika virus; Central nervous system; Ocular

The Virus and Transmission

The Zika virus (ZIKV) is a mosquito-borne flavivirus that is closely related with yellow fever, the dengue, and West Nile viruses [1]. It was first identified in rhesus monkeys in Uganda in 1947, and in human beings from Uganda and Tanzania in 1952 [2,3]. Until the early 2000s, no epidemic outbreaks of ZIKV were reported. However, in 2007, the first ZIKV outbreak occurred in Micronesia [4]. Then another epidemic occurred in French Polynesia from 2013 to 2014, where the first case of Guillain-Barre Syndrome (GBS) was identified [5,6]. ZIKV autochthonous transmission was first confirmed in Brazil in April 2015 [7]. Since then, over 1 million Brazilians have had ZIKV infections, and the epidemic has spread to America and Singapore [8]. The rapid geographical expansion reflected the ZIKV capacity to cause worldwide scale outbreaks where the primary mosquito vectors (*Aedes* species) were endemic [9].

Besides vector transmission from mosquito to human, other forms of transmission have also been reported, such as vertical transmission from mother to fetus, sexual transmission from infected men to their partners, and blood transfusion [10-12]. Since the RNA of ZIKV has been detected in urine, amniotic fluid, breast milk and saliva, other modes of person-to-person transmission may also exist [5,13-15].

Clinical Manifestations

It is estimated that around 80% of cases of ZIKV disease are asymptomatic or oligo-symptomatic [16]. When symptoms appear, they usually develop within 3 to 12 days after the bite of a vector mosquito [17]. The clinical presentations are described as “influenza-like”, which include fever, headache, arthralgia, myalgia, retro-orbital pain, non-purulent conjunctivitis and a maculopapular rash [18].

ZIKV infection has also been associated with neurologic complications. It was reported that an unusual increase of microcephaly cases was coincidentally observed six months after ZIKV outbreak in Brazil [19]. In addition to microcephaly, other

abnormalities related with congenital ZIKV intrauterine infection were reported as the congenital Zika syndrome (CZS) subsequently, which included hearing deficits, arthrogryposis, and ocular lesions [16,20-22]. In adults with ZIKV infection, GBS was identified in a small portion of patients, in which the immune system attacked the peripheral neurons, leading to muscle weakness and paralysis [23].

Ophthalmic Anomalies

In January 2016, the first cases of ophthalmic abnormalities in infants with microcephaly and presumed ZIKV intrauterine infection were reported in Brazil after the outbreak. Macular pigment mottling and foveal reflex loss were detected unilaterally in all three cases, with one showing well-delineated macular atrophy [20]. Subsequently, the same group reported 10 other cases with microcephaly which manifested similar chorioretinal atrophy and optic nerve alternations [21]. In February 2016, de Paula Freitas et al. reported 10 of 29 infants with ZIKV-related microcephaly from Salvador, Bahia and Brazil, had significant ocular lesions including focal pigment clumping, chorioretinal atrophy, optic nerve changes, bilateral iris coloboma and lens subluxation [16]. In August 2016, Miranda HA et al. described vascular changes and hemorrhagic retinopathy in three cases of maculopathy along with microcephaly [24]. Since microcephaly was found in all of these cases, it was considered that the microcephaly may be a causative agent or at least a risk factor in the development of ophthalmic abnormalities [16,20,25]. However, Ventura CV et al. defined neurological and ocular findings in an infant without microcephaly but was positive for IgM antibody capture (MAC)-ELISA of ZIKV in the cerebral spinal fluid [26]. Therefore, it is still debatable whether the eye lesions are directly caused by ZIKV infection or secondary to microcephaly [27]. In this way, microcephaly should not be set as a criterion in the diagnosis of ZIKV infection in infants [26].

Manifestations of eye diseases were also reported in adults infected by ZIKV [28-31]. Unilateral acute idiopathic maculopathy (UAIM) was found in a 64-year-old white man with strongly indicative of recent ZIKV infection according to the serum plaque reduction

neutralization technique (PRNT) assay performed by Centers for Disease Control and Prevention (CDC). He did not receive any treatment for the maculopathy, and the vision improved to 20/20 within 6 weeks [28]. A case of bilateral hypertensive iridocyclitis was described in a 39-year-old man diagnosed with ZIKV infection clinically [31]. Furtado JM et al. identified bilateral anterior uveitis in a man in his early 40s with positive result for ZIKV on RT-PCR from the aqueous sample [29]. In another 26-year-old white man with bilateral posterior uveitis, both eyes had mild vitreous inflammation, and one of them showed retinal pigment epithelium and chorioretinal lesions on optical coherence tomography (OCT) imaging and indocyanine green dye (ICG) angiography [30]. In these three cases, the patients received topical glucocorticoid therapy for at least one week. Resolutions of visual acuity, lowering of intraocular pressure, as well as complete remission of symptoms were achieved [29-31].

Diagnosis and Deferential Diagnosis

Confirmation of ZIKV infection is based on serology for ZIKV, which include the Zika IgM antibody capture enzyme-linked immunosorbent assay (Zika MAC-ELISA) and the PRNT assay [28,32]. Real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay is used for molecular test in serum specimen [30]. Since ZIKV infection shows nonspecific "influenza-like" manifestations which resemble other flavivirus infections, particularly, Dengue and Chikungunya viruses share the same geographic distribution with ZIKV, differential diagnosis are required [10]. Moreover, the chorioretinal lesions shown in ZIKV infection are nonspecific as well; serology tests for toxoplasmosis, syphilis, cytomegalovirus, rubella, herpes simplex virus are also required [33].

Conclusion

ZIKV infection is becoming one of the greatest concerns nowadays globally. Its rapid geographic spread and the damage to the CNS both in infants and adults emerge as serious public health care threats. To control the epidemic of this new emerging pathogen, new strategies are needed to prevent vertical, sexual and other forms of transmission. Microcephaly, GBS and ocular anomalies have been associated with ZIKV infection since its first outbreak in Brazil. As to eye lesions, it is still unclear whether they are the results of microcephaly or caused by ZIKV infection directly. Since ZIKV can penetrate the blood-brain and blood-retina barriers, many other ophthalmic manifestations might be defined in the future [31]. Clinicians should encourage all newborns and adults with suspected infection, especially those have ocular complaints, to undergo a complete ophthalmologic examination.

References

- Balm MN, Lee CK, Lee HK, Chiu L, Koay ES, et al. (2012) A diagnostic polymerase chain reaction assay for Zika virus. *J Med Virol* 84: 1501-1505.
- DICK GW, KITCHEN SF, HADDOW AJ (1952) Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg* 46: 509-520.
- DICK GW (1952) Zika virus. II. Pathogenicity and physical properties. *Trans R Soc Trop Med Hyg* 46: 521-534.
- Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, et al. (2009) Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 360: 2536-2543.
- Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D (2014) Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill* 19.
- Oehler E, Watrin L, Larre P, Leparac-Goffart I, Lastere S, et al. (2013) Zika virus infection complicated by Guillain-Barre syndrome-case report, French Polynesia, December 2013. *Euro Surveill* 19 pii: 20720.
- Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, et al. (2015) First report of autochthonous transmission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz* 110: 569-572.
- Rifkin LM, Duker JS (2016) Use of Retinal Optical Coherence Tomography to Detect Congenital Zika Syndrome. *JAMA Ophthalmol* 134: 1427-1428.
- Falcao MB, Cimerman S, Luz KG, Chebabo A, Brigido HA, et al. (2016) Management of infection by the Zika virus. *Ann Clin Microbiol Antimicrob* 15: 57.
- Slenczka W (2016) Zika Virus Disease. *Microbiol Spectr* 4.
- Musso D, Roche C, Robin E, Nhan T, Teissier A, et al. (2015) Potential sexual transmission of Zika virus. *Emerg Infect Dis* 21: 359-361.
- Motta JJ, Spencer BR, Cordeiro da Silva SG, Arruda MB, Dobbin JA, et al. (2016) Evidence for Transmission of Zika Virus by Platelet Transfusion. *N Engl J Med* 375: 1101-1103.
- Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M (2015) Detection of Zika virus in urine. *Emerg Infect Dis* 21: 84-86.
- Musso D, Roche C, Nhan TX, Robin E, Teissier A, et al. (2015) Detection of Zika virus in saliva. *J Clin Virol* 68: 53-55.
- Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, et al. (2016) Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 47: 6-7.
- de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, et al. (2016) Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil. *JAMA Ophthalmol* 134: 529-535.
- Hamel R, Liégeois F, Wicht S, Pompon J, Diop F1, et al. (2016) Zika virus: epidemiology, clinical features and host-virus interactions. *Microbes Infect* 18: 441-449.
- Zanluca C, Dos Santos CN (2016) Zika virus - an overview. *Microbes Infect* 18: 295-301.
- Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, et al. (2016) Brazilian Medical Genetics Society-Zika Embryopathy Task Force. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 65: 59-62.
- Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R Jr (2016) Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet* 387: 228.
- Ventura CV, Maia M, Ventura BV, Linden VV, Araújo EB, et al. (2016) Ophthalmological findings in infants with microcephaly and presumed intra-uterus Zika virus infection. *Arq Bras Oftalmol* 79: 1-3.
- Miranda-Filho Dde B, Martelli CM, Ximenes RA, Araújo TV, Rocha MA1, et al. (2016) Initial Description of the Presumed Congenital Zika Syndrome. *Am J Public Health* 106: 598-600.
- Dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, et al. (2016) Zika Virus and the Guillain-Barré Syndrome - Case Series from Seven Countries. *N Engl J Med* 375: 1598-1601.
- Miranda HA, Costa MC, Frazão MA, Simão N, Franchischini S, et al. (2016) Expanded Spectrum of Congenital Ocular Findings in Microcephaly with Presumed Zika Infection. *Ophthalmology* 123: 1788-1794.
- Ventura CV, Maia M, Travassos SB, Martins TT, Patriota F, et al. (2016) Risk Factors Associated With the Ophthalmoscopic Findings Identified in Infants With Presumed Zika Virus Congenital Infection. *JAMA Ophthalmol* 134: 912-918.
- Ventura CV, Maia M, Dias N, Ventura LO, Belfort R Jr (2016) Zika: neurological and ocular findings in infant without microcephaly. *Lancet* 387: 2502.
- Moshfeghi DM, de Miranda HA, Costa MC (2016) Zika Virus, Microcephaly, and Ocular Findings. *JAMA Ophthalmol* 134: 945.

-
28. Parke DW, Almeida DR, Albin TA, Ventura CV, Berrocal AM, et al. (2016) Serologically Confirmed Zika-Related Unilateral Acute Maculopathy in an Adult. *Ophthalmology* 123: 2432-2433.
 29. Furtado JM, Espósito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA (2016) Uveitis Associated with Zika Virus Infection. *N Engl J Med* 375: 394-396.
 30. Kodati S, Palmore TN, Spellman FA, Cunningham D, Weistrop B, et al. (2017) Bilateral posterior uveitis associated with Zika virus infection. *Lancet* 389: 125-126.
 31. Fontes BM (2016) Zika virus-related hypertensive iridocyclitis. *Arq Bras Oftalmol* 79: 63.
 32. de Oliveira Dias JR, Ventura CV, Borba PD, de Paula Freitas B, Pierroti LC (2017) Infants with Congenital Zika Syndrome and Ocular Findings From São Paulo, Brazil: Spread Of Infection. *Retin Cases Brief Rep*.
 33. Jampol LM, Goldstein DA (2016) Zika Virus Infection and the Eye. *JAMA Ophthalmol* 134: 535-536.